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Lifetime number of ovulatory cycles and epithelial ovarian cancer risk in African American women

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Abstract

Purpose—Incessant ovulation has been consistently linked to epithelial ovarian cancer (EOC). Although reproductive characteristics differ substantially by race, the association between incessant ovulation and EOC has been evaluated only in populations of predominantly white

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

women. In the present study, we examined the association between lifetime number of ovulatory cycles (LOCs) and EOC risk among African American (AA) women.

Methods—We used data from 534 cases and 722 controls enrolled in the African American Cancer Epidemiology Study (AACES). LOCs were determined using the standard method, with modifications to include episodes of irregular or missed periods. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between LOCs and EOC risk overall and by age, while adjusting for appropriate confounders.

Results—The mean number of LOCs was 378.2 ± 105.8 for cases and 346.4 ± 117.3 for controls. Women in the highest tertile of LOCs had a 59% higher odds of EOC compared to women in the lowest tertile (OR=1.59; 95% CI=1.15–2.20). When examining this relationship by age, the positive association with EOC was stronger among women <50 years of age (OR for highest vs. lowest tertile=2.61; 95% CI=1.15–5.94), followed by women aged 50–60 years (OR=2.27; 95% CI=1.30–3.94). Yet, no association was present among women aged >60 years (OR=0.79; 95% CI=0.45–1.40).

Conclusions—In a population of AA women, we observed a positive association between LOCs and EOC risk, providing further support for the hypothesis that incessant ovulation contributes to the etiology of EOC.

Keywords

Ovulation; ovarian cancer; African American women; lifetime ovulatory cycles

INTRODUCTION

One of the leading hypotheses for epithelial ovarian cancer (EOC) development is incessant ovulation.[1, 2] The causal mechanism as to how the ovulatory process contributes to carcinogenesis is unknown, yet several theories have been proposed. During ovulation, the ovarian surface epithelium is damaged and then repaired through extensive cellular proliferation, increasing genomic instability and the likelihood of spontaneous errors during DNA replication.[3] Gonadotropin and steroid hormone exposure during ovulation is suspected to facilitate transformation, either directly or indirectly through estrogen.[4, 5] Ovulation is also linked to inflammation, which is now considered a hallmark of all cancers.[6] During ovulation, many inflammatory mediators, such as cytokines and prostaglandins, are elevated and may enhance mutagenesis.[7] The incessant ovulation hypothesis is supported by the consistent positive association between the lifetime number of ovulatory years or cycles and EOC risk in the literature.[8–13] In addition, risk reduction for EOC has been observed for reproductive factors that interrupt ovulation (e.g., pregnancy, use of oral contraceptives, and breastfeeding).[8, 14–16] It is also important to note that the reproductive characteristics used to calculate LOCs may impact ovarian cancer risk through additional mechanisms, independent of ovulation suppression. [17, 18]

The majority of the literature examining the relationship between incessant ovulation and EOC risk has been in study populations of primarily white women. However, there are considerable differences in reproductive characteristics by race that may impact the distribution of lifetime number of ovulatory cycles (LOC) and potentially its relationship to

EOC risk. In comparison to white women, African American (AA) women are more likely to have a greater number of pregnancies [19], which would result in fewer ovulations. Also, AA women are less likely to use oral contraceptives and breastfeed [19] and typically have an earlier age at menarche [20], which would contribute to a greater number of ovulations. To date, no studies have evaluated the association between LOCs and ovarian cancer risk among AA women. Therefore, we used the largest case-control study of EOC in AA women, the African American Cancer Epidemiology Study (AACES), to examine the relationship between LOCs and the risk of EOC in AA women.

METHODS

Study Population

AACES is a population-based case-control study of self-identified AA women with incident invasive EOC in 11 geographic locations in the United States (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). The methods for AACES have been previously described.[21] In brief, cases were identified through rapid case ascertainment at cancer registries, hospitals, and gynecologic oncology clinics. The eligibility criteria for cases included women who self-identified as AA race, were 20–79 years of age, and were diagnosed with incident EOC between December 1, 2010 and December 31, 2015. Random digit dialing was used to identify controls, who were frequency-matched to cases by geographic location and 5-year age categories. Controls were excluded if they had a previous diagnosis of EOC, did not have an intact ovary, and identified as a race other than AA. Participants completed a baseline survey by telephone that included detailed questions on demographic characteristics, reproductive and medical history, exogenous hormone use, personal and family history of cancer, and lifestyle behaviors (e.g., smoking, physical activity). A shortened version of this questionnaire was given to participants who may have otherwise refused. In total, 602 cases and 752 controls were enrolled in AACES, with 71 women completing the short version of the questionnaire (52 cases and 19 controls). The response rate was 40% for cases and 52% for controls, and the cooperation rate was 62% for cases and 68% for controls. [21]

Assignment of Menopausal Status and Age at Menopause

Given the complex nature of determining menopausal status and the age at menopause, we developed an algorithm that utilized self-reported menstrual history to assign menopausal status and age at menopause, while considering menopausal symptoms, premenopausal hysterectomy, and menopausal hormone use. Women were considered premenopausal if they reported that their periods were still occurring naturally and had an intact uterus at the time of diagnosis/interview, and perimenopausal if they reported that their periods were still occurring but sometimes noticed skipped months or noticed changes in their cycle. Women were considered postmenopausal if they reported that their periods stopped naturally or stopped due to chemotherapy or radiation. Women who were taking menopausal hormones before their periods stopped were considered perimenopausal if they had taken menopausal hormones for less than two years or postmenopausal if they had taken hormones for more than 2 years. Women who reported a premenopausal hysterectomy without bilateral oophorectomy were considered premenopausal if they did not report any menopausal

symptoms and were aged 47 or younger, and women were considered perimenopausal if they did not report any menopausal symptoms and were between the ages of 47 and 50, or if they reported menopausal symptoms for less than 2 years and were younger than 50 years at diagnosis/interview. Otherwise, women who had a premenopausal hysterectomy were considered post-menopausal if they were over 50 at the time of diagnosis/interview (age at menopause was estimated as 50 years) or if they were younger than 50 at the time of diagnosis/interview and reported menopausal symptoms for more than 2 years (age at menopause was estimated as the minimum of the age when 2 years of menopausal symptoms had been experienced and age 55).

Lifetime Number of Ovulatory Cycles

The number of ovulatory cycles was calculated using the standard method in the Cancer and Steroid Hormone (CASH) Study [9, 13], with modifications to account for periods of amenorrhea as suggested by Moorman, et al.[11] To calculate the total number of ovulatory years, we subtracted the age at menarche from the age at menopause for postmenopausal women or the reference age for pre or perimenopausal women (age at diagnosis for cases and age at interview for controls). The number of ovulatory years was then reduced by months of pregnancy, oral contraceptive use, breastfeeding, and episodes of irregular or missed periods. We then multiplied the total number of ovulatory years by an average cycle length of 28.1 days (13 cycles per year) to estimate the total number of ovulatory cycles. The total number of LOCs was divided into tertiles based on the distribution of LOCs in the controls to create categories of low (≤304), medium (305–410), and high LOCs (≥411).

Statistical Analysis

Detailed breastfeeding data was only available in the long version of the AACES questionnaire and therefore, we excluded women who completed the short questionnaire from the analyses. A total sample of 534 cases and 722 controls with complete data on all reproductive characteristics and covariates were included in the analyses for the present study. The distribution of LOCs and each component of the LOC calculation (e.g., months of pregnancy, oral contraceptive use, breastfeeding, periods of amenorrhea) were estimated overall and by case-control status. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between LOCs and EOC risk, overall and by age (<50 years, 50–60 years, and >60 years). All models were adjusted for the study design variables, age (years) and study site (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). We also present results where we additionally adjusted for several well-established and suspected risk factors for ovarian cancer, including: family history of ovarian or breast cancer in a first-degree relative (yes, no); tubal ligation that occurred at least 1 year prior to the diagnosis date for cases or the interview date for controls (yes, no); premenopausal hysterectomy that occurred at least 1 year prior to the diagnosis date for cases or the interview date for controls (yes, no), body powder exposure (any genital use, only nongenital use, never use); smoking (never, former, current smokers); body mass index (BMI; normal weight or BMI <25 kg/m^2, overweight or BMI 25–29.9 kg/m^2, obese or ≥30 kg/m^2); endometriosis (yes, no); pelvic inflammatory disease (PID; yes, no); any recreational physical activity 1 year prior to the diagnosis date for cases or the interview date

for controls (yes, no); and any non-steroidal anti-inflammatory drug (NSAID) use (yes, no). Body powder exposure is defined as any use of talc, cornstarch, baby, or deodorizing powders at least one time per month for a duration of at least 6 months [22], and NSAID use is defined as the use of aspirin or non-aspirin NSAIDs at least once a week or at least 5 days out of the month for a duration of 6 months or longer. [23] Given the high correlation of LOCs with age, we also evaluated whether higher-order terms for age (e.g., age^2 and age^3) should be included in the regression models; however, these polynomial terms did not improve model fit and were not included in subsequent analyses. Given that EOC is a heterogeneous disease, we also repeated these analyses stratified by histology. Serous and endometrioid EOC were each evaluated separately, but due to the low prevalence of mucinous, clear cell, mixed and other epithelial histologic sub-types in AACES, we did not have adequate power to evaluate each separately and instead, grouped them together in an 'other histology' category.

RESULTS

The distribution of AACES participant characteristics overall and by case-control status are provided in Table 1. As expected, cases were significantly more likely to have a family history of breast or ovarian cancer, endometriosis, pelvic inflammatory disease, and any genital use of body powders, and cases were less likely to have a history of tubal ligation. The majority of cases were diagnosed with serous EOC (71%), had more late stage disease (64% Stage 3–4), and had high grade tumors (67% Grade 3–4).

Reproductive events are provided in Table 2 by case-control status and age. In the total population, the mean number of ovulatory cycles was 359.9 ± 113.6. A significantly higher number of LOCs was observed among cases compared to controls (378.2 ± 105.8 and 346.4 ± 117.3, respectively). When evaluating the components of the LOC individually, we observed that controls had a greater mean number of months spent pregnant, using oral contraceptives, breastfeeding, and missed or irregular cycles. There were virtually no differences in age at menarche between cases and controls; however, cases had a slightly higher mean age at last period compared to controls (47.6 years and 46.3 years, respectively). There was also a considerable difference in the mean time between menarche and the last period between cases (351.0 months) and controls (322.5 months). When examining reproductive events by age, we observed that the mean number of LOCs increased as age increased. However, a significant difference in the number of LOCs by case-control status was only observed among women aged 60 or younger. Among women aged <50 years, cases were significantly more likely to have an older age at last period and a greater number of months between menarche and last period, and cases were significantly less likely to have a greater number of months spent pregnant as well as breastfeeding. Similar results were observed among women aged 50–60 years, with cases significantly more likely to have a greater number of months between menarche and last period, yet less months of oral contraceptive use and breastfeeding. No significant differences in reproductive events were observed among women older than 60 years of age.

Table 3 provides the estimated ORs and 95% CIs for the relationship between LOCs and EOC risk overall and by age (<50 years, 50–60 years, >60 years). Overall, in the fully

adjusted model, women in the highest tertile of LOCs had a 59% greater odds of EOC compared to women in the lowest tertile of LOCs (OR=1.59; 95% CI=1.15–2.20). When examining this relationship by age, the positive association with EOC risk was more pronounced among women younger than 50 years of age, irrespective of LOC category. The highest risk was observed among women younger than 50 years who had a high number of LOCs (OR=2.61; 95% CI=1.15–5.94). Among women aged 50–60 years, a positive association was still present among women who had a high number of LOCs, OR=2.27 (95% CI=1.30–3.94), although less pronounced. Yet, no association was observed in women older than 60 years of age for any tertile of LOCs.

Histologic subtype-specific analyses are presented in Table 4. Among serous EOC, medium and high numbers of LOCs were associated with a significantly increased EOC risk after adjustment for confounding (Medium: OR=1.56; 95% CI=1.08–2.25 and High: OR=1.73; 95% CI=1.19–2.52). When restricting to intermediate and high-grade serous EOC (grade 2–4), a slightly more pronounced association is observed, OR comparing high to low tertile of LOCs=1.76; 95% CI=1.18–2.63 (data not shown). A more pronounced association was observed among women with endometrioid EOC, where over a 2-fold increased risk was present for the high category of LOCs (OR=2.83; 95% CI=1.26–6.40). No association was observed among the other histologic subtypes.

DISCUSSION

In a population of AA women, we observed a significant increase in EOC risk as the lifetime number of ovulatory cycles increased. This association was more pronounced among women younger than 50 years of age, yet no association was present among women older than 60 years. There were also marked differences by histology, with a stronger association present for women with endometrioid EOC and a significant positive association still present among serous EOC.

Our findings suggested that the association between LOCs and EOC risk was strongest among women younger than 50 years of age, which is consistent with several studies that evaluated this association by age or menopausal status and noted a more pronounced association among younger or premenopausal women, and a null or slightly positive, but not statistically significant, association among older or postmenopausal women.[10, 12, 24] Similarly, a reduced effect of oral contraceptive use, a component of the LOC calculation, on ovarian cancer risk has been observed among older women.[24–26] The stronger effects among younger women could be due to several suspected factors. First, it could be due to a latency effect. As with most cancers, there is a relatively long time period between disease initiation and clinical detection.[27] It may be that excess ovulations occurring at younger ages are the most influential in initiation of ovarian cancer, conferring a more pronounced risk in the group of women younger than 50 years of age in the present study. Additionally, as women age, there are considerable fluctuations in hormone levels associated with ovulation. Gonadotropin levels increase with age, yet estradiol levels are relatively stable until menopause, where they significantly decline.[28] Given that estrogen may mediate ovulation [4, 5], reduced estradiol levels at older ages may contribute to the reduced effect observed in older women. Temporal differences in reproductive characteristics may also

contribute to the differences in effect by age. For example, older birth cohorts tended to have larger families and used oral contraceptives more frequently than younger birth cohorts.[29] This would result in a reduced number of ovulatory cycles for older birth cohorts, and may manifest as a reduced effect on EOC risk among older women. Lastly, a stronger LOC and EOC risk association was observed among endometrioid tumors, which typically occur at younger ages than serous tumors. This is evident in AACES where the mean age of endometrioid cases was approximately 4 years younger than serous cases (54.8 years and 58.6 years, respectively).

We observed a more pronounced association among endometrioid EOC cases, yet a significant positive association was still present among serous EOC cases. Unfortunately, due to small numbers of other non-serous EOC cases diagnosed in AACES, we had inadequate power to evaluate each of the other non-serous subtypes separately. In three other studies that examined histologic-specific results [8, 10, 12], the most pronounced magnitude of effect was observed in clear cell, endometrioid, and other epithelial EOC; however, a significant positive association was also present among serous EOC. In a manuscript by Schildkraut, et al. [9], a more pronounced association between lifetime number of LOCs and EOC risk was observed among cases with p53 mutations. We now know that a high frequency of p53 mutations are observed in high-grade serous EOC cases, while in the other histologic subtypes of EOC, there are virtually no p53 mutations present.[30] This suggests that the result of a more pronounced association among cases with p53 mutations in Schildkraut, et al. [9] may be reflective of serous EOC, and would be consistent with our findings by histologic subtype. However, a subsequent study by Webb, et al.[31] did not replicate the findings by Schildkraut, et al. [9] and instead, observed no association between LOCs and EOC risk among cases with p53 mutations. It is also important to note that the pathology review to confirm diagnosis and histology is still ongoing in AACES, which may result in misclassification by histologic subtype. However, histologic subtype was changed for less than 10% of the cases that have undergone pathology review and it is unlikely that misclassification by histologic subtype will have an impact on our results.

In an attempt to evaluate how our findings differ from those observed in other races, we compared our findings to those presented in Moorman, et al. [11], where data from a population of predominately white women was used for the analyses and a similar algorithm was used to calculate LOCs as in the present study. In Moorman, et al. [11], the mean number of LOCs among cases was 325.6 and 305.6 among controls, while in our study, the mean number of LOCs was slightly more elevated, 378.2 in cases and 346.4 in controls. It appears that the number of LOCs in AA women may be higher than in white women; however, these differences in LOCs could also be due to the differences in algorithms used in each study as well as the considerable differences in the number of missed or irregular periods between both studies. In our study, a small proportion of women reported having episodes of missed or irregular periods (12%) and the average number of months of missed periods was 2.4 months, while in Moorman, et al. [11], the mean was much greater, at 27.6 months. Given the heterogeneity of analytic techniques used to calculate LOCs and the varying distribution of race in the existing literature examining this association, it is difficult to make any definitive conclusions as to how our findings in AA women differ in comparison to other races.

A limitation of studies on this topic is the inability to accurately characterize the lifetime number of ovulatory cycles. The calculation of LOCs is dependent on self-reported data of reproductive characteristics. Although recalling pregnancies and other reproductive exposures has been reported with good reproducibility and reliability, menstrual cycle characteristics, including episodes of missed periods, may be more difficult to report with accuracy.[32, 33] Errors in recall could impact findings if recollection of reproductive characteristics differed between cases and controls. However, it is unlikely that cases and controls would vary in their recall, and if any bias did occur, it would likely be nondifferential misclassification and attenuate our effect estimates. In addition, it is important to note that not all cycles are ovulatory and not all periods of amenorrhea are anovulatory [34], which may also impact misclassification errors. For women who have had a premenopausal hysterectomy, determination of LOCs is challenging because these women will continue to ovulate after surgery, but it is impossible to know for how long. In an attempt to accurately estimate LOCs for these women, we considered if and when menopausal symptoms were experienced after surgery to estimate age at menopause. To evaluate any effect this may have had on our results, we repeated our analyses excluding women who had a premenopausal hysterectomy, and no substantial differences were observed between these results and our overall findings. There are considerable variations in how LOCs are calculated across studies. A recent study by Yang, et al. [35] identified 18 different algorithms that have been used to calculate LOCs in the literature. Irrespective of the differences in these algorithms, they were all highly correlated with one another. Due to this finding as well as the consistency of our results with previous studies, it is unlikely that our study is greatly affected by this potential bias.

In summary, our findings among AA women support previous research suggesting that incessant ovulation contributes to the etiology of ovarian cancer, especially among younger women. Due to the small numbers of AA women with EOC in other available datasets (e.g., the Black Women's Health Study, the Ovarian Cancer Association Consortium), pooling data on AA women from AACES and other studies will offer the best attempt at testing the incessant ovulation hypothesis in AA women. Future studies need to evaluate this relationship in racially heterogeneous populations in order to make direct comparisons by race-ethnicity; only then will we be able to determine whether racial differences in reproductive characteristics impact the distribution of LOCs and its association with EOC. It is also clear that further research is needed at the molecular level to understand the biologic mechanism with which incessant ovulation influences ovarian cancer risk and why ovulation may have a greater impact on cancer development among younger women.

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Table 1

Distribution of AACES participant characteristics for 534 invasive EOC cases and 722 controls (N=1,256)

	Cases (n=534)	Controls (n=722)	
	n (%)	n (%)	p-value
Age at Diagnosis or Interview			
Years, Mean (SD)	57.5 (10.8)	54.9 (11.8)	<0.001
Study Site			
Alabama	34 (10)	73 (10)	
Georgia	86 (16)	140 (19)	
Illinois	4 (1)	39 (5)	
Louisiana	41 (8)	58 (8)	
Michigan	39 (7)	62 (9)	
North Carolina	100 (19)	112 (16)	
New Jersey	37 (7)	57 (8)	
Ohio	31 (6)	71 (10)	
South Carolina	81 (15)	59 (8)	
Tennessee	23 (4)	0 (0)	
Texas	58 (11)	51 (7)	
First Degree Family History of Breast or Ovarian Cancer			
No	389 (73)	592 (82)	<0.001
Yes	145 (27)	130 (18)	
BMI (kg/m^2)[a]			
Underweight or normal (<25)	80 (15)	135 (19)	0.22
Overweight (25–29.9)	142 (27)	184 (24)	
Obese (≥30)	312 (58)	403 (56)	
Smoking Status			
Never smoker	297 (56)	422 (58)	0.05
Current smoker	96 (18)	150 (21)	
Former smoker	141 (26)	150 (21)	
Endometriosis			
No	476 (89)	687 (95)	<0.001
Yes	58 (11)	35 (5)	
Pelvic Inflammatory Disease			
No	491 (92)	685 (95)	0.04
Yes	43 (8)	37 (5)	
Body Powder Exposure[b]			
Never use	198 (37)	338 (47)	<0.001
Any genital use	234 (44)	245 (34)	
Only non-genital use	102 (19)	139 (19)	
Any NSAID Use[c]			
No	340 (64)	468 (65)	0.67

	Cases (n=534)	Controls (n=722)	
	n (%)	n (%)	p-value
Yes	194 (36)	254 (35)	
Any Recreational Physical Activity[a]			
No	195 (37)	233 (32)	0.14
Yes	339 (63)	489 (68)	
Tubal Ligation[a]			
No	340 (64)	430 (60)	0.14
Yes	194 (36)	292 (40)	
Premenopausal Hysterectomy[a]			
No	410 (77)	560 (78)	0.74
Yes	124 (23)	162 (22)	
Histology[d]			
Serous	364 (71)		
Mucinous	28 (5)		
Endometrioid	60 (12)		
Clear cell	15 (3)		
Mixed	9 (2)		
Other epithelial	36 (7)		
Stage[e]			
I	116 (24)		
II	46 (10)		
III	274 (58)		
IV	38 (8)		
Grade[f]			
1	45 (10)		
2	104 (23)		
3	298 (66)		
4	2 (1)		

AACES: African American Cancer Epidemiology Study; EOC: epithelial ovarian cancer; SD: standard deviation; BMI: body mass index; NSAID: non-steroidal anti-inflammatory drugs

[a] 1 year before diagnosis date for cases and interview date for controls.

[b] Talc, cornstarch, baby, or deodorizing powder use at least one time per month for a duration of at least 6 months.

[c] Aspirin and non-aspirin NSAID use at least once a week or at least 5 days out of the month for a duration of ≥6 months.

[d] 22 cases are missing histology.

[e] 60 cases are missing stage.

[f] 85 cases are missing grade.

Table 2

Reproductive events among AACES participants overall and by age

	All Ages		<50 years		50–60 years		>60 years	
	Cases (n=534)	Controls (n=722)	Cases (n=132)	Controls (n=219)	Cases (n=188)	Controls (n=278)	Cases (n=214)	Controls (n=225)
Reproductive Events	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age at menarche, years	12.6 (1.8)	12.6 (2.1)	12.6 (2.0)	12.5 (1.9)	12.6 (1.8)	12.7 (2.3)	12.7 (1.7)	12.6 (1.9)
Age at last period, years	47.6 (6.6)*	46.3 (7.6)	42.8 (6.9)*	40.1 (7.7)	49.0 (5.1)	48.2 (5.7)	49.3 (6.1)	49.9 (5.8)
Months between menarche and last period	351.0 (97.6)*	322.5 (107.9)	299.5 (95.2)*	251.1 (103.7)	368.8 (94.9)*	339.8 (92.6)	367.0 (90.5)	370.6 (93.5)
Months of pregnancy	23.0 (17.6)	23.7 (15.3)	17.1 (14.9)*	21.8 (14.5)	19.5 (15.0)	22.0 (13.9)	29.7 (19.0)	27.5 (16.8)
Months of oral contraceptive use	42.6 (67.4)*	53.6 (71.0)	43.6 (64.6)	53.1 (71.9)	46.6 (74.1)*	60.6 (75.0)	38.3 (62.9)	45.5 (64.0)
Months of breastfeeding	2.7 (7.6)*	4.1 (10.6)	1.5 (3.9)*	5.4 (15.0)	1.6 (4.5)*	3.7 (8.8)	4.3 (10.5)	3.2 (6.5)
Months of missed or irregular cycles	1.9 (9.7)	2.8 (16.3)	2.3 (7.3)	3.5 (13.5)	3.2 (14.8)	3.6 (22.4)	0.5 (2.8)	1.1 (7.2)
Total number of ovulatory cycles	378.2 (105.8)*	346.4 (117.3)	322.0 (102.1)*	268.2 (111.7)	396.1 (103.8)*	364.2 (101.3)	397.1 (97.7)	400.3 (101.0)

AACES: African American Cancer Epidemiology Study; SD: standard deviation

*$p<0.05$

Table 3

Estimated odds ratios and 95% confidence intervals for the association between lifetime number of ovulatory cycles and EOC risk overall and by age

	Cases	Controls	Model 1[a]	Model 2[b]
Lifetime Ovulatory Cycles	**n (%)**	**n (%)**	**OR (95% CI)**	**OR (95% CI)**
All ages				
Low (≤304)	115 (22)	235 (33)	1.00 (Referent)	1.00 (Referent)
Medium (305–410)	188 (35)	247 (34)	1.40 (1.03–1.91)	1.38 (1.01–1.89)
High (≥411)	231 (43)	240 (33)	1.69 (1.23–2.32)	1.59 (1.15–2.20)
<50 years				
Low (≤304)	50 (38)	129 (59)	1.00 (Referent)	1.00 (Referent)
Medium (305–410)	54 (41)	69 (31)	1.79 (1.01–3.16)	1.76 (0.96–3.24)
High (≤411)	28 (21)	21 (10)	2.55 (1.18–5.52)	2.61 (1.15–5.94)
50–60 years				
Low (≤304)	29 (15)	67 (24)	1.00 (Referent)	1.00 (Referent)
Medium (305–410)	60 (32)	105 (38)	1.35 (0.78–2.34)	1.49 (0.84–2.64)
High (≥411)	99 (53)	106 (38)	2.25 (1.32–3.81)	2.27 (1.30–3.94)
>60 years				
Low (≤304)	36 (17)	39 (17)	1.00 (Referent)	1.00 (Referent)
Medium (305–410)	74 (36)	73 (32)	1.01 (0.56–1.79)	0.90 (0.49–1.65)
High (≥411)	104 (49)	113 (50)	0.93 (0.54–1.60)	0.79 (0.45–1.40)

EOC: epithelial ovarian cancer; OR: odds ratio; CI: confidence interval

[a] Model 1 adjusted for the study design variables, including age and study site.

[b] Model 2 is additionally adjusted for family history of breast or ovarian cancer in a first degree relative, tubal ligation, premenopausal hysterectomy, BMI, physical activity, smoking status, body powder exposure, any NSAID use, endometriosis, and pelvic inflammatory disease.

Table 4

Estimated odds ratios and 95% confidence intervals for the association between lifetime number of ovulatory cycles and EOC risk by histology

	Cases	Controls	Model 1[a]	Model 2[b]
Lifetime Ovulatory Cycles	**n (%)**	**n (%)**	**OR (95% CI)**	**OR (95% CI)**
Serous, All ages				
Low (≤304)	68 (19)	235 (33)	1.00 (Referent)	1.00 (Referent)
Medium (305–410)	134 (37)	247 (34)	1.60 (1.12–2.29)	1.56 (1.08–2.25)
High (≥411)	162 (45)	240 (33)	1.85 (1.28–2.66)	1.73 (1.19–2.52)
Endometrioid, All ages				
Low (≤304)	14 (23)	235 (33)	1.00 (Referent)	1.00 (Referent)
Medium (305–410)	10 (17)	247 (34)	0.72 (0.30–1.75)	0.64 (0.26–1.60)
High (≥411)	36 (60)	240 (33)	3.09 (1.42–6.71)	2.84 (1.26–6.40)
Other histology[c], All ages				
Low (≤304)	25 (32)	235 (33)	1.00 (Referent)	1.00 (Referent)
Medium (305–410)	30 (38)	247 (34)	1.05 (0.58–1.93)	0.97 (0.53–1.79)
High (≥411)	24 (30)	240 (33)	0.88 (0.45–1.70)	0.73 (0.37–1.46)

EOC: epithelial ovarian cancer; OR: odds ratio; CI: confidence interval

[a]Model 1 adjusted for the study design variables, including age and study site.

[b]Model 2 is additionally adjusted for family history of breast or ovarian cancer in a first degree relative, tubal ligation, premenopausal hysterectomy, BMI, physical activity, smoking status, body powder exposure, any NSAID use, endometriosis, and pelvic inflammatory disease.

[c]Other histology includes mucinous, clear cell, mixed and other EOC.