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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: 01/06/2023
To: "Holly Harris" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1972

RE: Manuscript Number ONG-22-1972

Racial differences in the association of endometriosis and uterine leiomyomas with risk of ovarian cancer

Dear Dr. Harris:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 01/27/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

REVIEWER COMMENTS:

Reviewer #1: Review of Manuscript ONG-22-1972 "Racial differences in the association of endometriosis and uterine leiomyomas with risk of ovarian cancer"

A manuscript that combines collected data from 6 case control studies in an attempt to evaluate the potential associations of endometriosis as well as leiomyomas in black and white women has been submitted. As noted the authors included date that was both case control in and of itself as well as two nested case control studies within a prospective cohort. Importantly, and as noted by the authors, only 5 of the 6 included studies collecting information on endometriosis while an overlapping but different 5 studies for leiomyomas. To that end, did the authors consider limiting the assessments to the 4 studies - AACES, BWHS, NCOCS and LACOCS which included both? The authors did not include a Strobe checklist, which although this is composite case control data may be needed. I have the following questions and comments.

Title - Consider noting this is from Case control data.

Précis - No comments.

Abstract - Line 68 - does eg need to be used?

Line 75 - Should it be a higher likelihood rather than risk?

Introduction - Please provide background data on the role of gynecologic surgery, including hysterectomy and the lower observed rates of ovarian cancer.

Methods - See previous comment about study selection.

Line 140 - Just to confirm pathology reports were reviewed to confirm the specific histologic subtypes?

Line 165 - Although much of the data was collected prior to universal genetic testing for women with EOC, was this ever added and collected?

Line 167 - Was information on salpingectomy and/or oophorectomy - unilateral and/or bilateral collected in addition to performance of hysterectomy.
Also information on route/surgical technique (TVH, TAH, TLH, etc.)?

Results - Line 200 - Consider listing the total number of individuals from the collected case control studies used.

Line 215/6 - Interesting observation of differential histologic subtypes.

Line 268 - May this observation be secondary to having myomas that did not require surgery yet surgery was later performed, including a hysterectomy, for cancer?

Discussion - Line 289 - Why do you think that hysterectomy appeared to be "protective" for White but not Black participants?

Line 316 - As comment above, please provide other thoughts on why this difference may be present. Clearly, the role of salpingectomy is less of a concern here as noted, as it is associated with HG serous ovarian cancer, rather than the clear cell and endometrioid which are being explored further.

Tables - Table 1 - The age is a bit lower than one might expect for sporadic ovarian cancers. I am curious how many of these may in fact have been HBOC? Are you able to assess the same outcomes if those with a first degree relative were excluded?

What is synchronous referring to - both ovaries? Ovarian and another primary malignancy?

Table 2 - Consider ordering the columns based on the incidence of the different histologic subtypes.

Also consider bolding the statistically significant findings.

Table 3 & 6 - No comments other than bolding the significant observations. Curiou if these could be supplemental?

Table 4 - Mirror comments about Table 1

Table 5 - No comments

Figures - None

Supplemental - No comments.

Reviewer #2: The authors analyze data from 4 case-control and 2 nested case control studies to examine the association between endometriosis and leiomyomas with epithelial ovarian cancer risk. The impact of hysterectomy, oral contraceptive use and post-menopausal hormone therapy use on these associations was also examined. This study assesses differences in ovarian cancer risk and highlights disparities between white and black races. However, the study is limited by its methodology as it relies on self-report. As the incidence of endometriosis and fibroid disease in the study population is significantly lower than the incidence in the general population, it calls into question the validity of this form of assessment for these disease processes.

Methods, line 126-127: how was the study population selected? How were the six studies selected from the OCWAA consortium?

Methods, line 141-142: what was the rationale for only including epithelial ovarian cases? The exclusion of non-epithelial cases limits the generalizability of study findings.

Methods, line 159-160: were any characteristics of patient's menstrual history/risk factors obtained such as early

menarche or last menopause? Was genetic mutation carrier status (i.e., BRCA mutations) taken into consideration for confounding factors?

Methods, line 167-172: when the authors refer to premenstrual hysterectomy is there data/consideration of the removal of adnexa at the time of surgery (i.e., salpingectomy vs. salpingo-oophorectomy). As subsequent risk for these two patient groups significantly differ.

Results, line 233-241: Historically ovarian cancer incidence endometriosis diagnosis is higher in white women (as reviewed in introduction). Per study findings, Black participants were noted to have a higher odds ratio regardless of hysterectomy status when compared to White participants. Do the authors have a hypothesize to explain this discrepancy in their findings?

Results, line 315-316: Any speculation on this persistent risk in Black participants?

Discussion, line 323-324: the self-reporting of pathology is a major limitation of this study. Not only due to possible misclassification but possible recall biases. Author should address this also. Limitations are described but lacks strengths.

Tables: tables are lengthy and numerous, consider trimming/condensing for readability.

Reviewer #3:

This paper presents analyses on the associations between (1) endometriosis and incident ovarian cancer and (2) uterine leiomyomas (fibroids) and incident ovarian cancer. These conditions are all common but understudied. Most of the data presented here are pooled from 6 studies (4 case-control, 2 case control nested within prospective cohorts). The authors did also briefly present meta-analytic estimates, which combined separate estimates from the 6 distinct studies. Key secondary analyses examined whether associations differed (1) between Black and White women or (2) based on history of premenopausal hysterectomy. The findings here do not have immediate clinical application but address important population-health questions about dual burdens of non-gynecologic and gynecologic conditions as well as offering hypothesis-generating results about the etiology of ovarian cancer.

STRENGTHS

MAJOR
1. bringing attention to understudied conditions whose etiology and population burden are not well understood

2. Examining fibroids: While previous studies (including some represented in these data) have examined associations between endometriosis and ovarian cancer, they authors state that few have examined ovarian cancer associations with fibroids.

3. Focus on Black women: Stratified analyses among a large sample size of Black women in the US. This is a notable strength, given that most research in this area in the US has been restricted to White women

4. Exposure and outcome classification: Use of self-reported data for fibroids and endometriosis may mitigate against racial and geographic biases in access diagnosis, especially for surgery required for definitive diagnosis with endometriosis. Classification of ovarian cancer also strong, with rich information about subtypes.

CONCERNS/LIMITATIONS

MAJOR
5. Alternative explanations for findings (e.g., possible confounding) could be more thoroughly explored.

-- For instance, two major potential sources of bias that could inflate associations between endo/fibroids and ovarian cancer are detection bias and recall bias.

Detection bias: the workups or health care contact required for the diagnosis of endometriosis or fibroids may in and of itself be a surrogate marker of more health care seeking or which could increase the rate of diagnosis with ovarian cancer.

Recall bias: after diagnosis, ovarian cancer patients may have examined their gynecologic-related health history in more detail than those without ovarian cancer and may be more likely to report previous conditions than controls are.

The authors do mention these possibilities in their write-up but don't perform analyses to address them. One analysis could be a sensitivity analysis restricted just to the 2 prospective cohort studies, where recall bias at least would be less of a factor than in the case-control studies.
Similarly, one possible bias influencing the finding that the associations were weaker among those who had a

premenopausal hysterectomy could be that detection bias associated with diagnosis of endometriosis and fibroids would be less of a factor distinguishing cases and controls when both cases and controls had a history of hysterectomy and its related work-ups. It would be good to comment on this possibility and evaluate it empirically.

6. Concern about analyzing the pooled data. The authors justify the decision to pool the data because "no significant heterogeneity by study" was detected. But, even with no heterogeneity among results when they were analyzed in a study-specific manner, Simpson's Paradox could still lead a pooled estimate to be misleading, especially when some of the study sample sizes are so much bigger than others. And for the racial group-specific analyses, the studies contribute very different proportions of each racial group. More justification would be helpful to me as a reader.

7. FINAL CONCLUSION. The final sentence of the paper ("Further research is needed to understand how racial differences in diagnosis of these conditions, and differential access to care and treatment options, impact or modify ovarian cancer risk") and the final sentence of the abstract ("Understanding how racial differences these conditions and of access to care and treatment options may help guide future risk reduction strategies" [sic]) do not clearly flow from the Results and Discussion. In the Discussion especially, the authors should explicitly connect how the findings lead to this particular call for further research (final sentence) and this particular assertion of how we can insight into future risk reduction strategies.

MINOR
8. Mediation analyses, explanation in Methods: I'm unclear how the mediation analysis was performed. The authors say that the "product method" was used, citing MacKinnon et al (2007). Then later they say that they used a Valeri and vanderWeele macro (which isn't directly cited). At the least the mediation method should be clarified in text and clearly cited.

9. Mediation analyses, interpretation: The authors should justify the extent to which they believe the assumptions (eg, no-confounding between mediators and outcomes?) are met in their interpretation of the mediation analyses.

10. Generalizability (Discussion section): The authors note that the prevalence of endometriosis and fibroids is lower in the control group in their sample than contemporary national statistics. They note 3 potential explanations: underreporting by their participants, true differences in prevalence because of secular increases in diagnosis over time, or "cohort effects in incidence." They could evaluate the likelihood that differences are because of secular increases in diagnosis, for instance, by comparing nationally representative surveillance data to similarly-aged study participants. If this is the true reason, it's less concerning as a bias than systematic underreporting among their control population.

11. METHODS: "no significant heterogeneity by study" was detected based on I2 statistics and 95% confidence intervals. Please clarify the cutpoint used to classify "significant heterogeneity." For instance, is a p-value of p=0.06 not considered significant heterogeneity?

STATISTICAL EDITOR COMMENTS:

lines 71-73: Should also include that there was NS difference in the association between risk of OC and hysterectomy by race, as there was in lines 68-69.

lines 209-210, 215-216, 218-220 and 222-223: The direct comparisons by race of each of these pairs are each NS, so they are not "stronger". The differences are only numerical, as can be seen from the wide CIs. Insufficient stats power makes many of these NS comparisons not generalizable from these data.

General: Although within a particular study, cases and controls may have been matched, they have not been matched overall, so should provide forest plots, funnel plots as in meta-analysis of these studies. Also, since these studies were each case control design, one cannot from these data put the ORs in context with absolute rates, rather only differences in odds, given a case and matched control.

Table 2: To some extent, the differences in statistical heterogeneity are a result of the differences in sample sizes by race.

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Sincerely,
Jason D. Wright, MD
Editor-in-Chief

The Editors of Obstetrics & Gynecology

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time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

February 17, 2023

Dr. Jason D. Wright
Editor-in-Chief

Dear Dr. Wright,
We are pleased to submit the enclosed revised manuscript entitled “Racial differences in the association of endometriosis and uterine leiomyomas with risk of ovarian cancer” for consideration in Obstetrics & Gynecology.

This study investigated the associations between endometriosis and uterine leiomyomas and risk of ovarian cancer in the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium. Most prior research examining the associations between endometriosis and leiomyomas and ovarian cancer risk has been conducted in predominantly White populations and very few studies have compared effect estimates for by race. The OCWAA consortium was established with the objective to understand racial differences as they relate to risk factors and outcomes in epithelial ovarian cancer. We observed that Black and White participants with endometriosis had a higher risk of ovarian cancer, and hysterectomy modified this association only 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. We hope that you will find this manuscript of interest for the readership of Obstetrics & Gynecology. We assert that neither these data nor any portion of this manuscript has been published or is under consideration for publication elsewhere and no similar paper is in press or under review elsewhere. The University of Virginia Institutional Review Board provided approval for this study. We have previously presented these results as a virtual poster 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. Please do not hesitate to contact me if I can be of any further assistance.

Sincerely,

Holly R. Harris, ScD, MPH
Associate Professor
Fred Hutchinson Cancer Center

Reviewer #1: Review of Manuscript ONG-22-1972 "Racial differences in the association of endometriosis and uterine leiomyomas with risk of ovarian cancer"

Reviewer comment: A manuscript that combines collected data from 6 case control studies in an attempt to evaluate the potential associations of endometriosis as well as leiomyomas in black and white women has been submitted. As noted the authors included date that was both case control in and of itself as well as two nested case control studies within a prospective cohort. Importantly, and as noted by the authors, only 5 of the 6 included studies collecting information on endometriosis while an overlapping but different 5 studies for leiomyomas. To that end, did the authors consider limiting the assessments to the 4 studies - AACES, BWHS, NCOCS and LACOCS which included both? The authors did not include a Strobe checklist, which although this is composite case control data may be needed. I have the following questions and comments.
Response: To maximize power, particularly for histotype specific analyses, we felt it was important to include all studies that assessed endometriosis and all studies that assessed fibroids, regardless of

whether these studies overlapped. We have now included a Strobe checklist with the submission.

Reviewer comment: Title - Consider noting this is from Case control data.

Response: We have modified the title to indicate that this study was conducted in the OCWAA consortium. Since we have both case-control studies and nested case-control studies in the OCWAA consortium we would prefer not to include case-control study in the title since that might indicate to a reader that all data was collected retrospectively when in the case of the prospective cohorts it was not.

Reviewer comment: Abstract - Line 68 - does eg need to be used?

Response: Because we only present the ORs for the endometrioid histotype, and not clear cell, we feel the use of e.g. is appropriate.

Reviewer comment: Line 75 - Should it be a higher likelihood rather than risk?

Response: The odds ratio can be considered to be similar to the risk ratio when an outcome is rare (such as ovarian cancer). If preferred we can change risk to odds based on the editors' discretion.

Reviewer comment: Introduction - Please provide background data on the role of gynecologic surgery, including hysterectomy and the lower observed rates of ovarian cancer.

Response: We have added information on the association between hysterectomy and ovarian cancer to the introduction (lines 114-118).

Reviewer comment: Methods - See previous comment about study selection.

Response: To maximize power, particularly for histotype specific analyses, we felt it was important to include all studies that assessed endometriosis and all studies that assessed fibroids, regardless of whether these studies overlapped.

Reviewer comment: Line 140 - Just to confirm pathology reports were reviewed to confirm the specific histologic subtypes?
Response: All OCWAA studies verified diagnoses through pathology reports with some studies further confirming through centralized pathology review. Histotype was determined by using a combination of the morphology and grade information to best represent the most recent diagnostic guidelines as detailed in the 2014 WHO Classification of Tumors of Female reproductive organs.

Reviewer comment: Line 165 - Although much of the data was collected prior to universal genetic testing for women with EOC, was this ever added and collected?

Response: While some individual studies have genetic data on a subset of cases in the OCWAA database we do not have data on genetic testing from the participants.

Reviewer comment: Line 167 - Was information on salpingectomy and/or oophorectomy - unilateral and/or bilateral collected in addition to performance of hysterectomy. Also information on route/surgical technique (TVH, TAH, TLH, etc.)?

Response: Information on route/type of hysterectomy was not collected for the OCWAA database. For inclusion in the studies, women had to have at least one ovary in order to be at risk for ovarian cancer. Salpingectomy as a separate individual procedure was not collected. Given the time frame during which the majority of the hysterectomies occurred within the study population (i.e, prior to current understanding of the fallopian tube origins of ovarian cancer and the potential benefits of opportunistic salpingectomy), it seems highly likely that both the fallopian tube(s) and ovary/ovaries were left in situ as standard for total hysterectomies by any route at the time.

Reviewer comment: Results - Line 200 - Consider listing the total number of individuals from the collected case control studies used.

Response: We have added those numbers to the results (lines 138-139, lines 227-228, and lines 282-283).

Reviewer comment: Line 215/6 - Interesting observation of differential histologic subtypes.

Response: We agree, this is an interesting observation.

Reviewer comment: Line 268 - May this observation be secondary to having myomas that did not require surgery yet surgery was later performed, including a hysterectomy, for cancer?

Response: We assume the observation the reviewer is referring to is that participants who did not report a premenopausal hysterectomy had a higher risk of ovarian cancer if they reported a leiomyoma. These associations were consistent whether we included pre-menopausal only or pre- and post-menopausal hysterectomies (described at the end of the results section). While there is the possibility that fibroids were found on hysterectomy specimens done for ovarian cancer, it is very unlikely this would be routinely reported to patients. Importantly, most of the case-control studies asked about fibroids prior to ovarian cancer diagnosis (see Supplemental Table 1).

Reviewer comment: Discussion - Line 289 - Why do you think that hysterectomy appeared to be "protective" for White but not Black participants? Line 316 - As comment above, please provide other thoughts on why this difference may be present. Clearly, the role of salpingectomy is less of a concern here as noted, as it is associated with HG serous ovarian cancer, rather than the clear cell and endometrioid which are being explored further.

Response: While this is not something we can address with our data we might hypothesize that White women with endometriosis who received a hysterectomy might have a more complete removal of endometriosis lesions prior to or at the time of hysterectomy due to differences of quality of surgical care received between the two racial groups. If Black women with endometriosis received less adequate removal of endometriosis lesions they would be at higher risk of ovarian cancer regardless of hysterectomy status. Another possible, not mutually exclusive, possibility is that White women were more likely to have pre- and/or post-operative treatments that could potentially be protective against subsequent ovarian cancer development, such GnRH agonists, continuous oral contraceptives, etc, because of access/affordability issues. We have not included this in the manuscript as it is a working hypothesis that cannot be strongly supported by the literature at this time.

Reviewer comment: Tables - Table 1 - The age is a bit lower than one might expect for sporadic ovarian cancers. I am curious how many of these may in fact have been HBOC? Are you able to assess the same outcomes if those with a first degree relative were excluded? Table 4 - Mirror comments about Table 1.

Response: In general, case-control studies of ovarian cancer (which are the majority of our included studies) tend to capture more younger cases compared to cohort studies (see Table 1 in Fu, et al. JNCI 2023 Jan 23, and Supplemental Table 1 in Dixon, et al. British Journal of Cancer, 2017;116:1223-1228). We have also conducted sensitivity analyses excluding those with a first degree relative and effect estimates were similar or slightly attenuated but nearly all significant results remained significant (see end of document for tables), indicating that results were not drive by inclusion or exclusion of HBOC cases This is as expected given that HGSOC will account for the majority of family history related cases and HGSOC is not strongly associated with endometriosis.

Reviewer comment: What is synchronous referring to - both ovaries? Ovarian and another primary malignancy?

Response: Synchronous is an endometrial and ovarian cancer diagnosed at the same time.

Reviewer comment: Table 2 - Consider ordering the columns based on the incidence of the different histologic subtypes.

Response: We have ordered histotypes as is standard for all of our OCWAA manuscripts and as is standard for most epidemiologic examinations of ovarian cancer (for example, see Table 1 in Fu, et al. JNCI 2023 Jan 23).

Reviewer comment: Also consider bolding the statistically significant findings.

Response: We have bolded the statistically significant findings.

Reviewer comment: Table 3 & 6 - No comments other than bolding the significant observations. Curious if these could be supplemental?

Response: As examination of the association by hysterectomy was a primary aim of our study we prefer to keep Tables 3 and 6 as main tables. We have bolded the statistically significant findings.

Reviewer comment: Reviewer #2: The authors analyze data from 4 case-control and 2 nested case control studies to examine the association between endometriosis and leiomyomas with epithelial ovarian cancer risk. The impact of hysterectomy, oral contraceptive use and post-menopausal hormone therapy use on these associations was also examined. This study assesses differences in ovarian cancer risk and highlights disparities between white and black races. However, the study is limited by its methodology as it relies on self-report. As the incidence of endometriosis and fibroid disease in the study population is significantly lower than the incidence in the general population, it calls into question the validity of this form of assessment for these disease processes.

Response: We agree that there is some misclassification of endometriosis and fibroids diagnosis in that some participants with these conditions will be classified as unexposed. These issues impact nearly all studies in the field that are not based at clinical settings. However, validation studies, including the BWHS which is included in our analyses, demonstrate the validity of self-report of fibroids diagnosis. Self-reported fibroids have been validated in the BWHS, with a confirmed diagnosis among 96% of those whose medical records were reviewed. Given the rarity of ovarian cancer, It would be unfeasible to conduct a study such as ours with serial ultrasounds to diagnosis fibroids and then follow for ovarian

cancer incidence. In regards to endometriosis, our results for the endometriosis and ovarian cancer association is in line with what prior studies have observed, indicating that if non-differential misclassification is present it has not invalidated our results. Another partial explanation for the lower report of these conditions compared to the general population is that many of the participants in these studies were of reproductive age (i.e. the time in a participants life course when these conditions would have been most likely to be diagnosed) 10-30 years prior to ovarian cancer diagnosis and these conditions may not have been diagnosed as often during those calendar time periods (e.g. 1960s-1980s). We have included a section on the limitations of self-report of these conditions in the discussion section (lines 364-367).

Reviewer comment: Methods, line 126-127: how was the study population selected? How were the six studies selected from the OCWAA consortium?

Response: The six studies selected were those in that had data on fibroids and/or endometriosis. We have modified the Study Population Methods section to describe this more clearly (lines 135-137). For inclusion into OCWAA, studies had to have at least 40 cases of ovarian cancer in Black women.

Reviewer comment: Methods, line 141-142: what was the rationale for only including epithelial ovarian cases? The exclusion of non-epithelial cases limits the generalizability of study findings.

Response: Ovarian cancer is a generic term often used for any primarily malignant ovarian tumor, but it is misleading term in the sense that ovarian cancer is not just one disease and may not always originate from the ovary. Ovarian cancers with epithelial differentiation represent the majority of malignant tumors and most ovarian cancer-related deaths which is why they were the focus of the OCWAA consortium.

Reviewer comment: Methods, line 159-160: were any characteristics of patient's menstrual history/risk factors obtained such as early menarche or last menopause? Was genetic mutation carrier status (i.e., BRCA mutations) taken into consideration for confounding factors?

Response: We did adjust for age at menarche, but had only included this in the table footnotes, apologies for this omission. We have now modified the methods section to include age at menarche in our list of confounders (line 186). At the reviewers request we additionally examined models adjusted for age at menopause as a confounder. This analysis was limited to those who were postmenopausal and results were not materially different than our final regression models among those who are postmenopausal without this adjustment variable. We do not have data on mutation carrier status for the participants in the OCWAA database. As BRCA mutations are not associated with endometriosis or fibroids they would not be a traditional confounder so are unlikely to impact the observed associations.

Reviewer comment: Methods, line 167-172: when the authors refer to premenstrual hysterectomy is there data/consideration of the removal of adnexa at the time of surgery (i.e., salpingectomy vs. salpingo-oophorectomy). As subsequent risk for these two patient groups significantly differ.

Response: As noted in one of our responses to Reviewer #1, information on route/type of hysterectomy was not collected. For inclusion in the studies, women had to have at least one ovary in order to be at risk for ovarian cancer. Salpingectomy as a separate individual procedure was also not collected. Given the time frame during which the majority of the hysterectomies occurred within the study population (i.e, prior to current understanding of the fallopian tube origins of ovarian cancer and the potential benefits

of opportunistic salpingectomy), it seems highly likely that both the fallopian tube(s) and ovary/ovaries were left in situ as standard for total hysterectomies by any route at the time.

Reviewer comment: Results, line 233-241: Historically ovarian cancer incidence endometriosis diagnosis is higher in white women (as reviewed in introduction). Per study findings, Black participants were noted to have a higher odds ratio regardless of hysterectomy status when compared to White participants. Do the authors have a hypothesize to explain this discrepancy in their findings?

Response: The odds ratio between an exposure (e.g., endometriosis) and outcome is not impacted by the prevalence of the exposure in a population therefore we would not consider the findings discrepant in regards to the prevalence of endometriosis diagnosis in Black and White women. However, we do agree that the higher risk in Black women is an important finding given their lower/under diagnosis of endometriosis compared to White women and this issue certainly deserves further study. A measure such as race-specific population attributable risk scores (PARs) is more applicable to the reviewer's comment in that PARs account for both the relative risk and prevalence of exposure, and is especially helpful when the distribution of exposure differs across two groups. Using the Bruzzi method we calculated point estimates of the PARs for endometriosis and fibroids. For endometriosis the PAR% for White women was 3.3% (1.9-4.5%) and for Black women was 4.5% (2.8-5.5%), with corresponding PARs% for fibroids of 4.4% (1.4-7.1%) among White women and 11.7% (5.2-18.3%) among Black women. PARs for multiple exposures associated with ovarian cancer risks have previously been calculated within OCWAA (including for endometriosis) and are described in further detail elsewhere (Peres, LC et al. JNCI 2021). Because we are currently near the manuscript word limit we have not added these additional analyses to the text but can add them if given additional space.

Reviewer comment: Results, line 315-316: Any speculation on this persistent risk in Black participants?

Response: As mentioned in a similar question from reviewer #1 above, while this is not something we can address with our data, we might hypothesize that White women with endometriosis who received a hysterectomy might have a more complete removal of endometriosis lesions prior to or at the time of hysterectomy due to differences of quality of surgical care received between the two racial groups. If Black women with endometriosis received less adequate removal of endometriosis lesions they would be at higher risk of ovarian cancer regardless of hysterectomy status. Another possible, not mutually exclusive, possibility is that White women were more likely to have pre- and/or post-operative treatments that could potentially be protective against subsequent ovarian cancer development, such GnRH agonists, continuous oral contraceptives, etc, because of access/affordability issues. We have not included this in the manuscript as it is a working hypothesis that is cannot be strongly supported by the literature at this time.

Reviewer comment: Discussion, line 323-324: the self-reporting of pathology is a major limitation of this study. Not only due to possible misclassification but possible recall biases. Author should address this also. Limitations are described but lacks strengths.

Response: We have now addressed the possibility of recall bias in the discussion (lines 364-367). Due to journal word limits we have not been able to include strengths of our study in the discussion.

Reviewer comment: Tables: tables are lengthy and numerous, consider trimming/condensing for readability.

Response: If there are particular areas that the reviewer believes are redundant we would welcome the opportunity to review those sections. However, given that we are the largest study of these associations in Black women we have erred on the side of including all analyses we feel add value to the literature.

This paper presents analyses on the associations between (1) endometriosis and incident ovarian cancer and (2) uterine leiomyomas (fibroids) and incident ovarian cancer. These conditions are all common but understudied. Most of the data presented here are pooled from 6 studies (4 case-control, 2 case control nested within prospective cohorts). The authors did also briefly present meta-analytic estimates, which combined separate estimates from the 6 distinct studies. Key secondary analyses examined whether associations differed (1) between Black and White women or (2) based on history of premenopausal hysterectomy. The findings here do not have immediate clinical application but address important population-health questions about dual burdens of non-gynecologic and gynecologic conditions as well as offering hypothesis-generating results about the etiology of ovarian cancer.

STRENGTHS
MAJOR
1. bringing attention to understudied conditions whose etiology and population burden are not well understood
2. Examining fibroids: While previous studies (including some represented in these data) have examined associations between endometriosis and ovarian cancer, they authors state that few have examined ovarian cancer associations with fibroids.
3. Focus on Black women: Stratified analyses among a large sample size of Black women in the US. This is a notable strength, given that most research in this area in the US has been restricted to White women
4. Exposure and outcome classification: Use of self-reported data for fibroids and endometriosis may mitigate against racial and geographic biases in access diagnosis, especially for surgery required for definitive diagnosis with endometriosis. Classification of ovarian cancer also strong, with rich information about subtypes.

CONCERNS/LIMITATIONS
MAJOR

Reviewer comment: 5. Alternative explanations for findings (e.g., possible confounding) could be more thoroughly explored.
-- For instance, two major potential sources of bias that could inflate associations between endo/fibroids and ovarian cancer are detection bias and recall bias.
Detection bias: the workups or health care contact required for the diagnosis of endometriosis or fibroids may in and of itself be a surrogate marker of more health care seeking or which could increase the rate of diagnosis with ovarian cancer.
Recall bias: after diagnosis, ovarian cancer patients may have examined their gynecologic-related health history in more detail than those without ovarian cancer and may be more likely to report previous conditions than controls are.

Response: We have added information to the discussion section on the potential for recall bias (lines 364-367). Detection bias is theoretically possible, but if that were occurring we would expect to see differences in stage distribution between those with and without fibroids, which, as Table 4 shows, is not the case for fibroids, indicating that gynecologic surveillance is unlikely to explain the results.

Reviewer comment: The authors do mention these possibilities in their write-up but don't perform analyses to address them. One analysis could be a sensitivity analysis restricted just to the 2 prospective cohort studies, where recall bias at least would be less of a factor than in the case-control studies. Similarly, one possible bias influencing the finding that the associations were weaker among those who had a premenopausal hysterectomy could be that detection bias associated with diagnosis of endometriosis and fibroids would be less of a factor distinguishing cases and controls when both cases and controls had a history of hysterectomy and its related work-ups. It would be good to comment on this possibility and evaluate it empirically.

Response: In regards to analyses only among prospective studies we are considerable underpowered for those sensitivity analyses. In the analysis for endometriosis there is only prospective study (BWHS) which only includes Black women and with only 92 cases and 606 controls. For fibroids, there are 2 prospective studies (BWHS & SCCS), but still only 1 study in White women (SCCS). Across both studies there are 145 Black cases, 948 Black controls, 37 White cases, and 227 White controls, with that small number of cases in each racial group analyses of these prospective studies would not be sufficiently robust. However, as mentioned in the prior response, we have examined the distribution of fibroids and endometriosis cases across cases and controls with within cases by histotype and stage and those distribution do not indicate that detection bias is likely a major driver of our results.

Reviewer comment: 6. Concern about analyzing the pooled data. The authors justify the decision to pool the data because "no significant heterogeneity by study" was detected. But, even with no heterogeneity among results when they were analyzed in a study-specific manner, Simpson's Paradox could still lead a pooled estimate to be misleading, especially when some of the study sample sizes are so much bigger than others. And for the racial group-specific analyses, the studies contribute very different proportions of each racial group. More justification would be helpful to me as a reader.

Response: As we show in the forest plots (see new Figures 1 and 2), the ORs are very similar among studies, within Black and White stratifications, so in addition to the p-value indicating the lack of heterogeneity among the results we can see visually that there is not an issue with pooling the data. Further, we also controlled for study site in pooled analyses. These methods have been used across multiple OCWAA analyses. In addition, to further inspect for site heterogeneity, we attempted to fit random effects of endometriosis and uterine leiomyomas by site. We attempted to add these random effects into the models of endometriosis and uterine leiomyomas within all histotypes, separately by race and pooled together. However, the only model where random effects converged was within the model of endometriosis within White women, and the odds ratio associated with endometriosis was almost equivalent to the model without random effects: 1.59 (1.26-2.04) vs 1.28 (1.26-1.98). Thus, random effects of site did not affect our estimates, and we presented models without random effects throughout for simplicity and to avoid overfitting the models.

Reviewer comment: 7. FINAL CONCLUSION. The final sentence of the paper ("Further research is needed to understand how racial differences in diagnosis of these conditions, and differential access to care and treatment options, impact or modify ovarian cancer risk") and the final sentence of the abstract ("Understanding how racial differences these conditions and of access to care and treatment options may help guide future risk reduction strategies" [sic]) do not clearly flow from the Results and Discussion. In the Discussion especially, the authors should explicitly connect how the findings lead to this particular call for further research (final sentence) and this particular assertion of how we can insight into future risk reduction strategies.

Response: We have edited the conclusions (lines 382-383).

MINOR
Reviewer comment: 8. Mediation analyses, explanation in Methods: I'm unclear how the mediation analysis was performed. The authors say that the "product method" was used, citing MacKinnon et al (2007). Then later they say that they used a Valeri and vanderWeele macro (which isn't directly cited). At the least the mediation method should be clarified in text and clearly cited.

Response: The first reference is the reference for the macro, and the second reference justifies the use of the weights. We have edited the methods text and references to describe this more clearly (lines 199-203).

Reviewer comment: 9. Mediation analyses, interpretation: The authors should justify the extent to which they believe the assumptions (eg, no-confounding between mediators and outcomes?) are met in their interpretation of the mediation analyses.

Response: To the best of our ability given the variables available to use we have adjusted for confounding between (1) exposure and outcome, (2) mediators and the outcome, (3) exposure and mediators, and (4) mediator-outcome confounders affected by exposure, as we have an extensive but appropriate list of covariates adjusted for in the model. Before beginning the analyses we created causal diagrams (DAGs) to conceptualize the relations between the variables to address these potential issues. If there is a particular variable the reviewer is concerned about we would be welcome the opportunity to discuss it.

Reviewer comment: 10. Generalizability (Discussion section): The authors note that the prevalence of endometriosis and fibroids is lower in the control group in their sample than contemporary national statistics. They note 3 potential explanations: underreporting by their participants, true differences in prevalence because of secular increases in diagnosis over time, or "cohort effects in incidence." They could evaluate the likelihood that differences are because of secular increases in diagnosis, for instance, by comparing nationally representative surveillance data to similarly-aged study participants. If this is the true reason, it's less concerning as a bias than systematic underreporting among their control population.

Response: Unfortunately, surveillance data does not exist for endometriosis or fibroids at the level to address secular trends in time—the only potential data source would be surgical procedures within survey such as the National Hospital Discharge Survey or the National Inpatient Sample, but teasing out differences in regional practices, changes in diagnostics and alternatives treatments to surgery, coding changes, etc would have its own uncertainties. As we include in the discussion section, this underdiagnosis likely impacts cases and controls in a similar manner thus we do not feel it has biased our results.

Reviewer comment: 11. METHODS: "no significant heterogeneity by study" was detected based on I2 statistics and 95% confidence intervals. Please clarify the cutpoint used to classify "significant heterogeneity." For instance, is a p-value of p=0.06 not considered significant heterogeneity?

Response: We used a threshold of $p<0.05$ for significant heterogeneity. P-values for I^2 statistics are now displayed in forest plots (see Figures 1 and 2).

STATISTICAL EDITOR COMMENTS:

Reviewer comment: lines 71-73: Should also include that there was NS difference in the association between risk of OC and hysterectomy by race, as there was in lines 68-69.

Response: We have added p-values to the abstract (lines 72 and 74).

Reviewer comment: lines 209-210, 215-216, 218-220 and 222-223: The direct comparisons by race of each of these pairs are each NS, so they are not "stronger". The differences are only numerical, as can be seen from the wide CIs. Insufficient stats power makes many of these NS comparisons not generalizable from these data.

Response: We have modified the text and to not described results as different/stronger between Black and White women unless the p-value indicates heterogeneity (lines 235-246).

Reviewer comment: General: Although within a particular study, cases and controls may have been matched, they have not been matched overall, so should provide forest plots, funnel plots as in meta-analysis of these studies. Also, since these studies were each case control design, one cannot from these data put the ORs in context with absolute rates, rather only differences in odds, given a case and matched control.

Response: To clarify, the case-control studies included were frequency matched as part of their original study designs while the included prospective cohorts were individually matched. We have now added forest plots and meta-analysis results to the manuscript (Figures 1 and 2). Prior literature supports unconditional logistic regression in our setting, where "unconditional" logistic regression refers to a regression adding the matching factors as covariates. "When the study design involves other complex features or the computational burden is high, matching in loose-matching data can be ignored for negligible loss in testing and estimation if the distributions of matching variables are not extremely different between cases and controls." Kuo, Chia-Ling & Duan, Yinghui & Grady, James. (2018). Unconditional or Conditional Logistic Regression Model for Age-Matched Case-Control Data?. Frontiers in Public Health. 6. 10.3389/fpubh.2018.00057. See also: Pearce, Neil. Analysis of match case-control studies. BMJ, 2016;352. Since matching is at least 1:6 in the matched sites, reducing the problem of sparse data, we conducted a competing conditional logistic regression (as defined in the prior reference) by adding the matching indicators into the model. Due to similarity and closeness of the estimates between conditional and original models, we decided to retain the original results. Any potential bias from the unconditional analysis is expected to be conservative. Mansournia AM, et al. Matched designs and causal diagrams. IJE 2013: 42: 860-869. Due to similar comparative analyses, efficiency gains due to matching were judged to be negligible.

Reviewer comment: Table 2: To some extent, the differences in statistical heterogeneity are a result of the differences in sample sizes by race.

Response: We appreciate this point. We are unclear how or if the reviewer is suggesting we address this in the manuscript.

Odds ratios* and 95% confidence intervals for the association between endometriosis, overall and by race, for all ovarian cancer and stratified by histotype, **excluding women with family history of breast or ovarian cancer**

	All histotypes	High-Grade Serous	Low-Grade Serous	Endometrioid	Clear Cell	Mucinous	$p_{heterogeneity}$ between histotypes	Low-Grade Serous, Endo, & Clear Cell
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)		OR (95% CI)
All participants (cases/controls)	2431/4108	1448/4108	91/4108	217/4108	167/4108	164/4108		475/4108
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.59 (1.29-1.96)**	1.25 (0.96-1.63)	1.32 (0.56-3.15)	**3.17 (2.14-4.72)**	**3.27 (2.08-5.14)**	1.13 (0.58-2.20)	**<0.001**	**2.84 (2.09-3.86)**
Black participants (cases/controls)	700/1502	440/1502	26/1502	59/1502	25/1502	41/1502		110/1502
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**2.08 (1.41-3.08)**	**1.73 (1.06-2.81)**	1.33 (0.16-11.16)	**7.58 (3.76-15.29)**	2.03 (0.44-9.37)	1.17 (0.27-5.16)	0.107	**4.52 (2.48-8.22)**
White participants (cases/controls)	1731/2606	1008/2606	65/2606	158/2606	142/2606	123/2606		365/2606
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.38 (1.07-1.76)**	1.09 (0.79-1.49)	1.36 (0.52-3.58)	**1.96 (1.18-3.27)**	**3.17 (1.95-5.17)**	1.05 (0.50-2.24)	0.006	**2.27 (1.58-3.26)**
$p_{heterogeneity}$ by race	0.10	0.21	0.95	**0.001**	0.41	0.98		

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

Odds ratios* and 95% confidence intervals for the association between uterine leiomyoma, overall and by race, for all ovarian cancer and stratified by histotype, **excluding women with family history of breast or ovarian cancer**

	Overall	High-Grade Serous	Low-Grade Serous	Endometrioid	Clear Cell	Mucinous	p-het (between histotypes)	Low-Grade Serous, Endo, & Clear Cell
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)		OR (95% CI)
All participants (cases/controls)	2280/4157	1363/4157	80/4157	194/4157	154/4157	138/4157		428/4157
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.23 (1.08-1.40)**	**1.23 (1.05-1.43)**	0.94 (0.52-1.70)	**1.54 (1.10-2.17)**	1.08 (0.72-1.62)	**1.53 (1.02-2.29)**	0.16	1.24 (0.97-1.59)
Black participants (cases/controls)	711/1734	444/1734	24/1734	59/1734	24/1734	38/1734		107/1734
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.31 (1.07-1.62)**	1.25 (0.98-1.60)	2.25 (0.79-6.40)	**1.94 (1.07-3.51)**	1.69 (0.69-4.14)	1.93 (0.92-4.06)	0.005	**1.78 (1.14-2.76)**
White participants (cases/controls)	1569/2423	919/2423	56/2423	135/2423	130/2423	100/2423		321/2423
No	1.00	1.00	1.00	1.00	1.00	1.00		1.00
Yes	**1.19 (1.00-1.40)**	1.19 (0.98-1.45)	0.62 (0.26-1.44)	1.44 (0.93-2.22)	1.08 (0.67-1.74)	1.51 (0.91-2.50)	0.760	1.13 (0.83-1.54)
$p_{heterogeneity}$ by race	0.46	0.08	0.52	0.26	0.36	0.25		

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