Original Contribution

Premenopausal Hysterectomy and Risk of Ovarian Cancer in African-American Women

Lauren C. Peres*, Anthony J. Alberg, Elisa V. Bandera, Jill Barnholtz-Sloan, Melissa Bondy, Michele L. Cote, Ellen Funkhouser, Patricia G. Moorman, Edward S. Peters, Ann G. Schwartz, Paul D. Terry, Sarah E. Abbott, Fabian Camacho, Frances Wang, and Joellen M. Schildkraut

* Correspondence to: Lauren C. Peres, University of Virginia, Department of Public Health Sciences, P.O. Box 800765, Charlottesville, Virginia 22903 (e-mail: lcp3t@virginia.edu).

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Although the inverse association between hysterectomy and epithelial ovarian cancer (EOC) was considered well established, investigators in recent studies including women diagnosed after 2000 have observed modest increases in risk. Most studies have been conducted in white women with little representation of African-American women. We examined the relationship between premenopausal hysterectomy and EOC in African-American women and explored whether hormone therapy (HT) modified this association in 614 cases and 743 controls enrolled in the African American Cancer Epidemiology Study (2010–2015). Premenopausal hysterectomy was inversely associated with the odds of EOC (odds ratio (OR) = 0.75, 95% confidence interval (CI): 0.56, 1.01). Qualitative interaction by estrogen-only HT was present; among never users of estrogen-only HT, premenopausal hysterectomy was associated with a significantly decreased odds of EOC (OR = 0.65, 95% CI: 0.46, 0.92), whereas among users of estrogen-only HT, a positive association was observed (OR = 1.71, 95% CI: 0.76, 3.84). In a population of African-American women diagnosed after 2000, our overall results are consistent with the inverse association observed in the era before 2000, yet the effect modification by HT suggests that HT use among women who have had hysterectomies may negate the protective effects of hysterectomy on EOC, creating the appearance of a null or slightly increased risk.

African Americans; hormone therapy; hysterectomy; ovarian cancer

Abbreviations: AACES, African American Cancer Epidemiology Study; CI, confidence interval; EOC, epithelial ovarian cancer; HT, hormone therapy; OR, odds ratio.

It has long been reported that women who have undergone a hysterectomy with conservation of 1 or both ovaries have a lower risk of epithelial ovarian cancer (EOC), with authors of a meta-analysis estimating a summary relative risk of 0.74 (95% confidence interval (CI): 0.65, 0.84) (1). Precisely how hysterectomy reduces risk is uncertain, although several potential mechanisms have been proposed, including blockage of carcinogens travelling through the female genital tract (2) and an alteration in hormones due to fewer ovulations (3–5). Contrary to the majority of studies published prior to 2000, investigators in studies published during the past decade observed a modest increase in EOC risk following hysterectomy (6–9). In a recent meta-analysis, Jordan et al. (10) found evidence to

suggest that there may be a temporal shift in the relationship between hysterectomy and EOC risk, with an inverse relationship present for women diagnosed prior to 2000 (relative risk = 0.70, 95% CI: 0.65, 0.76) but an 18% increase in risk for women diagnosed after 2000 (relative risk = 1.18, 95% CI: 1.06, 1.31). It is possible that more recent studies, inclusive of women diagnosed after 2000, may suffer from biases that could have affected their results. However, temporal changes in factors influencing the relationship between hysterectomy and EOC risk, such as changes in hysterectomy practices or the changing recommendations for hormone therapy (HT) use among women who have had hysterectomies, may have also contributed to the shift observed in recent studies.

The majority of studies examining premenopausal hysterectomy and EOC risk have been conducted primarily in white women. Because African-American women are more likely to undergo hysterectomy compared with white women (11, 12), partially due to a higher prevalence of uterine fibroids among African-American women (13), a differing risk profile may be present in African-American women than in white women. To our knowledge, only 1 study (9) has addressed race-specific analyses for the association between hysterectomy and EOC; the results suggested no significant differences by race, but the study included only 111 cases and 189 controls among African Americans. To fill this evidence gap, we used data from the largest case-control study of African-American women with EOC to date—the African American Cancer Epidemiology Study (AACES)—to examine the relationship between premenopausal hysterectomy and EOC among African-American women. Because the women in AACES were diagnosed in 2010 and later, we aimed to further clarify this association in a population of women diagnosed with EOC after 2000. In addition, we examined whether use of HT is an effect modifier of the association between hysterectomy and EOC risk, to explore whether HT is a possible contributor to the suggested temporal shift.

METHODS

Study population

We used data from AACES, an ongoing population-based case-control study examining EOC in African-American women in 11 geographic locations, including Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas. The study protocol was approved by the institutional review board at each participating site. A detailed description of AACES methods have been described elsewhere (14). Briefly, rapid case ascertainment from the Surveillance, Epidemiology, and End Results Program (SEER) and state cancer registries, gynecologic oncology departments, or hospitals was used to identify incident EOC cases. Cases were eligible for the study based on the following criteria: new diagnosis of invasive EOC from December 1, 2010, to December 31, 2015; self-identification of African-American race; and aged 20–79 years. Random-digit dialing was used to identify African-American controls, who were frequency-matched to cases by state of residence and 5-year age category. Controls were eligible for the study if they had at least 1 intact ovary and did not have a history of EOC. Enrolled participants provided informed consent and completed an extensive baseline telephone interview, including questions on demographic characteristics, reproductive history, exogenous hormone use, family history of cancer, medical history, and a variety of lifestyle behaviors (e.g., smoking and physical activity). Women who would have otherwise refused to participate in the study were offered a short form of the questionnaire in an effort to increase participation. AACES enrollment was ongoing during the time of the data analysis, so we included cases and controls who completed the interview as of January 2016 ($n = 1,380$; 628 cases and 752 controls). Of those, 73 completed the short form of the questionnaire: 54 cases and 19 controls. The response rates for AACES cases and controls

were 42% and 52%, respectively, and the cooperation rates were 64% and 68% (14).

Premenopausal hysterectomy

Women who reported no longer menstruating were asked the reason that their periods had stopped. If their periods stopped due to surgery, women were then asked what type of surgery had been performed. If a woman reported that the surgery was a hysterectomy in which 1 or both ovaries were left intact, she was categorized as having a premenopausal hysterectomy. Women were also asked their age at hysterectomy and the reason(s) that their hysterectomy was performed. Any woman reporting a hysterectomy during the year prior to their cancer diagnosis ($n = 3$), or interview date for controls ($n = 6$), was categorized as not having a hysterectomy so as not to include a hysterectomy performed due to symptoms of an undiagnosed EOC.

Hormone therapy

Women were asked to recall any hormone use for reasons other than birth control. Women who responded affirmatively to ever use of HT were asked more detailed questions related to the name of hormone, the form of hormone (pill, patch, shot, cream, or suppository), duration of use, and age at first and last use. The names of each hormone were reviewed to determine whether the therapy consisted of estrogen, progestin, or a combination of estrogen and progestin hormones. A woman reporting use of any of those therapies was considered an ever user of HT, and a woman reporting use of estrogen-only HT at any point in time was considered an ever user of estrogen-only HT. If a woman reported initiation of HT use within a year prior to diagnosis (cases) or interview (controls), they were categorized as never users. Also, any HT use that occurred prior to premenopausal hysterectomy ($n = 2$) was categorized as never use due to likely misclassification.

Statistical analysis

χ^2 tests were used to test for differences in the distribution of participant characteristics according to case-control status. Odds ratios and 95% confidence intervals for the association between premenopausal hysterectomy and odds of EOC were estimated using multivariable logistic regression. The year in which hysterectomy was performed was also included in regression models to evaluate secular trends in this relationship (no hysterectomy, hysterectomy prior to 1980, hysterectomy during 1980–2001, and hysterectomy in 2002 or later). These time periods reflect significant temporal changes in HT use: Prior to 1980, HT was widely used, especially estrogen therapy; during 1980–2001, combined estrogen-progestin therapy was widely used; in 2002 and later, there were rapid declines in HT use overall (15). Three different models were examined with different adjustment sets. Model 1 adjusted for study design variables including age at diagnosis for cases or time of interview for controls (years, continuous) and study site (Alabama, Georgia and Tennessee combined (due to geographic similarities and sample size), Illinois and Michigan combined (due to geographic similarities and sample size),

Louisiana, New Jersey, North Carolina, Ohio, South Carolina, or Texas). Model 2 adjusted for variables in model 1 and a priori confounders, including family history of ovarian or breast cancer in a first-degree relative (yes, no), parity (0, 1, 2, ≥ 3 live births), body mass index (calculated as weight (kg)/height (m)², and categorized as underweight and normal weight: <25 , overweight: 25–29.9, or obese: ≥ 30), duration of oral contraceptive use (never use, <5 years, ≥ 5 years), and tubal ligation (yes, no). Model 3 adjusted for variables in model 2 as well as 3 benign gynecologic conditions that are indications of hysterectomy, including history of uterine fibroids (yes, no), history of endometriosis (yes, no), and history of ovarian cysts (yes/no). We also repeated these analyses by histotype (serous, nonserous) versus all controls.

Effect modification by HT use (overall and estrogen-only) was assessed on both the additive and multiplicative scales. Although we cannot assess the magnitude of additive interaction due to the case-control study design, the direction can be determined using the relative excess risk due to interaction (16). The relative excess risk due to interaction and 95% confidence intervals were calculated to estimate whether the additive interaction was positive, negative, or null. To test for multiplicative interaction, a cross-product term (premenopausal hysterectomy $\times$ hormone therapy) was included in the regression model, and a likelihood ratio test was used to evaluate models with and without the cross-product term. We also calculated the ratio of odds and 95% confidence interval for the product term. The results of the interaction analyses are presented as recommended by Knol and VanderWeele (17), including analyses stratified by HT as well as the estimation of odds ratios using a single reference category (women who did not have a premenopausal hysterectomy and did not use HT). All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The analyses were restricted to those participants who provided data on all covariates and comprised a final sample of 614 cases and 743 controls. As expected, cases were more likely to be nulliparous and to have a family history of breast or ovarian cancer in a first-degree relative, and they were less likely to have a history of oral contraceptive use and a history of tubal ligation (Table 1). Cases also had a slightly higher body mass index than controls. We observed case-control differences in the prevalence of benign gynecologic conditions that are indications for hysterectomy, with cases more likely to have a history of endometriosis, uterine fibroids, and ovarian cysts. The majority of cases were diagnosed with serous EOC (74%).

A slightly higher prevalence of premenopausal hysterectomy was observed among cases compared with controls (23% vs. 22%, respectively; crude OR = 1.09, 95% CI: 0.84, 1.41). Indications for premenopausal hysterectomy included uterine fibroids (68%), excessive vaginal bleeding (48%), painful periods (19%), and pelvic pain (11%). Up to 5% of participants reported endometriosis, pelvic organ prolapse, stress incontinence, cervical dysplasia, ovarian cysts, or other cancers as the reason for surgery (data not shown).

Percentages exceed 100% because women could report more than 1 indication. The odds ratios and 95% confidence intervals for the association between premenopausal hysterectomy and EOC are shown in Table 2. In model 1, women who had a premenopausal hysterectomy had slightly decreased, but not significant, odds of EOC (odds ratio (OR) = 0.92, 95% CI: 0.70, 1.20). Additional adjustment for a priori confounders (model 2) resulted in no substantive change (OR = 0.91, 95% CI: 0.69, 1.20). Further adjustment for hysterectomy indication (model 3) strengthened the inverse association to a borderline significant 25% decrease in odds of EOC (OR = 0.75, 95% CI: 0.56, 1.01). No significant differences in the overall association by histology were observed (serous: OR = 0.81, 95% CI: 0.59, 1.12; nonserous: OR = 0.76, 95% CI: 0.46, 1.26) (data not shown).

To assess the presence of secular trends, the overall analyses were repeated using categorized year of hysterectomy (Table 2). A positive, but not statistically significant, association was observed for women who had hysterectomies prior to 1980 (OR = 1.62, 95% CI: 0.89, 2.94). Inverse associations were observed for women who had hysterectomies after 1980, with a slightly more pronounced association among women who had hysterectomies in 2002 or later (OR = 0.55, 95% CI: 0.30, 1.01) than among women who had hysterectomies during 1980–2001 (OR = 0.63, 95% CI: 0.44, 0.91).

We also evaluated whether HT use overall is an effect modifier in the relationship between premenopausal hysterectomy and EOC (Table 3). Five women did not provide information on HT use and were removed from the analyses ($n = 1,352$). We found suggestive evidence of effect modification by overall HT use: $P = 0.07$ on the additive scale and $P = 0.08$ on the multiplicative scale. Stratification by HT use revealed that premenopausal hysterectomy was inversely associated with EOC among never users of HT (OR = 0.65, 95% CI: 0.46, 0.92), but the association was weakly in the positive direction among ever users of HT (OR = 1.12, 95% CI: 0.60, 2.09). When a common reference group (women who did not have a premenopausal hysterectomy and did not use HT) was applied, an inverse association was observed for women who had a premenopausal hysterectomy and did not use HT (OR = 0.66, 95% CI: 0.47, 0.92). Although not statistically significant, an attenuated inverse association was observed for all other exposure categories when comparing with the common reference group.

Evaluation of interaction by estrogen-only HT use is presented in Table 4. A total of 51 women reported HT regimens other than estrogen-only therapy (e.g., estrogen-progestin therapy, progestin therapy) and were excluded from these analyses (leaving $n = 1,301$). We observed positive interaction on the additive ($P = 0.04$) and multiplicative ($P = 0.05$) scales, suggestive of qualitative interaction. Among women who never used HT, premenopausal hysterectomy was inversely associated with EOC (OR = 0.65, 95% CI: 0.46, 0.92), whereas a positive association was observed among users of estrogen-only HT but was not statistically significant (OR = 1.71, 95% CI: 0.76, 3.84). The results from the analyses using a common reference category were similar to the results for HT use overall, where an inverse association was observed for women who had hysterectomies but did not use estrogen-only HT in comparison with women who did not

Table 1. Characteristics of Cases and Controls Among Participants Who Provided Data on All Covariates ($n = 1,357$), African American Cancer Epidemiology Study, 2010–2015

Characteristic	Cases ($n = 614$)		Controls ($n = 743$)		P Value
	No.	%	No.	%	
Age group, years					
<50	135	22	199	27	0.002
50–59	211	35	278	37	
60–69	168	27	192	26	
≥ 70	100	16	74	10	
Parity					
0	110	18	96	13	0.07
1	117	19	140	19	
2	149	24	199	27	
≥ 3	238	39	308	41	
Family history of breast or ovarian cancer ^a					
No	455	74	611	82	<0.001
Yes	159	26	132	18	
Tubal ligation					
No	404	66	445	60	0.03
Yes	210	34	298	40	
BMI ^b					
<25	88	14	140	19	0.07
25–29.9	162	26	195	26	
≥ 30	364	59	408	55	
Oral contraceptive use					
Never	208	34	180	24	<0.001
<5 years	229	37	314	42	
≥ 5 years	177	29	249	34	
History of endometriosis					
No	550	90	708	95	<0.001
Yes	64	10	35	5	
History of uterine fibroids					
No	323	53	449	60	0.003
Yes	291	47	294	40	
History of ovarian cysts					
No	509	83	657	88	0.004
Yes	105	17	86	12	
Histology ^c					
Serous	420	74			
Mucinous	29	5			
Endometrioid	74	13			
Clear cell	13	2			
Mixed	14	2			
Other	20	4			

Abbreviation: BMI, body mass index.

^a Family history of breast or ovarian cancer in a first-degree relative.^b Body mass index was calculated as weight (kg)/height (m)². A BMI of <25 was categorized as underweight or normal weight, 25–29.9 as overweight, and ≥ 30 as obese.^c There were 44 cases missing data for histology.

Table 2. Estimated Odds Ratios for the Association of Premenopausal Hysterectomy, Overall and According to Year of Hysterectomy, and Ovarian Cancer ($n = 1,357$), African American Cancer Epidemiology Study, 2010–2015

Hysterectomy	Cases ($n = 614$)		Controls ($n = 743$)		Model 1 ^a		Model 2 ^b		Model 3 ^c	
	No.	%	No.	%	OR	95% CI	OR	95% CI	OR	95% CI
Premenopausal hysterectomy										
No	470	77	580	78	1.00	Referent	1.00	Referent	1.00	Referent
Yes	144	23	163	22	0.92	0.70, 1.20	0.91	0.69, 1.20	0.75	0.56, 1.01
Year of premenopausal hysterectomy ^d										
No hysterectomy	470	78	580	79	1.00	Referent	1.00	Referent	1.00	Referent
Prior to 1980	40	7	21	3	1.82	1.03, 3.24	1.72	0.96, 3.11	1.62	0.89, 2.94
1980–2001	72	12	100	13	0.80	0.57, 1.12	0.79	0.56, 1.11	0.63	0.44, 0.91
2002 or after	19	3	37	5	0.68	0.38, 1.22	0.71	0.40, 1.27	0.55	0.30, 1.01

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Model 1 adjusted for the study design variables, age, and study site.

^b Model 2 adjusted for the study design variables in model 1 and family history of ovarian or breast cancer in a first-degree relative, parity, oral contraceptive use, body mass index, and tubal ligation.

^c Model 3 adjusted for all factors in model 2 as well as history of endometriosis, history of uterine fibroids, and history of ovarian cysts.

^d There were 18 women missing data for the year at which their hysterectomy was performed.

have hysterectomies and did not use estrogen-only HT (OR = 0.66, 95% CI: 0.47, 0.93).

DISCUSSION

In a population of African-American women diagnosed after 2000, we observed a modest inverse association between premenopausal hysterectomy and EOC. Further, estrogen-only HT was identified as a moderator of this relationship; premenopausal hysterectomy was strongly inversely associated with EOC among women who did not use estrogen-only HT, but among estrogen-only HT users, premenopausal hysterectomy was associated with a null or slightly increased odds of EOC.

The presence of this qualitative interaction is compatible with the inference that estrogen-only HT use may actually negate the protective benefits of hysterectomy on EOC.

Although more recent studies have reported increases in EOC risk due to hysterectomy, in this population of African-American women diagnosed after 2000 we observed the classic inverse relationship. The findings of the present study thus contrast with the temporal shift reported by Jordan et al. (10), who observed a positive association for studies with a diagnosis after 2000. Their findings may not be directly applicable to our study population due to a few factors: The majority of studies included in the meta-analysis (10) were composed of white women, and there are considerable differences

Table 3. Estimated Joint Effect^a of Premenopausal Hysterectomy and Use of Hormone Therapy on the Odds of Ovarian Cancer ($n = 1,352$), African American Cancer Epidemiology Study, 2010–2015

HT Use	Premenopausal Hysterectomy								Premenopausal Hysterectomy Within Strata of HT Use	
	No				Yes					
	No. of Cases	No. of Controls	OR ^b	95% CI	No. of Cases	No. of Controls	OR ^b	95% CI	OR ^b	95% CI
Never	412	512	1.00	Referent	90	117	0.66	0.47, 0.92	0.65	0.46, 0.92
Ever	56	67	0.77	0.51, 1.16	53	45	0.90	0.56, 1.43	1.12	0.60, 2.09

Abbreviations: CI, confidence interval; HT, hormone therapy; OR, odds ratio.

^a Measure of interaction on the additive scale: relative excess risk due to interaction = 0.47, 95% CI: −0.05, 0.99; $P = 0.07$. Measure of interaction on the multiplicative scale: ratio of ORs = 1.78, 95% CI: 0.93, 3.41; $P = 0.08$.

^b ORs were adjusted for age at diagnosis/interview, study site, family history of ovarian or breast cancer in a first-degree relative, parity, body mass index, duration of oral contraceptive use, tubal ligation, history of endometriosis, history of uterine fibroids, and history of ovarian cysts.

Table 4. Estimated Joint Effect^a of Premenopausal Hysterectomy and Use of Estrogen-Only Hormone Therapy on the Odds of Ovarian Cancer ($n = 1,301$), African American Cancer Epidemiology Study, 2010–2015

Estrogen-Only HT Use	Premenopausal Hysterectomy								Premenopausal Hysterectomy Within Strata of Estrogen-Only HT Use	
	No				Yes					
	No. of Cases	No. of Controls	OR ^b	95% CI	No. of Cases	No. of Controls	OR ^b	95% CI	OR ^b	95% CI
Never	412	512	1.00	Referent	90	117	0.66	0.47, 0.93	0.65	0.46, 0.92
Ever	32	43	0.68	0.41, 1.14	52	43	0.92	0.57, 1.48	1.71	0.76, 3.84

Abbreviations: CI, confidence interval; HT, hormone therapy; OR, odds ratio.

^a Measure of interaction on the additive scale: relative excess risk due to interaction = 0.58, 95% CI: 0.03, 1.13; $P = 0.04$. Measure of interaction on the multiplicative scale: ratio of ORs = 2.05, 95% CI: 0.99, 4.23; $P = 0.05$.

^b ORs were adjusted for age at diagnosis/interview, study site, family history of ovarian or breast cancer in a first-degree relative, parity, body mass index, duration of oral contraceptive use, tubal ligation, history of endometriosis, history of uterine fibroids, and history of ovarian cysts.

according to race in both the prevalence of hysterectomy and HT use. In comparison with white women, studies have shown a higher prevalence of hysterectomy among African-American women (11, 12) but lower HT use (9, 18). Additionally, AACES represents a much more recent study population—all participants were diagnosed in 2010 or later.

Our results suggested the presence of substantial confounding due to indication. A more than 20% change in the odds ratio was observed after adjustment for hysterectomy indication (OR = 0.91, 95% CI: 0.69, 1.20 (model 2) compared with OR = 0.75, 95% CI: 0.56, 1.01 (model 3)). A limitation of recent studies reporting a positive association in the relationship between hysterectomy and EOC (6–9) is that they did not account for indication in their analyses. Interestingly, the majority of classic studies reporting an inverse association did not control for hysterectomy indications, either (19–23). Because the majority of studies examining the relationship between hysterectomy and EOC did not take indication into account, it is unlikely that residual confounding by indication is contributing to the reported positive associations observed in more recent studies. Given that indication is a considerable confounder in this relationship, more studies should collect data on benign gynecological conditions to include in their analyses.

The qualitative interaction by HT observed in this study provides suggestive evidence that HT may be contributing to the secular changes in the relationship between hysterectomy and EOC. Over the past 50 years, attitudes and practices regarding HT use in women with a hysterectomy have fluctuated considerably. Historically, estrogen therapy was a popular practice used to alleviate menopausal symptoms regardless of whether a woman had a uterus; however, in the 1970s, several studies linked HT, particularly estrogen therapy, to an increased risk of endometrial cancer, resulting in a decline in HT use overall (24, 25). In the 1980s, it was discovered that adding progestin to estrogen therapy could mitigate the harmful effects of estrogen therapy on the endometrium, and the use of HT, particularly estrogen-progestin therapy, increased (24, 26, 27). However, because women who have had hysterectomies no longer have an endometrium and are not at risk for endometrial cancer, the addition of progestin to estrogen therapy was

deemed unnecessary, and an estrogen-only regimen continued as the recommended HT regimen for those women (28). We speculate that because all women, regardless of having a uterus, used the same HT regimen prior to the 1980s, the inverse relationship between premenopausal hysterectomy and EOC remained constant until the recommendations for HT use in women with and without a uterus diverged, resulting in more women with a premenopausal hysterectomy taking estrogen therapy than among the general population. Because HT, specifically estrogen therapy, has been shown to increase the risk of EOC (29–35) and because ovarian carcinogenesis can take decades to become clinically apparent, the more recent positive or null associations observed between premenopausal hysterectomy and EOC could possibly be due to the harmful effects of estrogen therapy on EOC negating the inverse association between premenopausal hysterectomy and EOC.

Although significant differences in the relationship between hysterectomy and EOC were not observed by year of hysterectomy, a more pronounced inverse association was observed for women who had had hysterectomies in the year 2000 or later. This finding could possibly be due to changes in HT practices in more recent years. In the early 2000s, 2 randomized controlled trials were terminated early due to increased risks of breast cancer and cardiovascular disease outcomes with HT use, and this led to substantial declines in the prevalence of HT use (15, 36, 37). Using data from the National Health and Nutrition Examination Survey, Sprague et al. (38) reported a dramatic decline in postmenopausal HT use, almost exclusively estrogen-only HT use, among women who had had hysterectomies in the early 2000s. We also observed positive, albeit not statistically significant, odds of EOC among women who had had hysterectomies performed prior to 1980. During this time period, estrogen therapy was the recommended HT regimen, which has now been shown to increase risk of EOC (29–35). If the secular changes in the relationship between hysterectomy and EOC are due to changes in HT recommendations and practices, we would expect a positive association among women who had had hysterectomies prior to 1980, due to the predominant use of estrogen therapy, and a stronger inverse association among women who had had

hysterectomies in 2000 and later, because HT use has been recommended less frequently since 2000. Our study findings are consistent with this hypothesis.

We performed sensitivity analyses to determine whether the cutpoint of a premenopausal hysterectomy a year prior to diagnosis for cases (or interview for controls) was appropriate. Virtually no changes were observed when these women were excluded—or when no cutpoint or a more stringent cutpoint of 2 years was used. In addition, we examined whether categorizing women who reported HT use 1 year prior to the reference date as nonuse influenced our findings; no substantial changes to the results were observed.

Our study has several strengths. The present study is, to our knowledge, the first to explore the relationship between premenopausal hysterectomy and EOC risk in an adequately powered sample of African-American women. AACES is the largest study of EOC among African-American women and provides a rich data resource to answer this study question. Although AACES has a relatively large sample size, there was limited statistical precision for the stratified analyses due to the low prevalence of HT use in this population. However, our results are suggestive of a potentially important public health concern that should be explored further in a larger sample. Given that AACES is a study exclusively of African-American women, our results may not be generalizable to other racial/ethnic groups. There is also a potential for recall bias and misclassification, especially with respect to HT regimen. Although a manual review of HT name was conducted, 47 women who reported using estrogen therapy could not remember the specific name of the therapy used.

In summary, we found evidence that the classic inverse association between premenopausal hysterectomy and EOC is present in African-American women who were diagnosed after 2000. We also provide suggestive evidence that estrogen-only HT moderates the association between premenopausal hysterectomy and EOC. To the extent that these findings are replicated in other study populations, our findings have important public health and clinical implications. The inverse association between premenopausal hysterectomy and EOC was isolated to women who did not use HT, implying that a focus should be placed on reducing estrogen-only HT among women who have had a premenopausal hysterectomy. It is important to consider the risks and benefits of HT before any recommendation of HT use is made. We cannot rule out any additional factors, such as changes in hysterectomy practices over time, that may be contributing to the secular trends in the association between hysterectomy and EOC. Insight into these complex questions would be improved by future studies, particularly studies that have data on prescribing patterns of HT use among women who have had hysterectomies, larger study populations, and diverse racial/ethnic composition.

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Author affiliations: Department of Public Health Sciences, School of Medicine, University of Virginia, Charlottesville, Virginia (Lauren C. Peres, Sarah E. Abbott, Fabian Camacho, Joellen M. Schildkraut); Hollings Cancer Center, Medical University of South Carolina, Charleston,

South Carolina (Anthony J. Alberg); Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina (Anthony J. Alberg); Cancer Prevention and Control Program, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey (Elisa V. Bandera); Case Comprehensive Cancer Center, School of Medicine, Case Western Reserve University, Cleveland, Ohio (Jill Barnholtz-Sloan); Cancer Prevention and Population Sciences Program, Baylor College of Medicine, Houston, Texas (Melissa Bondy); Department of Oncology and the Karmanos Cancer Institute Population Studies and Disparities Research Program, Wayne State University School of Medicine, Detroit, Michigan (Michele L. Cote, Ann G. Schwartz); Division of Preventive Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama (Ellen Funkhouser); Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina (Patricia G. Moorman, Frances Wang); Department of Epidemiology, School of Public Health, Louisiana State University Health Sciences Center, New Orleans, Louisiana (Edward S. Peters); and Department of Medicine, University of Tennessee Medical Center—Knoxville, Knoxville, Tennessee (Paul D. Terry).

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