NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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.
RE: Manuscript Number ONG-22-1529

Executive Summary of the Ovarian Cancer Evidence Review Conference

Dear Dr. O'Hara:

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 Nov 08, 2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Thank you for your submission. The Editors extensively discussed the overall executive summary as well as the manuscript focused on disparities. Based on these discussion and comments from our reviewers we feel that the work would be strengthened by combining both submissions into a single manuscript. While the revision is at the discretion of the authors we believe that many of the sections in the executive summary can be reduced substantially to allow incorporation of an abbreviated section on disparities.

Please combine this with ONG 22-1528 and submit a single revised manuscript. You are receiving "revision letters" for both submissions, but please decline one of them when your group has made final decisions about what you are sending back for consideration.

* 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.

* All submissions that are considered for potential publication are run through CrossCheck for originality. The content in the abstract matches too closely to the prior ACOG Executive Summary on Uterine Cancer. Please try to add some variance to the final wording.

REVIEWER COMMENTS:

Reviewer #1: This is an Executive Summary commissioned by CDC and written by member of ACOG and SASGOG with participation by SGO members, to provide educational materials on the prevention and early diagnosis of ovarian cancer. This is overall a well-written and comprehensive summary.
Recommend: Revise and Accept.
1. Line 45: All of the primary research questions should be displayed early within the manuscript, in a Figure/Box perhaps. The reader currently needs to dig into the Supplemental Appendices to find the primary questions. Some of the Appendices list the questions and others do not.

2. Line 22: I suggest reorganizing this paragraph. It is slightly odd that the first sentence is about breast cancer. Could this sentence more broadly introduce CDC initiatives in multiple cancers?

3. Line 428 This section and the companion paper (which I have also reviewed) seem to go off the initially planned topic, beyond addressing "prevention and early detection," and into disparities in ovarian cancer treatment and outcomes. While this is a very worthy topic of research/a review, it is unclear why the 2 manuscripts need to be linked. The companion really does not qualify as an Executive Summary or Guideline paper and should likely be submitted separately under a different category.

4. Line 497 It is unclear why management of advanced stage ovarian cancer (neoadjuvant chemotherapy versus primary debulking) is part of the scope of this paper. If the scope includes treatment, that should be reflected in the research questions.

5. Special Considerations: This section might be best classified as summarizing survivorship issues (fertility preservation, menopausal symptoms), which also do not strictly fall under "prevention and early detection". The scope of the study should be made clear at the outset.

Reviewer #2: This is a clearly written, excellent review of the literature, to include up-to-date professional societies guidelines. It will be beneficial to those practicing general Ob/Gyn and its specialties.

Line 100-101, consider changing to: High-grade serous carcinoma represents the majority of ovarian cancers, however, most do not arise from the ovary but form the fallopian tube.
(High-grade serous carcinoma represent approximately 45% of epithelial ovarian carcinomas. Although it is postulated that most high-grade advanced stage serous carcinoma arise in the fimbria of the fallopian tube, this is not the case in early-stage and all advanced-stage cases).

Lines 223-226, The lifetime risk of ovarian cancer for the mutations listed do not match the percentages listed in Table 1. (BRIP1, RAD51C, RAD51D 2% risk of ovarian cancer (line 224-226) versus >10% (table 1), versus 12%, 11%, 13%, respectively (table 2).

Reviewer #3: This is a very good summation of what is very complex subject matter.

Under menopausal hormone therapy the paper comes across as recommending not treating patients due to increased ovarian cancer risk. Recommend that some guidance in terms of lowest dose for shortest duration possible, as perimenopausal and early postmenopausal women do not seem to have this increased risk. An absolute risk increase would also be helpful to understand the risk as practitioners make treatment decisions.

Within infertility, recommend some further discussion about borderline ovarian tumors is discussed. The risk is very low and the tumor type has a favorable prognosis. The insignificant but present increased risk should be stated.

Other medications: beta blockers have also been shown to decrease risk

Risk reduction: the statement that no prospective studies exist on opportunistic salpingectomy is incorrect. This has been looked at by Subramaniam A et al (PMID: 29889762; PMID: 30477808)

Screening: I would like to see caution more clearly stated. The section opens with almost a favorable opinion of screening. It should be clearly stated from the outset that screening is not recommended. Psychologic trauma to the patient and receipt of unnecessary surgery should be cited. In the study out of Kentucky it should also be pointed out that this was a high risk population that was being screened. Not asymptomatic low risk screening.

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Sincerely,
Jason D. Wright, MD
Editor-in-Chief
In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.
November 29, 2022

Jason D. Wright, MD
Editor-in-Chief
*Obstetrics & Gynecology*

RE: Manuscript Number ONG 22-1529

Dear Dr. Wright,

Thank you for the thoughtful reviewer comments and opportunity to submit a revised manuscript, which we have done. Please note that our revision is still blinded. Below, please find a point-by-point response to the reviewer and editor comments. We have pasted the reviewer comments in black and our responses in red. Changes to the manuscript have been made with the MS Word track changes feature. Where appropriate, the response indicates the line number of the corresponding revisions as viewed in the document with the tracked changes visible.

The lead author and corresponding author have read the Instructions for Authors. This revision has been developed in consultation with our co-authors and each author has given approval to the final form of the revision.

Thank you,

[Signature]

Julia O’Hara, MPH
Program Director, Gynecology
American College of Obstetricians and Gynecologists
Washington, DC
EDITOR COMMENTS:

Thank you for your submission. The Editors extensively discussed the overall executive summary as well as the manuscript focused on disparities. Based on these discussion and comments from our reviewers we feel that the work would be strengthened by combining both submissions into a single manuscript. While the revision is at the discretion of the authors we believe that many of the sections in the executive summary can be reduced substantially to allow incorporation of an abbreviated section on disparities.

Thank you. We are very appreciative of Dr Wright’s meeting with our team. After these discussions, we would like to continue with separate manuscripts. As with our uterine cancer evidence summary, where separate manuscripts were accepted by the Green Journal, we feel a different level of detail is merited for the disparities material. While for most of the material, an executive summary level of detail with referral to online appendices is adequate, we think the disparities material merits publication in detail. Presenting full detail for one section mixed with executive summary level detail for others in a single manuscript is awkward and flows poorly. Other than the material that reviewers requested so that the disparities manuscript could stand alone, the two separate manuscripts are not much longer than a single combined one. Given the current national focus on identifying and addressing disparities we are hoping the journal will be amenable to giving the disparities details the attention it deserves via publication in the journal as opposed to an online appendix, which by its nature will be read much less. We hope that the editors and reviewers will agree that these updates have strengthened the work, and we are open to further discussion as needed.

Please combine this with ONG 22-1528 and submit a single revised manuscript. You are receiving "revision letters" for both submissions, but please decline one of them when your group has made final decisions about what you are sending back for consideration.

Thank you. As noted in the comment above, we were given discretion in whether to combine. After discussion with Dr Wright and for the reasons noted above, we are submitting revised manuscripts for ONG 22-1528 and ONG 22-1529.

* 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.

Thank you. The lead author and corresponding author have reviewed the Revision Checklist and made the applicable edits.

* All submissions that are considered for potential publication are run through CrossCheck for originality. The content in the abstract matches too closely to the prior ACOG Executive Summary on Uterine Cancer. Please try to add some variance to the final wording.

Thank you. Since the process for the uterine cancer and ovarian cancer projects were similar in nature and part of the same initiative the information presented in the Abstract will be similar. However, we have made small edits to the Abstract (lines 25-40) to add some variance as requested. Please let us know if additional changes are required.

REVIEWER COMMENTS:

Reviewer #1: This is an Executive Summary commissioned by CDC and written by member of ACOG and SASGOG with participation by SGO members, to provide educational materials on the prevention and early diagnosis of ovarian cancer. This is overall a well-written and comprehensive summary.
Recommend: Revise and Accept.

Thank you.

1. Line 45: All of the primary research questions should be displayed early within the manuscript, in a Figure/Box perhaps. The reader currently needs to dig into the Supplemental Appendices to find the primary questions. Some of the Appendices list the questions and others do not. We have inserted the primary research questions as Box 1 (lines 1021-1023).

2. Line 22: I suggest reorganizing this paragraph. It is slightly odd that the first sentence is about breast cancer. Could this sentence more broadly introduce CDC initiatives in multiple cancers? We reorganized the Introduction section (lines 25-31) to clarify.

3. Line 428 This section and the companion paper (which I have also reviewed) seem to go off the initially planned topic, beyond addressing "prevention and early detection," and into disparities in ovarian cancer treatment and outcomes. While this is a very worthy topic of research/a review, it is unclear why the 2 manuscripts need to be linked. The companion really does not qualify as an Executive Summary or Guideline paper and should likely be submitted separately under a different category. Thank you for this perspective. The addition of Box 1 (lines 1021-1023) clarifies that health disparities are within the scope of the project. We have addressed Reviewer concerns about ONG 22-1528 separately in our response letter and revisions for that manuscript.

4. Line 497 It is unclear why management of advanced stage ovarian cancer (neoadjuvant chemotherapy versus primary debulking) is part of the scope of this paper. If the scope includes treatment, that should be reflected in the research questions. Please see the addition of Box 1 (lines 1021-1023), which clarifies that an “overview of diagnosis and care coordination for the primary care practitioner” is within the scope of this paper, more specifically, we were charged with providing a “brief summary of what will likely happen after referral at level for primary care practitioner to set expectations and provide anticipatory guidance for the patient”.

5. Special Considerations: This section might be best classified as summarizing survivorship issues (fertility preservation, menopausal symptoms), which also do not strictly fall under "prevention and early detection". The scope of the study should be made clear at the outset. Please see the addition of Box 1 (lines 1021-1023), which includes the following research question: “What special considerations do primary care practitioners need to be aware of throughout the ovarian cancer care continuum? How influential are these factors in the patient experience and outcome?” There is a note at the end of Box 1 to see Appendices 2-8 for PICO criteria used for each outline question. This PICO criteria lists the factors searched for (eg, fertility preservation, menopausal symptom management, resources for survivor care, psychosocial issues, etc.).

Reviewer #2: This is a clearly written, excellent review of the literature, to include up-to-date professional societies guidelines. It will be beneficial to those practicing general Ob/Gyn and its specialties.

Thank you.

1. Line 100-101, consider changing to: High-grade serous carcinoma represents the majority of ovarian cancers, however, most do not arise from the ovary but form the fallopian tube. (High-
grade serous carcinoma represent approximately 45% of epithelial ovarian carcinomas. Although it is postulated that most high-grade advanced stage serous carcinoma arise in the fimbria of the fallopian tube, this is not the case in early-stage and all advanced-stage cases. Lines 104–107 have been changed as suggested.

2. Lines 223–226, The lifetime risk of ovarian cancer for the mutations listed do not match the percentages listed in Table 1. (BRIP1, RAD51C, RAD51D 2% risk of ovarian cancer (line 224–226) versus >10% (table 1), versus 12%, 11%, 13%, respectively (table 2). Thank you. We adjusted the lifetime risk of ovarian cancer for BRCA1 and BRCA2 genetic mutations on lines 232–237 to be consistent with the table. The two sets of lifetime risks originally came from different references, and one adjusted for risk-reducing surgery (NCCN clinical practice guidelines in oncology. Genetic/familial high-risk assessment: Breast, ovarian and pancreatic v2.2022) while the other did not (Lederman et al, 2013). We used the NCCN data in the revised version. However, the manuscript says “BRIP1, RAD51C, and RAD51D have also been associated with an increased risk of ovarian cancer. Mutations in these three genes are estimated to be associated with 2% of ovarian cancer cases.” This is distinct from the absolute and lifetime risk percentages shown in the tables, which we confirmed are accurate as reported.

Reviewer #3: This is a very good summation of what is very complex subject matter. Thank you.

1. Under menopausal hormone therapy the paper comes across as recommending not treating patients due to increased ovarian cancer risk. Recommend that some guidance in terms of lowest dose for shortest duration possible, as perimenopausal and early postmenopausal women do not seem to have this increased risk. An absolute risk increase would also be helpful to understand the risk as practitioners make treatment decisions. We added a sentence (line 191–193) to address this statement. This is beyond the scope of our review, but we clarified that recommendations regarding the use of hormonal therapy should use a much broader assessment of risks and benefits than included here.

2. Within infertility, recommend some further discussion about borderline ovarian tumors is discussed. The risk is very low and the tumor type has a favorable prognosis. The insignificant but present increased risk should be stated. We clarified this point in lines 253–258 by adding data from two cohort studies (Stewart et al, 2013; van Leeuwen et al, 2011).

3. Other medications: beta blockers have also been shown to decrease risk Thank you for the recommendation. We added data from a cohort study (Baek et al, 2018) discussing the association between beta blockers and ovarian cancer risk (lines 269–271).

4. Risk reduction: the statement that no prospective studies exist on opportunistic salpingectomy is incorrect. This has been looked at by Subramaniam A et al (PMID: 29889762; PMID: 30477808) We appreciate the information and have incorporated the information into this section in the appropriate manner (lines 282–291).

5. Screening: I would like to see caution more clearly stated. The section opens with almost a favorable opinion of screening. It should be clearly stated from the outset that screening is not recommended. Psychologic trauma to the patient and receipt of unnecessary surgery should be
cited. In the study out of Kentucky it should also be pointed out that this was a high risk population that was being screened. Not asymptomatic low risk screening.

To clarify we changed the subheading on line 309 from “Screening Methods” to “Screening Methods That Have Been Proposed”. We moved a sentence from the end of the “Screening in Asymptomatic Average Risk Women” to be the opening sentence of that section on lines 326-327 clearly stating that our review found no major professional society recommending the use of ovarian cancer screening in asymptomatic women at average risk. We also expanded the last sentence of the section to state that the USPSTF concludes that “there is at least moderate certainty that the harms of screening for ovarian cancer outweigh the benefits.” The study out of Kentucky is described under the “Screening in High-Risk Patients” sub-section (lines 359-385) making it clear that it is a high-risk population that was being screened.