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A prospective study of reproductive factors and exogenous hormone use in relation to ovarian cancer risk among Black women

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Abstract

Purpose—Extensive data in White women have linked oral contraceptive use, tubal ligation, and parity to reduced risk of ovarian cancer; results on postmenopausal female hormone use are mixed. Few studies, all of which are case-control studies, have been undertaken among Black women. The aim of the present study was to prospectively assess associations of reproductive factors and exogenous hormones with ovarian cancer among Black women.

Methods—During follow-up from 1995 to 2013 in the Black Women’s Health Study, a prospective cohort study, 115 incident cases of ovarian cancer were identified. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the relation of the factors of interest to risk of ovarian cancer, with control for covariates.

Results—Oral contraceptive use was inversely associated with ovarian cancer risk: the HR for 10 years of use relative to <1 year was 0.50 (95% CI 0.30–0.98). For postmenopausal female hormone use, the HRs for ever use of estrogen with progestin and of estrogen alone were 1.37 (0.73–2.55) and 1.66 (0.90–3.07), respectively. The HRs for parity and tubal ligation were below 1.0, but were not statistically significant.

Conclusion—Overall, the findings indicate that the relation of reproductive factors and exogenous hormone use to risk of ovarian cancer is similar among Black and White women. The results on estrogen-only supplements and estrogen with progestin supplements add to evidence from Whites indicating that use of hormone supplements may be associated with increased risk of ovarian cancer.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Keywords

African American; women; ovarian cancer; reproductive factors

Introduction

There are striking racial differences in the prevalence of many risk factors for ovarian cancer, particularly reproductive risk factors. Black women tend to have earlier ages at menarche (1), earlier first pregnancies (2), more pregnancies (2), lower rates of lactation (3), less use of oral contraceptives (4), and higher rates of tubal ligation (4) than White women. A large body of literature in White women indicates that tubal ligation (5), oral contraceptive use (6), parity (6), and lactation (7, 8) are associated with reduced ovarian cancer risk, and that genital talc use (9, 10) is associated with increased risk. Findings for postmenopausal female hormone use (6, 11–13) have been mixed, but suggest a positive association. Until recently, published analyses of ovarian cancer risk factors included few Black cases (9, 14–17). The African American Cancer Epidemiology Study (AACES), a population-based case-control study of ovarian cancer in 11 states with a large sample size, is making major advances in elucidation of the epidemiology of ovarian cancer in U.S. Black women (18, 19). Because of the potential for both recall bias and selection bias in case-control studies, it is critical that results be confirmed in prospective studies. To that end, we carried out an analysis of hormonal and reproductive factors in relation to ovarian cancer incidence in a large cohort of Black women, the Black Women's Health Study.

Methods

Study population

The Black Women's Health Study (BWHS) is a prospective cohort study of 59,000 self-identified Black women who enrolled in 1995 by completing a mailed health questionnaire (20, 21). Most participants lived in 17 states across the United States and all women were ages 21–69 at baseline. The baseline questionnaire collected data on demographics, educational attainment, reproductive factors, medical history, and other factors. Biennial questionnaires update these data. Follow-up of the baseline cohort has been successful for 87% of potential person-years through the most recent completed questionnaire cycle in 2013. The study protocol was approved by the Boston University Medical Center Institutional Review Board and informed consent was obtained from all individual participants included in the study.

Case ascertainment

Cases were identified through self-report and through linkage to cancer registries in the 24 states in which 95% of BWHS participants live. The baseline and follow-up questionnaires asked about diagnoses of cancer, including ovarian cancer, and the year of diagnosis. Self-reported cancer cases were confirmed through hospital pathology reports and cancer registry data. Additional cases were identified from mortality data collected through linkage with the National Death Index Plus database (22). Data on histologic subtype (23, 24) was available for 67 (58.3%) cases (Table 1).

Exposures

At baseline, data were collected on number and timing of births; duration of breast feeding; age at initiation, duration, and recency of oral contraceptive (OC) use; and recency, duration, and type of postmenopausal female hormone use. Follow-up questionnaires updated this information. Age at tubal ligation was reported on the baseline questionnaire and on the 1997, 1999, and 2001 questionnaires.

Covariates

At baseline, participants reported height and weight; follow-up questionnaires updated weight. A validation study demonstrated accurate reporting of height and weight by BWHS participants (25). Body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Data on educational attainment was collected by the baseline and 2003 questionnaires. Baseline and follow-up questionnaires collected data on cessation of menstrual periods and the reason that the periods had stopped (e.g., natural causes, surgery), which were used to classify menopausal status. Questionnaire data collected on removal of the ovaries and of the uterus were used to classify participants as having had unilateral oophorectomy, bilateral oophorectomy, and/or hysterectomy.

Analytic sample

Participants were excluded from the analytic sample in the event of a prevalent ovarian cancer diagnosis ($N=57$), a prevalent diagnosis of any cancer other than non-melanoma skin cancer ($N=1,299$), a diagnosis of ovarian granulosa cell cancer ($N=7$), a bilateral oophorectomy ($N=4,480$), or missing data on menopausal status ($N=16$), leaving 53,141 women in the present analyses.

Statistical analysis

Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the relation of the exposures of interest to incident ovarian cancer. Each exposure of interest was also included as a potential covariate in analyses for the other exposures. Participants contributed person-time from enrollment in 1995 until incident ovarian cancer diagnosis, bilateral oophorectomy, death, or loss to follow-up or through 2013, whichever occurred first. Initial models controlled for age and questionnaire cycle. Multivariable models controlled for age, questionnaire cycle, educational attainment (< 16 years), BMI ($< 30 \text{ kg}/\text{m}^2$), hysterectomy (ever), and, as appropriate, parity (parous), lactation (ever breastfed), age at first birth (< 20 years old), age at last birth (< 30 years old), tubal ligation (ever), OC use (duration < 5 years), menopausal status (premenopausal), and postmenopausal female hormone use (duration < 1 year). Exposures and covariates were treated as time-varying using the Andersen-Gill data structure.(26) Tests for linear trend in the exposure variables were conducted by including a categorical variable in the regression model and assessing the term as a continuous variable. SAS 9.3 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

At baseline in 1995, most participants had graduated high school and had a BMI of 25 or greater (Table 2). Most participants were parous, had used oral contraceptives, and were premenopausal. During follow-up through 2013, there were 115 incident cases of ovarian cancer, with a mean age at diagnosis of 53.8 years (Table 1). Among the 67 cases for which we were able to ascertain histologic subtype, serous tumors were most common (49.3%), followed by endometrioid tumors (20.9%) and mucinous tumors (11.9%).

As shown in Table 3, ovarian cancer incidence decreased with increasing duration of OC use (p-trend <0.01), with an HR of 0.47 (0.28–0.79) for 10 years of use compared to a reference category of use for <1 year (i.e., never use or use of OCs for <1 year). Results were similar when the reference category was never use of OCs (HR=0.50, 95% CI 0.29–0.86). When duration and recency of OC use were considered together, the greatest reduction in risk was for duration 10 years and recency <10 years ago, with a HR of 0.38 (0.17–0.83). In analyses restricted to parous women, the HR for 10 years of OC use before the first birth was 0.18 (0.02–1.33) (data not shown).

As shown in Table 4, the HR for 5 years of use of postmenopausal female hormones among women age 45 or older, relative to never use of postmenopausal female hormones or use for <1 year in duration, was 1.42 (0.75–2.70). The association did not materially differ by recency of use. The HRs were 1.37 (0.73–2.55) for ever use of estrogen with progestin and 1.66 (0.90–3.07) for ever use of estrogen alone, relative to never use or use for <1 year. In a secondary analysis conducted among postmenopausal women of any age (N=56 cases), the HRs were 1.01 (0.50–2.04) for ever use of estrogen with progestin (N=11 cases among users) and 1.29 (0.64–2.61) for ever use of estrogen alone (N=13 cases among users).

The HR for parity versus nulliparity was 0.74 (95% CI 0.42–1.29) and there was no evidence of a trend with increasing parity (Table 5). There was also no evidence of a trend across age at first or last birth. Among parous women, the HR for ever lactation versus never lactation was 0.86 (0.54–1.37). There was evidence of a reduced risk of ovarian cancer for history of tubal ligation (HR=0.75, 95% CI 0.47–1.18), but there was not a linear trend in age at tubal ligation (p-trend=0.16) (Table 5).

Discussion

In this prospective cohort of Black women from across the U.S., oral contraceptive use was the only factor significantly associated with ovarian cancer risk; there was a trend of decreasing risk as duration of use increased. Associations with parity, lactation, and tubal ligation were suggestive of reduced risk, while associations for postmenopausal female hormone use were suggestive of increased risk.

Studies of the relation of OC use to risk of ovarian cancer in Black women have consistently demonstrated a reduction in risk (9, 14, 16, 17, 19). The reduction is particularly strong for long duration of OC use. For example, in the North Carolina Ovarian Cancer Study (17), OC use for 5 years was associated with a 48% reduced risk of ovarian cancer and, in AACES (18), OC use for 10 years was associated with a 40% reduction in risk. There was a similar

magnitude of association observed in the BWHS for 10 years of OC use. In the present study, the reduced risk of ovarian cancer observed for long duration of OC use is compatible with waning of an effect of long duration use as the time since last use increases. Previous studies on ovarian cancer risk among Black women have not published on the combined effect of duration and recency of OC use. However, the present finding is similar to results from the Collaborative Group on Epidemiological Studies of Ovarian Cancer (27). This study found a significant difference in the association for duration of OC use across strata of recency (p -heterogeneity <0.01) with the strongest associations among recent users of long duration.

No data have been published on type of postmenopausal female hormone use in relation to ovarian cancer risk among Black women. However, among White women, increased risk of ovarian cancer has been associated with estrogen taken with progestin and with estrogen alone in the Collaborative Group on Epidemiological Studies of Ovarian Cancer (28), the European Prospective Investigation into Cancer and Nutrition Study (11), the NIH-AARP Diet and Health Study (13), and the Ovarian Cancer Association Consortium (12). The relative risks ranged from 1.20 to 1.43 for ever or current use of estrogen with progestin postmenopausal hormones and from 1.35 to 1.69 for ever or current use of estrogen alone postmenopausal hormones (11–13, 28). Present findings in the BWHS are consistent with those estimates.

The 29% reduction in risk associated with parity observed in the present study is compatible with the 20–40% reductions in risk among Black women reported in other studies (9, 14, 16, 17, 19). Two studies examined 3 births: there was an OR of 0.52 (0.17–1.62), but no linear trend across parity, in the North Carolina Ovarian Cancer Study (17) and an OR of 0.61 (0.41–0.91) in AACES (19). Associations for age at first birth or lactation have been observed in AACES (18), but not in the present study or other studies among Black women (14, 16).

Previous studies of Black women have observed a reduced risk of ovarian cancer among women who had undergone tubal ligation, with relative risks ranging from 0.43 to 0.70 (9, 16–18). A similar association was observed in the BWHS, with no evidence of a trend across age at tubal ligation. The case-control studies of Black women have not reported on age at tubal ligation, but larger studies of Whites found a stronger association for younger age at tubal ligation (5, 29, 30) or no difference in risk by age (31).

Previous studies of ovarian cancer in Black women have ranged in size from 84 cases (16) to 641 cases (18). The present investigation, which included 115 cases, is the first prospective study among Black women. We had extensive data on the exposures under study and on important covariates. While we did not have data on type and dose of OC used, the reduction in ovarian cancer risk has appeared consistent across doses in some studies (32) but has differed in others (33). Ovarian cancer is a heterogeneous disease and, as in previous studies, we had insufficient numbers for analyses by histologic subtype. In White women, approximately two-thirds of epithelial tumors are of the serous subtype, followed by endometrioid, clear cell, and mucinous tumors (34, 35). Among BWHS cases with data on histologic subtype, 49.3% were serous tumors; case-control studies of Black women have

reported 55.5% (9) and 60.0% (18) serous tumors. While there is some evidence that risk factors for ovarian cancer vary by histologic subtype, associations for the well-established reproductive and hormonal risk factors – tubal ligation (36), OC use (37), and parity (37, 38) – appear consistent across histologic subtypes.

In summary, results from the BWHS, a prospective cohort of Black women, are consistent with those from previous case-control studies of ovarian cancer in Black women, including ACCES, the only study with more than 150 cases of ovarian cancer among Black women. The risk of ovarian cancer associated with use of estrogen with progestin, and of estrogen alone, has not previously been examined among Black women; results in the BWHS are consistent with findings in White women. Larger studies of ovarian cancer in Black women or collaborative analyses of existing studies with Black participants are needed to further delineate associations and determine whether findings vary by histologic subtypes.

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Table 1

Characteristics of 115 ovarian cancer cases in the Black Women's Health Study

Characteristic	N	%
Age at diagnosis		
<40	12	10.45%
40–49	29	25.2%
50–59	41	35.7%
60	33	28.7%
Histologic subtype ^a		
Serous	33	49.3%
Endometrioid	14	20.9%
Mucinous	8	11.9%
Clear cell	3	4.5%
Other	9	13.4%

^aHistology data were not available for 48 cases.

Table 2Baseline characteristics of the 53,141 BWHS participants in the analytic sample^a

Characteristic	N	%
Age, mean (SD)	37.8 ± 10.3	
Education, years		
12	9,706	18.3
13–16	19,245	36.2
16	24,086	45.3
Body mass index, kg/m ²		
<20	3,038	5.7
20–24	17,420	32.8
25–29	16,002	30.1
30	15,016	28.3
Parity		
Nulliparous	19,266	36.3
1 child	11,769	22.2
2 children	11,873	22.3
3 children	9,945	18.7
Age at first birth ^b		
<20	11,719	34.9
20–24	11,929	35.5
25–29	6,716	20.0
30	3,223	9.6
Age at last birth ^b		
<25	12,761	38.0
25–29	10,533	31.4
30	10,293	30.7
Ever breastfed ^b	13,798	41.1
Oral contraceptive use,		
Never	12,197	23.0
<5 years	24,188	45.5
5 years	16,756	31.5
Ever tubal ligation	13,542	25.5
Premenopausal status	44,139	83.1
Ever use of E+P female hormones	1,836	3.5
Ever use of E alone female hormones	2,477	4.7

Abbreviations: E+P, estrogen and progestin; E, estrogen; SD, standard deviation

^aValues are standardized to the age distribution of the study population. Frequencies may not add up to 100% due to rounding and missing data.^bAmong parous women only.

Table 3

Hazard ratios and 95% confidence intervals for the relation of oral contraceptive use to risk of ovarian cancer in the BWHS, 1995–2013

Characteristic	Cases (N=115)	Person-time (person-years)	Model 1 ^a		Model 2 ^b	
			HR	95% CI	HR	95% CI
Duration of OC use						
Never use or use <1 year	35	147,799	1.0	Reference	1.0	Reference
1–4 years	29	161,713	0.92	(0.55–1.53)	0.93	(0.56–1.57)
5–9 years	12	108,192	0.48	(0.24–0.94)	0.50	(0.25–0.98)
10 years	39	343,045	0.47	(0.28–0.79)	0.50	(0.30–0.83)
p-trend				<0.01		<0.01
Recency of OC use						
Never use or use <1 year	35	147,799	1.0	Reference	1.0	Reference
10 years ago	54	325,806	0.60	(0.38–0.96)	0.64	(0.40–1.02)
<10 years ago	18	261,813	0.49	(0.25–0.94)	0.50	(0.26–0.98)
p-trend				0.02		0.03
Duration and recency of OC use						
Never use or use <1 year	35	147,799	1.0	Reference	1.0	Reference
1–9 years, 10 years ago	25	154,039	0.65	(0.38–1.11)	0.68	(0.39–1.16)
1–9 years, <10 years ago	8	90,536	0.83	(0.34–2.00)	0.84	(0.35–2.03)
10 years, 10 years ago	29	171,768	0.53	(0.31–0.92)	0.57	(0.33–0.99)
10 years, <10 years ago	10	171,277	0.37	(0.17–0.80)	0.38	(0.17–0.83)

Abbreviations: HR, hazard ratio; CI, confidence interval; OC, oral contraceptive

^aModel 1 adjusts for age and questionnaire cycle.

^bModel 2 adjusts for age, questionnaire cycle, parity, lactation, age at first birth, age at last birth, hysterectomy, tubal ligation, menopausal status, use of postmenopausal female hormones, educational attainment, and body mass index.

Table 4

Hazard ratios and 95% confidence intervals for the relation of postmenopausal female hormone use to risk of ovarian cancer in the BWHS among participants age 45 or older, 1995–2013

Characteristic	Cases (N=86)	Person-time (person-years)	Model 1 ^a HR	Model 1 ^a 95% CI	Model 2 ^b HR	Model 2 ^b 95% CI
Duration of FH use						
Never use or use <1 year	61	267,254	1.0	Reference	1.0	Reference
1–4 years	11	47,176	0.95	(0.49–1.83)	1.04	(0.54–2.02)
5 years	14	36,386	1.21	(0.64–2.23)	1.42	(0.75–2.70)
p-trend				0.64		0.32
Recency of FH use						
Never use or use <1 year	61	267,254	1.0	Reference	1.0	Reference
1–4 years ago	16	64,406	0.95	(0.53–1.71)	1.10	(0.61–1.99)
5 years ago	9	19,156	1.39	(0.64–3.03)	1.50	(0.69–3.27)
p-trend				0.57		0.34
Use of E+P or E alone ^c						
Never used any or use <1 year	61	267,254	1.0	Reference	1.0	Reference
Ever used E+P	14	39,082	1.27	(0.68–2.35)	1.37	(0.73–2.55)
Ever used E alone	17	45,767	1.32	(0.75–2.35)	1.66	(0.90–3.07)

Abbreviations: HR, hazard ratio; CI, confidence interval; FH, female hormone; E+P, estrogen and progestin; E, estrogen

^aModel 1 adjusts for age and questionnaire cycle.

^bModel 2 adjusts for age, questionnaire cycle, parity, lactation, age at first birth, age at last birth, hysterectomy, tubal ligation, oral contraceptive use, educational attainment, and body mass index.

^cEver E+P and E alone are not mutually exclusive – participants may have used both E+P and E alone during follow-up.

Hazard ratios and 95% confidence intervals for the relation of reproductive variables to risk of ovarian cancer in the BWHS, 1995–2013

Table 5

Characteristic	Cases (N=115)	Person-time (person-years)	Model 1 ^a		Model 2 ^b	
			HR	95% CI	HR	95% CI
Parity						
Nulliparous	30	223,547	1.0	Reference	1.0	Reference
Parous	84	533,006	0.77	(0.50–1.20)	0.74	(0.42–1.29)
1 birth	24	189,656	0.76	(0.44–1.31)	0.78	(0.43–1.41)
2 births	24	190,539	0.64	(0.37–1.12)	0.67	(0.34–1.31)
3 births	36	152,811	0.95	(0.56–1.61)	0.84	(0.39–1.80)
p-trend				0.79		0.68
Age at first birth ^c						
<20	36	153,197	1.0	Reference	1.0	Reference
20–24	24	169,350	0.59	(0.35–0.99)	0.60	(0.35–1.01)
25–29	12	114,237	0.49	(0.26–0.95)	0.53	(0.27–1.05)
30	12	86,455	0.71	(0.36–1.38)	0.74	(0.33–1.69)
p-trend				0.09		0.14
Age at last birth ^c						
<25	23	149,880	1.0	Reference	1.0	Reference
25–29	26	149,880	1.04	(0.59–1.84)	1.32	(0.73–2.36)
30	33	212,965	0.93	(0.54–1.59)	1.29	(0.72–2.34)
p-trend				0.75		0.42
Lactation ^c						
Never	49	291,524	1.0	Reference	1.0	Reference
Ever	32	235,651	0.85	(0.54–1.33)	0.86	(0.54–1.37)
Tubal ligation						
Never	84	549,285	1.0	Reference	1.0	Reference
Ever	31	211,463	0.77	(0.50–1.19)	0.75	(0.47–1.18)
Age at tubal ligation						
Never	84	549,285	1.0	Reference	1.0	Reference
<30	10	71,049	0.92	(0.47–1.79)	0.78	(0.38–1.60)

Characteristic	Cases (N=115)	Person-time (person-years)	Model 1 ^a		Model 2 ^b	
			HR	95% CI	HR	95% CI
30–34	9	70,496	0.67	(0.33–1.35)	0.66	(0.32–1.36)
35	10	68,635	0.65	(0.33–1.28)	0.69	(0.34–1.37)
p-trend				0.13		0.16

Abbreviations: HR, hazard ratio; CI, confidence interval

^aModel 1 adjusts for age and questionnaire cycle.

^bModel 2 adjusts for age, questionnaire cycle, hysterectomy, tubal ligation, oral contraceptive use, menopausal status, use of postmenopausal female hormones, educational attainment, body mass index, and, as appropriate, parity, lactation, age at first birth, and age at last birth.

^cAmong parous women only.