HHS Public Access

Author manuscript

Obstet Gynecol. Author manuscript; available in PMC 2024 June 01.

Published in final edited form as:

Obstet Gynecol. 2023 June 01; 141(6): 1124–1138. doi:10.1097/AOG.0000000000005191.

Racial Differences in the Association of Endometriosis and Uterine Leiomyomas With the Risk of Ovarian Cancer

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Presented at the 2022 American Association for Cancer Research (AACR) Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, September 16–19, 2022, Philadelphia, Pennsylvania.

Each author has confirmed compliance with the journal's requirements for authorship.

Financial Disclosure

Elisa V. Bandera reports receiving payment from Pfizer, Inc. as an advisory board member of committee to enhance participation of minorities in clinical trials). The other authors did not report any potential conflicts of interest.

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Abstract

Objective: To evaluate associations between endometriosis and uterine leiomyomas with ovarian cancer risk by race and the impact of hysterectomy on these associations.

Methods: We used data from 4 case-control studies and 2 case-control studies nested within prospective cohorts in the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium. The study population included 3,124 Black participants and 5,458 White participants, of which 1,008 Black participants and 2,237 White participants had ovarian cancer. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of endometriosis and leiomyomas with ovarian cancer risk, by race, stratified by histotype and hysterectomy.

Results: The prevalence of endometriosis and leiomyomas were 6.4% and 43.2% among Black participants and 7.0% and 21.5% among White participants, respectively. Endometriosis was associated with an increased risk of endometrioid and clear cell ovarian cancer in both racial groups (e.g., ORs for endometrioid tumors for Black and White participants of 7.06 [95% CI=3.86–12.91] and 2.17 [95% CI=1.36–3.45], respectively, $p_{hetereogeneity}$=0.003). The association between endometriosis and ovarian cancer risk in White participants was stronger in those without a hysterectomy but no difference was observed in Black participants (all $p_{interaction}\geq 0.05$). Leiomyomas were associated with an elevated risk of ovarian cancer only in those without a hysterectomy in both Black (OR=1.34; 95% CI=1.11–1.62) and White participants (OR=1.22; 95% CI=1.05–1.41)(all $p_{interaction}\geq 0.05$).

Conclusions: Black and White participants with endometriosis had a higher risk of ovarian cancer, and hysterectomy modified this association among White participants. Leiomyomas were associated with an increased risk of ovarian cancer in both racial groups, with hysterectomy modifying the risk in both groups. Understanding how racial differences in access to care and treatment options (e.g., hysterectomy) may help guide future risk reduction strategies.

Précis

Black and White participants with endometriosis had a higher risk of ovarian cancer, and hysterectomy modified this association only among White participants.

Introduction

Endometriosis and uterine leiomyomas are common gynecologic conditions that have significant impact on reproductive age women.(1–12) At present, endometriosis is more

likely to be diagnosed among White women than Black women,(13) however, racial differences in the diagnosis of endometriosis may reflect disparities in access to care as opposed to biological differences in incidence.(14) Conversely, leiomyomas are two to three times more common in Black women than White women, but reasons for this difference are not well understood.(15)

The incidence of ovarian cancer is approximately 30% higher in White women than Black women.(16) Reproductive conditions such as endometriosis and leiomyomas and/or treatments related to these conditions (e.g., hysterectomy, hormone use) could contribute to this difference, but research has been limited in this area.(17) The association between hysterectomy and ovarian cancer risk is conflicting, with studies examining the association prior to 2000 indicating a lower risk of ovarian cancer among those with a hysterectomy, while post 2000 studies suggest a higher risk.(18) For endometriosis, the association with ovarian cancer is well-established with epidemiologic data indicating that women with endometriosis have two- to three-fold greater risk of endometrioid and clear cell ovarian cancer,(19–21) but these estimates are from studies comprised predominantly of White women. A consistent association of leiomyomas with ovarian cancer risk has not been demonstrated. However, leiomyomas may indirectly impact ovarian cancer risk, as leiomyomas are the most common indication for hysterectomy in the U.S.,(22, 23) and hysterectomy has been associated with lower ovarian cancer risk in women with leiomyomas.(24) The objective of the present study was to evaluate associations of endometriosis and uterine leiomyomas with epithelial ovarian cancer risk among Black and White participants, taking into consideration the impact of hysterectomy, oral contraceptive use, and post-menopausal hormone therapy use, on these associations.

Methods

The Ovarian Cancer in Women of African Ancestry (OCWAA) consortium was established with the objective to understand racial differences as they relate to risk factors and outcomes in epithelial ovarian cancer.(25) In this analysis, we included individual-level data from 6 OCWAA studies that collected data on endometriosis and/or leiomyomas (4 case-control studies and 2 case-control studies nested within prospective cohorts). Across the six studies, 8,682 total participants (3,124 Black participants and 5,458 White participants) were included with 1,008 Black and 2,237 White participants with ovarian cancer, and 2,116 Black and 3,221 White controls.

Five of the 6 studies collected data on endometriosis (African American Cancer Epidemiology Study [AACES], Black Women’s Health Study [BWHS], Cook County Case Study [CCCS], North Carolina Ovarian Cancer Study [NCOCS], Los Angeles County Ovarian Cancer Study [LACOCS]) and 5 of the 6 studies collected data on leiomyomas (AACES, BWHS, NCOCS, LACOCS, Southern Community Cohort Study [SCCS]). Each study collected demographic, reproductive history, lifestyle, and medical history data via self-administered questionnaires and/or interviews. All OCWAA studies classified race based on self-report. Each study obtained informed consent from its participants; the individual studies and the OCWAA Consortium were approved by the relevant Institutional Review Boards (University of Virginia, Duke University, Boston University School of

Medicine, University of Illinois at Chicago, University of Southern California, Vanderbilt University Medical Center, and Meharry Medical College).

Data on cancer diagnoses were abstracted from medical records and cancer registry reports. Only epithelial ovarian cancer cases defined using International Classification of Diseases for Oncology, Version 3, were eligible for inclusion. Tumor histotype was determined by combining morphology and grade information according to diagnostic guidelines for ovarian carcinomas in 2014 from the World Health Organization (WHO) Classification of Tumors of Female Reproductive Organs.(26) Each study collected data on the diagnosis of endometriosis and/or leiomyomas via standardized questionnaires that were either interviewer-administered or self-administered (Appendix 1, available online at http://links.lww.com/xxx).

Heterogeneity was quantified by calculating I^2 statistics and corresponding 95% confidence intervals.(27–29) As no significant heterogeneity by study was detected, data was pooled for all analyses.(29, 30) Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between endometriosis and leiomyomas with ovarian cancer risk, overall, and by race; polytomous models were used for analyses histotype (high-grade serous, low-grade serous, endometrioid, clear cell, mucinous). Wald joint χ^2 tests of histotype-specific coefficients were used to calculate p-values for heterogeneity between histotypes. We also examined the endometrioid, clear cell, and low-grade serous histotypes combined as these histotypes have previously been the most strongly associated with ovarian cancer risk among women with endometriosis.(19)

We defined potential confounders as factors potentially associated with both ovarian cancer and endometriosis and/or leiomyomas risk, including education (high school graduate/GED or less, some college, college graduate, graduate/professional school), parity (no full-term pregnancies, 1–2 full-term pregnancies, ≥3 full-term pregnancies), duration of oral contraceptive use (never, <5 years, ≥5 years), age at menarche, body mass index (BMI; <25.0 kg/m^2, 25.0–29.9 kg/m^2, 30.0–34.9 kg/m^2, ≥35.0 kg/m^2), smoking status (ever smoker, never smoker), tubal ligation (yes, no), first-degree family history of breast or ovarian cancer (yes, no), menopausal status, postmenopausal hormone use duration (never, <5 years, ≥5 years), and premenopausal hysterectomy (yes/no) with categories created for missing covariate data. Participants were classified as having a premenopausal hysterectomy if their age at hysterectomy was prior to the onset of menopause; participants were classified as not having a premenopausal hysterectomy if their age at hysterectomy was after the onset of menopause, if the reason for the hysterectomy was due to ovarian cancer, if the hysterectomy was less than a year before diagnosis, or if they never received a hysterectomy.

As hysterectomy, oral contraceptive use, and postmenopausal hormone use have the potential to be confounders or mediators of the endometriosis and/or leiomyomas and ovarian cancer relations, we examined their influence in two ways. First, we adjusted for each variable to examine as a potential confounder (described above). Second, we applied a counterfactual method of mediation to assess the presence of mediation on the endometriosis or leiomyomas and ovarian cancer risk relation by each of these variables.(31) This method is much more flexible than the product method, allows for non-linearity, and is equivalent

to the product method(32) when there are no exposure-mediator interactions. To fit logistic mediation models to this analysis based on both cohort and case-control studies in this consortia, adjustments were needed to satisfy the rare event assumption. Ovarian cancer rates were rare in the cohort studies, but were not in the case-control studies. To account for this, weights for participants in the case-control studies were calculated by a function of race-specific ovarian cancer prevalence in the general and study populations, and these weights were applied within the models of the mediator as the outcome.(33) To implement this, a SAS macro designed by Valeri and VanderWeele was slightly modified to include these weights in the appropriate regression models.(31)

Finally, we assessed effect modification by hysterectomy and postmenopausal hormone use as prior studies have observed differential associations between endometriosis and/or uterine leiomyomas and ovarian cancer risk by these factors.(24, 34, 35) The results from effect modification analysis include analyses stratified by the effect modifier of interest (i.e., hysterectomy and postmenopausal hormone use) and the estimation of ORs using a single reference category (e.g., women who did not report a history of endometriosis and who did not report a hysterectomy).(33, 36) Finally, we performed a sensitivity analysis using a variable that compared non-cancer related hysterectomies (including both pre- and postmenopausal hysterectomies) to no hysterectomy or cancer-related hysterectomies. This information was not available for BWHS or SCCS. All statistical analyses were performed using SAS 9.4 (Cary, NC).

Results

A total of 2,724 Black participants and 5,281 White participants were included in the endometriosis analysis. Among all participants, 6.4% of Black participants and 7.0% of White participants reported a history of endometriosis, with the corresponding values among cases of 81 (8.5%) for Black participants and 198 (9.0%) for White participants, and 92 (5.2%) and 173 (5.6%) for Black and White controls, respectively. Among Black and White participants with ovarian cancer, those reporting a history of endometriosis were more likely to have endometrioid and clear cell tumors compared to those not reporting a history of endometriosis. Both Black and White participants with endometriosis were more likely to report a premenopausal hysterectomy and to have ever used oral contraceptives than participants without endometriosis (Table 1). The mean age of endometriosis diagnosis was 35 years in both Black and White participants.

A history of endometriosis was associated with a higher risk of ovarian cancer in both Black participants (OR=2.12; 95% CI=1.50–3.00) and White participants (OR=1.58; 95% CI=1.26–1.98) ($p_{hetereogeneity}$=0.22). Statistically significant differences in the effect estimates across histotypes were identified when both Black and White participants were combined ($p_{hetereogeneity}$<0.001) and when associations were examined by race ($p_{hetereogeneity}$=0.047 for difference across histotypes for Black participants and $p_{hetereogeneity}$=0.004 for White participants). When stratified by histotype, the association with endometriosis was strongest for the endometrioid histotype among Black participants (OR=7.06; 95% CI=3.86–12.91) compared to White participants (OR=2.17; 95% CI=1.36–3.45) with a significant difference in the effect estimates by race for only the endometrioid

histotype ($p_{hetereogeneity}$=0.003). Black participants (OR=4.82; 95% CI=1.81–21.85) and White participants (OR=3.48; 95% CI=2.24–5.41) had a higher risk of clear cell ovarian cancer ($p_{hetereogeneity}$=0.64). A similar increased risk of high-grade serous ovarian cancer was observed in both Black and White participants (OR=1.63; 95% CI=1.06–1.64 and OR=1.31; 95% CI=1.00–1.72, respectively, $p_{hetereogeneity}$=0.56) (Table 2 and Figure 1).

Mediation analysis of endometriosis and ovarian cancer by oral contraceptive use showed evidence for a suppressive indirect effect (IE) overall (Percent mediated −3.9%; IE p=0.02) and among White participants (Percent mediated −7.5%; Indirect Effect p=0.01) and a non-significant effect in Black participants (Percent mediated −0.3%; IE p=0.91)(Appendix 2, available online at http://links.lww.com/xxx). Mediation analyses suggested that part of the association between endometriosis and ovarian cancer is attributable to hysterectomy overall (Percent mediated 4.6%, IE p=0.08), with a larger percent mediated among White participants (8.1%, IE p=0.36) than Black participants (1.7%, IE p=0.55), although none reached statistical significance (Appendix 3, available online at http://links.lww.com/xxx). No mediation was observed by postmenopausal hormone use (Appendix 3, http://links.lww.com/xxx).

When stratified by premenopausal hysterectomy, the association between endometriosis and ovarian cancer in White participants was stronger in those who did not report a premenopausal hysterectomy (OR=1.85, 95% CI=1.41–2.43) than those who did report a hysterectomy (OR=1.09, 95% CI=0.73–1.64) while in Black participants the higher odds of ovarian cancer among those with endometriosis was observed in both those with and without hysterectomy (OR=2.32, 95% CI=1.51–3.59 for no hysterectomy and OR=1.91, 95% CI=1.05–3.48 for hysterectomy). However, these differences were not statistically significant (all p>0.05) (Table 3). When pre- and postmenopausal hysterectomies were examined, the associations were similar (data not shown).

A total of 2,995 Black participants and 4,876 White participants were included in the leiomoyoma analysis. Among all participants, 43.2% of Black participants and 21.5% of White participants reported a history of leiomoyomas, with the corresponding values among cases of 444 (46.2%) for Black participants and 488 (24.5%) for White participants, and 851 (41.9%) and 559 (19.4%) for Black and White controls, respectively. Among Black and White participants with ovarian cancer, the distribution of histotypes was similar regardless of race or history of leiomyomas. Both Black and White participants with a history of leiomyomas were more likely to report a hysterectomy than those without a history of leiomyomas. While Black participants were more likely to report tubal ligation than White participants, the percentage reporting tubal ligation within each racial group did not vary materially by history of leiomyomas (Table 4). The mean age of leiomyoma diagnosis was 37 years in Black participants and 40 years in White participants.

A history of leiomyomas was associated with a slightly elevated risk of ovarian cancer overall (OR=1.26; 95% CI=1.12–1.41), and in Black (OR=1.34; 95% CI=1.11–1.62) and White participants (OR=1.22; 95% CI=1.05–1.41). Among Black participants, a history of leiomyomas was associated with a higher risk of all histotypes, with statistically significant associations observed for the endometrioid (OR=2.05; 95% CI=1.24–3.39) and

high-grade serous (OR=1.32; 95% CI=1.06–1.64) histotypes ($p_{heterogeneity}$ for differences across histotypes=0.002). No statistically significant associations were observed between leiomyomas and specific histotypes in White participants, however, suggestions of higher risk were present in all histotypes except low grade serous and no significant differences in the associations across histotypes were observed ($p_{heterogeneity}$=0.33) (Table 5 and Figure 2). No significant mediation of the association between leiomyomas and ovarian cancer was observed for hysterectomy, postmenopausal hormone use, or oral contraceptive use (all p>0.05).

When stratified by premenopausal hysterectomy, the association between leiomyomas and ovarian cancer was present only among those who did not report a premenopausal hysterectomy for both racial groups. Black participants who had a history of leiomyomas and no premenopausal hysterectomy had 53% greater odds of ovarian cancer (95% CI=1.23–1.89) compared to those without leiomyomas, while there was no association with leiomyomas in the premenopausal hysterectomy group (OR=0.92, 95% CI=0.62–1.36). This interaction was of borderline significance on both the multiplicative (p=0.05) and additive (p=0.08) scales. A similar pattern was observed among White participants (OR=1.31, 95% CI=1.10–1.55 among those with no premenopausal hysterectomy and OR=1.00, 95% CI=0.74–1.35 among those with a premenopausal hysterectomy), but the interaction was not significant on either the multiplicative (p=0.21) or the additive (p=0.28) scales (Table 6). When a common reference group was applied (those who did not have leiomyomas and did not have a hysterectomy), Black and White participants in all other exposure categories had a higher risk of ovarian cancer (Table 6). There were no significant interactions between hormone therapy and leiomyomas in any subset (Table 6). Associations were similar when pre- and postmenopausal hysterectomies were examined (data not shown).

Discussion

In this consortium of 6 studies, both Black and White participants with a history of endometriosis had a higher risk of ovarian cancer, with the strongest associations among Black participants for the endometrioid and clear cell histotypes. Hysterectomy modified the association between endometriosis and ovarian cancer, but only among White participants. Leiomyomas were associated with a modestly increased risk of ovarian cancer among both Black and White participants. When stratified by hysterectomy, this association persisted only among those without a premenopausal hysterectomy, irrespective of race.

Observational studies have consistently found an association between endometriosis and epithelial ovarian cancer, specifically endometrioid and clear cell ovarian cancer histotypes.(19–21) However, prior studies were conducted in predominantly White populations and did not compare effect estimates by race. The largest prior study of Black participants to examine this association was a pooled analysis including data from AACES, NCOCS, LACOCS (which are also included in our analyses) and 9 other case-control studies in the Ovarian Cancer Association Consortium, which also found a similar stronger association between endometriosis and ovarian cancer risk among Black participants compared to non-Hispanic White participants, but did not report associations for endometriosis-associated histotypes.(17)

Few studies have examined the association between leiomyomas and ovarian cancer risk and to our knowledge none have examined the association among Black women. A Danish registry study found an association between leiomyomas and ovarian cancer risk (OR=1.36; 95% CI=1.16–1.60). However, the association was present only among those who had been diagnosed with leiomyomas within the year preceding the ovarian cancer diagnosis, suggesting that detection bias might explain the observed association.(37) Dixon-Suen et al., also examined leiomyomas and ovarian cancer risk, and reported positive associations that persisted across all histotypes.(24) This is consistent with our study in which elevated effect estimates were present for most histotypes, although not all reached statistical significance.

Consistent with results from recent studies, hysterectomy modified the association between endometriosis(24, 34, 38) and leiomyomas(24) and ovarian cancer risk. In our analyses, the positive association between both endometriosis and leiomyomas and ovarian cancer risk was strongest among participants who had not had a premenopausal hysterectomy. The exception to this was among Black participants with endometriosis, who had a higher risk of ovarian cancer regardless of hysterectomy status. Hysterectomy eliminates the risk of leiomyoma recurrence, but it may not eliminate risk of recurrent endometriosis. Among those with endometriosis and leiomyomas, hysterectomy may indicate the duration or severity of these conditions, since alternative treatments for both conditions are available. It is possible that removal of the fallopian tubes along with the uterus may explain part of the lower risk of ovarian cancer observed among those with a hysterectomy, but this would be expected to impact primarily high-grade serous ovarian cancers that arise from the fallopian tube.

Limitations of this study include potential misclassification of endometriosis and leiomyomas through self-report. For both conditions, the prevalence among controls was lower than current population estimates, which may reflect under-reporting by participants, cohort effects in incidence, and/or period effects in diagnosis. While recall bias is a possibility in the retrospective case-control studies, in the prospective BWHS and SCCS (included in these analyses), we observed similar reporting patterns to that of the case-control studies indicating that recall bias does not likely explain our results. Thus, across our included studies, it is most likely that misclassification of endometriosis and leiomyomas was non-differential with respect to the outcome of ovarian cancer. In addition, the percentage of participants reporting endometriosis and leiomyomas differed across the included studies, with generally higher prevalence reported in more recent studies (Appendix 1, http://links.lww.com/xxx), suggesting period effects in diagnosis. In individual studies that included both Black and White participants, Black participants were more likely than White participants to report leiomyomas and White women were more likely than Black participants to report endometriosis, which is consistent with current diagnostic patterns.(13, 15) Racial differences in endometriosis diagnosis may reflect disparities in access to appropriate diagnostic methods, as opposed to biological differences in incidence.(14)

In conclusion, both Black and White participants with endometriosis had a higher risk of ovarian cancer, and hysterectomy modified this association among White participants. Leiomyomas were associated with a modestly increased risk of ovarian cancer among

Black and White participants, with hysterectomy modifying the risk in both groups. Further research is needed to understand how racial differences in access to care and treatment options (e.g., hysterectomy), impact or modify ovarian cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

This study is supported by the National Institutes of Health (R01-CA207260 to Schildkraut and Rosenberg and K01-CA212056 to Bethea). AACES was funded by NCI (R01-CA142081 to Schildkraut); BWHS was funded by NCI (R01-CA058420,UM1-CA164974, and U01-CA164974 to Rosenberg); CCCCS was funded by NIH/NCI (R01-CA61093 to Rosenblatt); LACOCS was funded by NCI (R01-CA17054 to Pike, R01-CA58598 to Goodman and Wu, and Cancer Center Core Grant P30-CA014089 to Henderson and Wu) and by the California Cancer Research Program (2II0200 to A. Wu); and NCOCS was funded by NCI (R01-CA076016 to Schildkraut). SCCS is supported by the NCI (grants R01-CA092447 and U01-CA202979 to Blot and Zheng) and data collection is performed by the Survey and Biospecimen Shared Resource, which is supported by the Vanderbilt-Ingram Cancer Center (P30-CA68485 to Pietenpol). In addition, support to add SCCS to OCWAA was provided by a Pilot Award (to Beeghly) from the NIH Precision Medicine and Health Disparities Collaborative (NIMHD/NHGRI U54-MD010722 to Wilkins).

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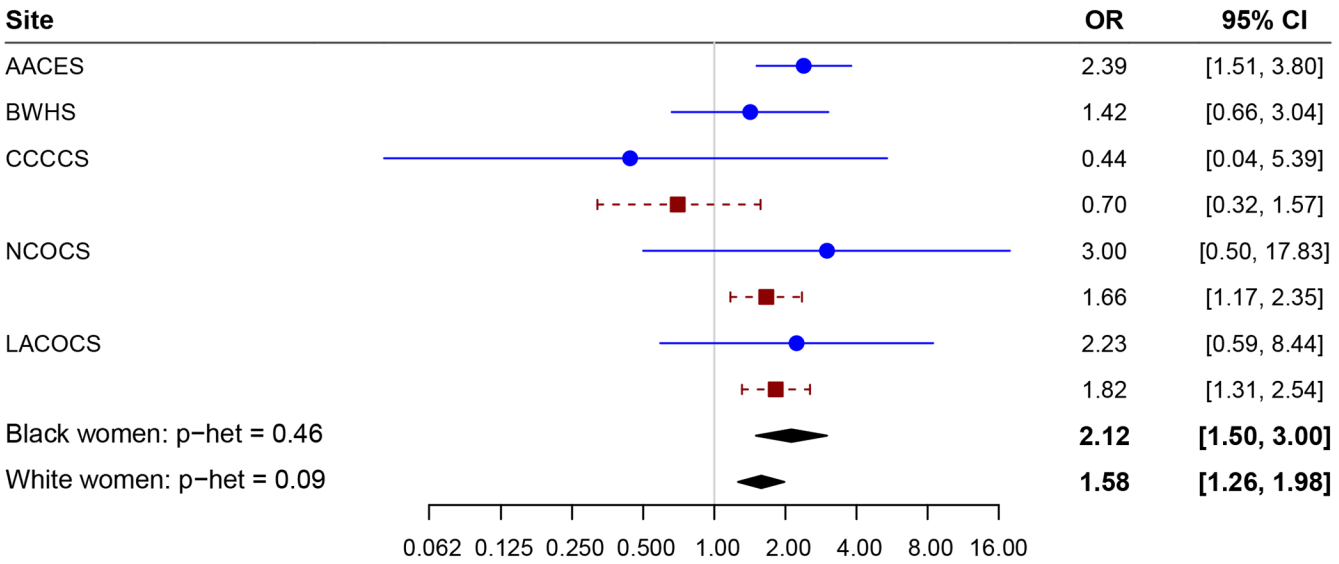

Figure 1.

Forest plot of endometriosis by study and race. Adjusting for age at diagnosis, education, parity, oral contraceptive duration, body mass index, smoking status, tubal ligation, family history of breast or ovarian cancer, menopausal status, postmenopausal hormone duration, age at menarche, and premenopausal hysterectomy. AACES, African American Cancer Epidemiology Study; BWHS, Black Women's Health Study; CCCCS, Cook County Case Study; NCOCS, North Carolina Ovarian Cancer Study; LACOCS, Los Angeles County Ovarian Cancer Study.

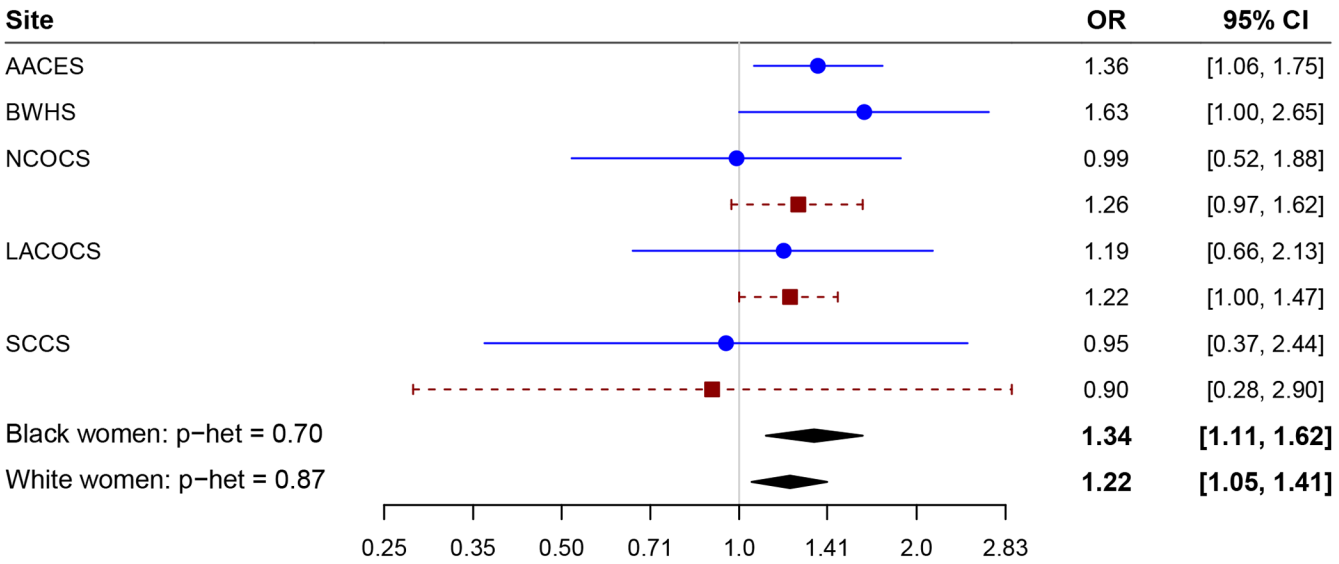

Figure 2.

Forest plot of leiomyoma by study and race. Adjusting for age at diagnosis, education, parity, oral contraceptive duration, body mass index, smoking status, tubal ligation, family history of breast or ovarian cancer, menopausal status, postmenopausal hormone duration, age at menarche, and premenopausal hysterectomy. AACES, African American Cancer Epidemiology Study; BWHS, Black Women's Health Study; NCOCS, North Carolina Ovarian Cancer Study; LACOCS, Los Angeles County Ovarian Cancer Study; SCCS, Southern Community Cohort Study.

Table 1.

Characteristics of the study population by history of endometriosis

N (%) or Mean (SD)	Black Participants N = 2724		White Participants N = 5281	
	Endometriosis = No (N = 2551)	Endometriosis = Yes (N = 173)	Endometriosis = No (N = 4910)	Endometriosis = Yes (N = 371)
Site				
AACES	1232 (48.3)	94 (54.3)	N/A	N/A
BWHS	644 (25.3)	54 (31.2)	N/A	N/A
CCCCS	116 (4.6)	7 (4.1)	617 (12.6)	36 (9.7)
LACOCS	260 (10.2)	11 (6.4)	2790 (56.8)	170 (45.8)
NCOCS	299 (11.7)	7 (4.1)	1503 (30.6)	165 (44.5)
Case-Control Status				
Cases	870 (34.1)	81 (46.8)	1998 (40.7)	198 (53.4)
Controls	1681 (65.9)	92 (53.2)	2912 (59.3)	173 (46.6)
Age at Ovarian Cancer Diagnosis or Interview	55.05±11.46	53.48±9.23	56.83±11.52	54.99±10.16
Histotype *				
High-Grade Serous	571 (65.6)	38 (46.9)	1218 (61.0)	97 (49.0)
Low-Grade Serous	31 (3.6)	1 (1.2)	76 (3.8)	5 (2.5)
Endometrioid	62 (7.1)	22 (27.2)	159 (8.0)	27 (13.6)
Clear Cell	29 (3.3)	6 (7.4)	144 (7.2)	33 (16.7)
Mucinous	50 (5.8)	2 (2.5)	133 (6.7)	11 (5.6)
Carcinosarcoma	21 (2.4)	3 (3.7)	40 (2.0)	2 (1.0)
Other epithelial	93 (10.7)	5 (6.2)	228 (11.4)	23 (11.6)
Synchronous	13 (1.5)	4 (4.9)	0 (0.0)	0 (0.0)
Stage *				
Localized	163 (18.7)	28 (34.6)	388 (19.4)	61 (30.8)
Regional	75 (8.6)	9 (11.1)	193 (9.7)	28 (14.1)
Distant	577 (66.3)	41 (50.6)	1398 (70.0)	104 (52.5)
Missing	55 (6.3)	3 (3.7)	19 (1.0)	5 (2.5)
Education				
HS or less	945 (37.0)	44 (25.4)	934 (19.0)	55 (14.8)
Some college	664 (26.0)	42 (24.3)	1149 (23.4)	97 (26.2)
College grad	543 (21.3)	45 (26.0)	1312 (26.7)	114 (30.7)
Grad/prof school	395 (15.5)	42 (24.3)	1515 (30.9)	105 (28.3)
Missing	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Parity				
No pregnancies	406 (15.9)	50 (28.9)	1044 (21.3)	112 (30.2)
1–2 pregnancies	1131 (44.3)	88 (50.9)	2310 (47.1)	182 (49.1)
≥3 pregnancies	1012 (39.7)	34 (19.7)	1556 (31.7)	77 (20.8)
Missing	2 (0.1)	1 (0.6)	0 (0.0)	0 (0.0)

N (%) or Mean (SD)	Black Participants N = 2724		White Participants N = 5281	
	Endometriosis = No (N = 2551)	Endometriosis = Yes (N = 173)	Endometriosis = No (N = 4910)	Endometriosis = Yes (N = 371)
Oral Contraceptive Duration				
Never	857 (33.6)	42 (24.3)	1833 (37.3)	83 (22.4)
<5 years	922 (36.1)	54 (31.2)	1647 (33.5)	146 (39.4)
≥5 years	746 (29.2)	75 (43.4)	1373 (28.0)	137 (36.9)
Missing	26 (1.0)	2 (1.2)	57 (1.2)	5 (1.4)
Body Mass Index, kg/m ^{2}				
<25	511 (20.0)	39 (22.5)	2631 (53.6)	194 (52.3)
25–29.9	763 (29.9)	54 (31.2)	1293 (26.3)	96 (25.9)
30–34.9	610 (23.9)	45 (26.0)	584 (11.9)	46 (12.4)
≥35	650 (25.5)	35 (20.2)	362 (7.4)	34 (9.2)
Missing	17 (0.7)	0 (0.0)	40 (0.8)	1 (0.3)
Smoking Status				
Never smoker	1398 (54.8)	94 (54.3)	2538 (51.7)	189 (50.9)
Former smoker	734 (28.8)	46 (26.6)	1708 (34.8)	134 (36.1)
Current smoker	417 (16.4)	33 (19.1)	642 (13.1)	46 (12.4)
Missing	2 (0.1)	0 (0.0)	22 (0.5)	2 (0.5)
Tubal Ligation Ever				
No	1567 (61.4)	118 (68.2)	4006 (81.6)	304 (81.9)
Yes	913 (35.8)	51 (29.5)	896 (18.3)	67 (18.1)
Missing	71 (2.8)	4 (2.3)	8 (0.2)	0 (0.0)
First-Degree Family History of Breast or Ovarian Cancer				
No	1952 (76.5)	130 (75.1)	3985 (81.2)	294 (79.3)
Yes	487 (19.1)	35 (20.2)	875 (17.8)	69 (18.6)
Missing	112 (4.4)	8 (4.6)	50 (1.0)	8 (2.2)
Menopausal Status				
Premenopausal	873 (34.2)	62 (35.8)	1547 (31.5)	131 (35.3)
Postmenopausal	1676 (65.7)	111 (64.2)	3355 (68.33)	240 (64.7)
Missing	2 (0.1)	0 (0.0)	8 (0.2)	0 (0.0)
Hormone Therapy Use Duration				
Never	2009 (78.8)	123 (71.1)	2879 (58.6)	194 (52.3)
<5 years	324 (12.7)	27 (15.6)	833 (17.0)	68 (18.3)
≥5 years	206 (8.1)	21 (12.1)	1104 (22.5)	97 (26.2)
Missing	12 (0.5)	2 (1.2)	94 (1.9)	12 (3.2)
Age at Menarche				
<11 years	274 (10.7)	20 (11.6)	313 (6.4)	33 (8.9)
11–12 years	1048 (41.1)	81 (46.8)	2002 (40.8)	154 (41.5)
13–14 years	903 (35.4)	52 (30.1)	2049 (41.7)	149 (40.2)
15–16 years	267 (10.5)	14 (8.1)	465 (9.5)	28 (7.6)

N (%) or Mean (SD)	Black Participants N = 2724		White Participants N = 5281	
	Endometriosis = No (N = 2551)	Endometriosis = Yes (N = 173)	Endometriosis = No (N = 4910)	Endometriosis = Yes (N = 371)
≥17 years	53 (2.1)	6 (3.5)	73 (1.5)	6 (1.6)
Missing	6 (0.2)	0 (0.0)	8 (0.2)	1 (0.3)
Premenopausal Hysterectomy				
No	1961 (76.9)	108 (62.4)	4148 (84.5)	246 (66.3)
Yes	576 (22.6)	65 (37.6)	744 (15.2)	123 (33.2)
Missing	14 (0.6)	0 (0.0)	18 (0.4)	2 (0.5)
History of Infertility †				
No	1714 (74.8)	99 (61.1)	1674 (79.0)	128 (63.7)
Yes	573 (25.0)	63 (38.9)	443 (20.9)	73 (36.3)
Missing	4 (0.2)	0 (0.0)	3 (0.1)	0 (0.0)

*Distributions of histotype and stage are only shown for cases

†History of infertility was not collected for LACOCS: 260 Black women without endometriosis, 11 Black women with endometriosis, 2790 White women without endometriosis, 170 White women with endometriosis

Table 2.

Odds ratios* and 95% confidence intervals for the association between endometriosis, overall and by race, for all ovarian cancer and stratified by histotype

	All histotypes	High-Grade Serous	Low-Grade Serous	Endometrioid	Clear Cell	Mucinous	$P_{heterogeneity}$	Low-Grade Serous, Endo, & Clear Cell
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	between histotypes	OR (95% CI)
All participants (cases/ controls)	3147/4858	1924/4858	113/4858	270/4858	212/4858	196/4858		595/4858
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.75 (1.45–2.11)**	**1.40 (1.11–1.76)**	0.97 (0.41–2.30)	**3.30 (2.31–4.71)**	**3.93 (2.64–5.83)**	1.31 (0.72–2.36)	**<0.001**	**3.05 (2.31–4.02)**
Black participants (cases/controls)	951/1773	609/1773	32/1773	84/1773	35/1773	52/1773		151/1773
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**2.12 (1.50–3.00)**	**1.63 (1.06–2.51)**	1.00 (0.13–7.99)	**7.06 (3.86–12.91)**	**4.82 (1.81–12.85)**	0.89 (0.21–3.82)	**0.047**	**4.91 (2.93–8.23)**
White participants (cases/controls)	2196/3085	1315/3085	81/3085	186/3085	177/3085	144/3085		444/3085
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.58 (1.26–1.98)**	1.31 (1.00–1.72)	0.98 (0.38–2.55)	**2.17 (1.36–3.45)**	**3.48 (2.24–5.41)**	1.41 (0.73–2.70)	**0.004**	**2.39 (1.71–3.34)**
$P_{heterogeneity}$ **by race**	0.22	0.56	0.94	**0.003**	0.64	0.50		

*Odd ratios were adjusted for site, age at diagnosis, education, parity, oral contraceptive use, BMI, smoking status, tubal ligation, family history of breast or ovarian cancer, menopausal status, post-menopausal hormone duration, age at menarche, and premenopausal hysterectomy.

Obstet Gynecol. Author manuscript; available in PMC 2024 June 01.

Table 3.

Estimated Joint Effect* of Premenopausal Hysterectomy or Hormone Therapy and Endometriosis on the Odds of Ovarian Cancer

	Endometriosis								Endometriosis within Strata of effect modifier		$RERI_a$	$RERI_m$
	No				Yes							
	N Cases	N Controls	OR†	95% CI	N Cases	N Controls	OR†	95% CI	OR†	95% CI		
Premenopausal Hysterectomy												
All participants												
No	2267	3842	1.00		184	170	**1.97**	**1.57–2.48**	**1.99**	**1.58–2.50**	−0.55 (−1.22–0.12) p=0.10	0.69 (0.46–1.02) p=0.07
Yes	582	738	**1.17**	**1.02–1.33**	93	95	**1.59**	**1.16–2.16**	1.32	0.94–1.84		
Black participants												
No	649	1312	1.00		52	56	**2.28**	**1.48–3.51**	**2.32**	**1.51–3.59**	−0.36 (−1.84–1.11) p=0.62	0.81 (0.39–1.65) p=0.56
Yes	211	365	1.09	0.88–1.36	29	36	**2.01**	**1.15–3.53**	**1.91**	**1.05–3.48**		
White participants												
No	1618	2530	1.00		132	114	**1.83**	**1.39–2.39**	**1.85**	**1.41–2.43**	−0.65 (−1.68–0.09) p=0.09	0.63 (0.39–1.01) p=0.06
Yes	371	373	**1.24**	**1.05–1.47**	64	59	1.42	0.98–2.07	1.09	0.73–1.64		
Hormone Therapy												
All participants												
No	1773	3115	1.00		161	156	**1.96**	**1.54–2.50**	**2.01**	**1.57–2.58**	−0.46 (−1.12–0.19) p=0.17	0.74 (0.51–1.07) p=0.11
Yes	1094	1465	1.13	1.00–1.26	116	109	**1.63**	**1.22–2.18**	**1.40**	**1.04–1.87**		
Black participants												
No	693	1316	1.00		56	67	**2.03**	**1.35–3.05**	**1.99**	**1.32–3.01**	0.34 (−1.45–2.13) p=0.71	1.10 (0.51, 2.41) p=0.80
Yes	176	362	1.11	0.87–1.41	23	25	**2.48**	**1.28–4.78**	**2.39**	**1.18–4.83**		
White participants												
No	1080	1799	1.00		105	89	**1.89**	**1.39–2.57**	**1.97**	**1.44–2.70**	−0.57 (−1.30–0.15) p=0.12	0.68 (0.44–1.06) p=0.09
Yes	918	1103	1.11	0.97–1.27	93	84	**1.43**	**1.03–1.98**	1.24	0.90–1.72		

*Measure of relative excess of interaction on the additive and multiplicative scales.

†Odd ratios were adjusted for site, age at diagnosis, education, parity, OC duration, BMI, smoking status, tubal ligation, family history of cancer, menopausal status, hormone therapy duration or premenopausal hysterectomy, and age at menarche.

Table 4.

Characteristics of the study population by history of uterine leiomyoma

N (%) or Mean (SD)	Black Participants N = 2995		White Participants N = 4876	
	Leiomyoma=No N = 1700	Leiomyoma=Yes N = 1295	Leiomyoma=No N = 3829	Leiomyoma=Yes N = 1047
Site				
AACES	760 (44.7)	569 (43.9)	N/A	N/A
BWHS	296 (17.4)	402 (31.0)	N/A	N/A
LACOCS	163 (9.6)	106 (8.2)	2283 (59.6)	663 (63.3)
NCOCS	194 (11.4)	110 (8.5)	1326 (34.6)	340 (32.5)
SCCS	287 (16.9)	108 (8.3)	220 (5.8)	44 (4.2)
Case-Control Status				
Cases	518 (30.5)	444 (34.3)	1504 (39.3)	488 (46.6)
Controls	1182 (69.5)	851 (65.7)	2325 (60.7)	559 (53.4)
Age at Ovarian Cancer Diagnosis or Interview	54.58±11.86	56.07±9.75	56.71±11.52	59.03±9.55
Histotype *				
High-Grade Serous	334 (64.5)	280 (63.1)	901 (59.9)	299 (61.3)
Low-Grade Serous	18 (3.5)	12 (2.7)	60 (4.0)	11 (2.3)
Endometrioid	35 (6.8)	47 (10.6)	119 (7.9)	41 (8.4)
Clear Cell	16 (3.1)	18 (4.1)	125 (8.3)	36 (7.4)
Mucinous	23 (4.4)	25 (5.6)	88 (5.9)	27 (5.5)
Carcinosarcoma	13 (2.5)	15 (3.4)	33 (2.2)	6 (1.2)
Other epithelial	70 (13.5)	39 (8.8)	178 (11.8)	68 (13.9)
Synchronous	9 (1.7)	8 (1.8)	0 (0.0)	0 (0.0)
Stage *				
Localized	95 (18.3)	92 (20.7)	289 (19.2)	94 (19.3)
Regional	51 (9.9)	40 (9.0)	153 (10.2)	51 (10.5)
Distant	339 (65.4)	283 (63.7)	1042 (69.3)	333 (68.2)
Missing	33 (6.4)	29 (6.5)	20 (1.3)	10 (2.1)
Education				
HS or less	794 (46.7)	381 (29.4)	707 (18.5)	136 (13.0)
Some college	407 (23.9)	365 (28.2)	918 (24.0)	250 (23.9)
College grad	317 (18.7)	288 (22.2)	1056 (27.6)	288 (27.5)
Grad/prof school	178 (10.5)	260 (20.1)	1148 (30.0)	373 (35.6)
Missing	4 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)
Parity				
No pregnancies	253 (14.9)	213 (16.5)	831 (21.7)	222 (21.2)
1–2 pregnancies	673 (39.6)	643 (49.7)	1812 (47.3)	509 (48.6)
≥3 pregnancies	772 (45.4)	436 (33.7)	1186 (31.0)	316 (30.2)
Missing	2 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)

N (%) or Mean (SD)	Black Participants N = 2995		White Participants N = 4876	
	Leiomyoma=No N = 1700	Leiomyoma=Yes N = 1295	Leiomyoma=No N = 3829	Leiomyoma=Yes N = 1047
Oral Contraceptive Duration				
Never	595 (35.0)	380 (29.3)	1309 (34.2)	354 (33.8)
<5 years	618 (36.4)	460 (35.5)	1287 (33.6)	390 (37.3)
≥5 years	458 (26.9)	445 (34.4)	1186 (31.0)	288 (27.5)
Missing	29 (1.7)	10 (0.8)	47 (1.2)	15 (1.4)
Body Mass Index, kg/m ^{2}				
<25	343 (20.2)	207 (16.0)	1942 (50.7)	530 (50.6)
25–29.9	492 (28.9)	401 (31.0)	1028 (26.9)	283 (27.0)
30–34.9	413 (24.3)	337 (26.0)	494 (12.9)	135 (12.9)
≥35	439 (25.8)	343 (26.5)	337 (8.8)	86 (8.2)
Missing	13 (0.8)	7 (0.5)	28 (0.7)	13 (1.2)
Smoking Status				
Never smoker	908 (53.4)	743 (57.4)	1977 (51.6)	569 (54.4)
Former smoker	460 (27.1)	366 (28.3)	1305 (34.1)	389 (37.2)
Current smoker	331 (19.5)	185 (14.3)	545 (14.2)	89 (8.5)
Missing	1 (0.1)	1 (0.1)	2 (0.1)	0 (0.0)
Tubal Ligation Ever				
No	1021 (60.1)	778 (60.1)	3059 (79.9)	858 (82.0)
Yes	645 (37.9)	474 (36.6)	764 (20.0)	189 (18.1)
Missing	34 (2.0)	43 (3.3)	6 (0.2)	0 (0.0)
First-Degree Family History of Breast or Ovarian Cancer				
No	1291 (75.9)	1009 (77.9)	3098 (80.9)	818 (78.1)
Yes	313 (18.4)	237 (18.3)	668 (17.5)	216 (20.6)
Missing	96 (5.7)	49 (3.8)	63 (1.7)	13 (1.2)
Menopausal Status				
Premenopausal	621 (36.5)	381 (29.4)	1196 (31.2)	217 (20.7)
Postmenopausal	1077 (63.4)	914 (70.6)	2633 (68.8)	830 (79.3)
Missing	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hormone Therapy Use Duration				
Never	1426 (83.9)	924 (71.4)	2347 (61.3)	480 (45.9)
<5 years	159 (9.4)	210 (16.2)	602 (15.7)	186 (17.8)
≥5 years	100 (5.9)	156 (12.1)	815 (21.3)	359 (34.3)
Missing	15 (0.9)	5 (0.4)	65 (1.7)	22 (2.1)
Age at Menarche				
<11 years	174 (10.2)	152 (11.7)	239 (6.2)	78 (7.5)
11–12 years	637 (37.5)	577 (44.6)	1560 (40.7)	447 (42.7)
13–14 years	596 (35.1)	432 (33.4)	1561 (40.8)	421 (40.2)
15–16 years	228 (13.4)	106 (8.2)	399 (10.4)	89 (8.5)

N (%) or Mean (SD)	Black Participants N = 2995		White Participants N = 4876	
	Leiomyoma=No N = 1700	Leiomyoma=Yes N = 1295	Leiomyoma=No N = 3829	Leiomyoma=Yes N = 1047
≥17 years	52 (3.1)	24 (1.9)	60 (1.6)	12 (1.2)
Missing	13 (0.8)	4 (0.3)	10 (0.3)	0 (0.0)
Premenopausal Hysterectomy				
No	1484 (87.3)	779 (60.2)	3322 (86.8)	690 (65.9)
Yes	207 (12.2)	511 (39.5)	497 (13.0)	356 (34.0)
Missing	9 (0.5)	5 (0.4)	10 (0.3)	1 (0.1)
History of Infertility †				
No	916 (73.3)	790 (73.1)	991 (74.7)	265 (77.9)
Yes	334 (26.7)	287 (26.6)	332 (25.0)	75 (22.1)
Missing	0 (0.0)	4 (0.4)	3 (0.2)	0 (0.0)

* Distributions of histotype and stage are only shown for cases

† History of infertility was not collected for SCCS & LACOCS: 450 Black participants without leiomyomas, 214 Black participants with leiomyomas, 2503 White participants without leiomyomas, 707 White women with leiomyomas.

Table 5.

Odds ratios* and 95% confidence intervals for the association between uterine leiomyoma, overall and by race, for all ovarian cancer and stratified by histotype

	Overall	High-Grade Serous	Low-Grade Serous	Endometrioid	Clear Cell	Mucinous	p-het	Low-Grade Serous, Endo, & Clear Cell
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	(between histotypes)	OR (95% CI)
All participants (cases/ controls)	2954/4917	1814/4917	101/4917	242/4917	195/4917	163/4917		538/4917
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.26 (1.12–1.41)**	**1.25 (1.09–1.43)**	0.99 (0.59–1.64)	**1.59 (1.18–2.15)**	1.26 (0.89–1.78)	**1.54 (1.07–2.23)**	**0.03**	**1.35 (1.09–1.68)**
Black participants (cases/ controls)	962/2033	614/2033	30/2033	82/2033	34/2033	48/2033		146/2033
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.34 (1.11–1.62)**	**1.32 (1.06–1.64)**	2.05 (0.83–5.07)	**2.05 (1.24–3.39)**	1.64 (0.77–3.48)	1.92 (0.99–3.69)	0.002	**1.92 (1.31–2.80)**
White participants (cases/ controls)	1992/2884	1200/2884	71/2884	160/2884	161/2884	115/2884		392/2884
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.22 (1.05–1.41)**	1.18 (0.99–1.41)	0.77 (0.39–1.53)	1.41 (0.95–2.10)	1.27 (0.84–1.90)	1.45 (0.91–2.32)	0.33	1.21 (0.92–1.59)
$p_{heterogeneity}$ **by race**	0.54	0.69	0.22	0.21	0.39	0.52		

*Odd ratios were adjusted for site, age at diagnosis, education, parity, oral contraceptive duration, BMI, smoking status, tubal ligation, family history of breast or ovarian cancer, menopausal status, post-menopausal hormone duration, age at menarche, and premenopausal hysterectomy.

Obstet Gynecol. Author manuscript; available in PMC 2024 June 01.

Table 6.

Estimated joint effect* of premenopausal hysterectomy or hormone therapy and uterine leiomyoma on the odds of ovarian cancer

	Leiomyoma								Leiomyoma within Strata of effect modifier		$RERI_a$	$RERI_m$
	No				Yes							
	N Cases	N Controls	OR†	95% CI	N Cases	N Controls	OR†	95% CI	OR†	95% CI		
Premenopausal Hysterectomy												
All participants												
No	1695	3111	1.00		577	892	**1.38**	**1.21–1.57**	**1.40**	**1.22–1.60**	**−0.41 (−0.74–−0.08) p=0.01**	**0.71 (0.55–0.91) p=0.01**
Yes	311	393	**1.29**	**1.08–1.53**	351	516	**1.26**	**1.06–1.48**	0.96	0.76–1.21		
Black participants												
No	435	1049	1.00		268	511	**1.48**	**1.20–1.83**	**1.53**	**1.23–1.89**	−0.52 (−1.10–0.06) p=0.08	0.66 (0.43–1.00) p=0.05
Yes	75	132	1.33	0.95–1.87	173	338	**1.29**	**1.01–1.66**	0.92	0.62–1.36		
White participants												
No	1260	2062	1.00		309	381	**1.29**	**1.08–1.53**	**1.31**	**1.10–1.55**	−0.24 (−0.67–0.19) p=0.28	0.81 (0.58–1.13) p=0.21
Yes	236	261	**1.26**	**1.02–1.55**	178	178	**1.31**	**1.03–1.66**	1.00	0.74–1.35		
Hormone Therapy												
All participants												
No	1292	2448	1.00		529	864	**1.30**	**1.13–1.50**	**1.33**	**1.15–1.54**	−0.08 (−0.35–0.19) p=0.57	0.93 (0.75–1.16) p=0.50
Yes	729	1054	1.08	0.94–1.23	402	545	**1.30**	**1.09–1.54**	1.19	0.99–1.43		
Black participants												
No	434	978	1.00		320	596	**1.37**	**1.11–1.68**	**1.37**	**1.11–1.69**	−0.12 (−0.65–0.42) p=0.67	0.89 (0.59–1.35) p=0.58
Yes	83	201	1.17	0.85–1.61	123	254	**1.42**	**1.05–1.92**	1.25	0.83–1.87		
White participants												
No	858	1470	1.00		209	268	1.23	1.00–1.52	**1.29**	**1.04–1.60**	−0.02 (−0.37–0.32) p=0.89	0.98 (0.73–1.31) p=0.89
Yes	646	853	1.01	0.87–1.18	279	291	1.22	0.99–1.51	1.18	0.96–1.46		

*Measure of relative excess of interaction on the additive and multiplicative scales.

†Odd ratios were adjusted for site, age at diagnosis, education, parity, OC duration, BMI, smoking status, tubal ligation, family history of cancer, menopausal status, hormone therapy duration or premenopausal hysterectomy, and age at menarche.