OBSTETRICS & GYNECOLOGY

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.

Date: Oct 17, 2019
To: "Sabrina Piedimonte" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1706

RE: Manuscript Number ONG-19-1706

Microinvasive tubal carcinomas: cases of poor outcome despite 'very early' diagnosis. A systematic review of the literature

Dear Dr. Piedimonte:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 07, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Precis - micro invasive tubal carcinoma at the time of prophylactic surgery for BRCA or high risk patients has the risk of recurrence potential and poor outcome
Abstract - Objective - invasive tubal carcinoma can be found in BRCA patients at the time of risk reducing salpingoophorectomy (RRSO) - systematic review to determine prevalence of mucinous tubal cancer in BRCA or high risk RRSo, evaluation of treatment, outcomes, recurrence and survival
Data source - systemic review of literature from 1946-2019
Methods of Study Selection - occult neoplasia of Fallopian tube, quality of studies assessed and survival analysis performed
Tabulation, Integration, and Results - 35 studies were qualitative and 27 were quantitative
6425 patients with RRSO between 1990-2019; 86 had occult tubal carcinoma with a prevalence of 1.34%; 47.5 months of follow up and 13 recurrences (15.1%), 27 cases of peritoneal cancer (0.42%)
BRCA1, older age, previous breast cancer and sampling of the fimbria were associated with occult malignancies
Conclusion - despite early diagnosis and aggressive chemotherapy, micro invasive tubal cancer at RRSO in high risk and BRCA patients has a recurrence potential and a poor outcome

Background - introduction to the concept of early diagnosis, then discussion of micro invasive tubal cancer at RRSO as an opportunity to evaluate if early diagnosis impacts outcome

Sources - systematic search from 1946-March of 2019
Inclusion criteria - 2 investigators evaluating microinvasive tubal cancer
Data extraction and synthesis - tables of data
Statistical analysis k- prevalence of micro invasive tubal cancer
Quality assessment - good quality score > 10

Results - 35 papers used for qualitative analysis and 27 used for quantitative analysis

6425 patients with RRSO in 35 studies from 1990-2019 and 2963 with BRCA1 and 1605 with BRCA2
86 with occult tubal cancer - incidence of 1.34%, 15.1% recurrence and 0.42% post-RRSO peritoneal cancer
advanced age, BRCA1, previous breast cancer, and sampling of fimbriated ends lead to more frequent diagnosis of tubal cancer
age - median ge 54 and all were found in patients age >40

Discussion - occult carcinoma at RRSO in BRCA or high risk patients with prevalence of 1.34% and recurrence of 15.1% despite adjuvant treatment

Implications - 15% recurrence, data incomplete about adjuvant chemotherapy - see comments below

Risk of bias - heterogeneity in design - some BRCA and some high risk, introduction of pathological protocol, and some were prophylactic oophorectomy, not salpingectomy

Quality of evidence - poor reporting, incomplete follow-up, only 17 studies had all outcomes

Conclusions - BRCA patients with occult carcinomas detected - more common in BRCA 1, patients > 40, and if incomplete resection

Comments:
1) Why did you query articles as far back as 1946 - so much has changed with management, diagnosis, treatment - it doesn't seem like the data from that long ago would be relevant or allow for adequate comparison

2) I am not sure the 1st paragraph of the background with the emphasis on size of tumor and doubling is the most appropriate start to this manuscript. Especially because tubal cancer in BRCA patients behaves high a high grade tumor and is perhaps different than tumors that are not associated with this mutation

3) should patients with BRCA really be compared to patients with "high risk" based on family history? It seems like these are 2 distinct groups with separate risks and should be evaluated separately.

4) quality score is reviewed, but what score were these studies given? Were studies of poor quality eliminated?

5) Results section - the reasons for exclusion of studies is mentioned, but the exclusion criteria was already addressed and doesn't need to be repeated.

6) under Implications - I don't understand the relevance or role in a systematic review for an in-depth discussion of 1 or 2 particular cases

7) under Implications - cases with out complete removal or without complete sampling of pathology shouldn't be considered

8) Under Implications - if there was a change in pathological protocol, doesn't this affect the ability to compare data. it seems that the review should be limited to evaluation of studies that occurred after the pathological protocol was implemented as the inconsistencies in pathological reporting would make a systematic review inaccurate

9) there is mention of incomplete data - if there is incomplete data and studies of poor quality, these should be eliminated

10) there is a discussion of STIC but if this is different than micro invasive disease it should not be considered in the same review as micro invasive disease

11) If some patients had prophylactic oophorectomy while others had BSO, these 2 groups cannot be compared due to the risk of tubal cancers

12) if the quality of the studies is poor it doesn't warrant a systematic review so please address the quality and limit study to only good quality studies

13) limit study to good quality studies after similar pathological protocol in BRCA patients and you would have a more meaningful review

Reviewer #2: Background
Information in the first paragraph does not add to the primary focus of your study.

Statistical analysis
Data from Kaplan Meier calculations to assess progression free-survival in BRCA 1 patients versus BRCA 2 patients is suspect as these patients were not uniformly treated with adjuvant chemotherapy.

Results
Why did you separate out patients with fallopian tube/ovarian cancer from patients with peritoneal cancer in your analysis?

Reviewer #3: Review: Microinvasive tubal carcinomas: cases of poor outcome despite 'very early' diagnosis. A systematic review of the literature

Overall: This is an interesting literature review project focusing on evaluating the prognosis of patients with early stage tubal carcinoma. The authors have performed a great deal of work with the literature search and have done a very nice job of describing studies that were screened, reviewed, and then ultimately included in this review. This is a large study on a very rare disease that has recently been described. The issue with many of these thorough reviews on rare topics is that the time frame of included studies is quite large. Additionally, including many small studies to make a large study does not eliminate all of the potential confounders with in small study. Simple questions such as pathology review and were all patients surgically staged with early tubal carcinoma? This review paper is well written and concise for such a large amount of data. I congratulate the author on completing this important work. Table 1 is an excellent summary for the reader. However, the average age of a patient in this review is 53- patients with BRCA mutations are recommended to undergo risk-reducing surgery prior to this age. Therefore we have already incorporated some these findings into treatment guidelines to help prevent the development of cancer. These data strengthen these RRSO recommendations. I find the results interesting and helpful. However, I do have some questions concerning this work. Please see list of specific concerns below.

Specifics

1. The authors quote STIC as serous tubal epithelial carcinoma- it really should be serous tubal intraepithelial carcinoma- stage O cancer.

2. Obstetrics & Gynecology is a scientific journal- I am not sure what "very early diagnosis" is or means? I would change the title.

3. Microinvasive tubal carcinoma and STIC lesions are 2 very different diagnosis- microinvasive disease is invasive cancer and STIC is no invasion. Please be clear in your review and discussion that these are separate entities.

4. A recurrence rate of 15% is very high for early stage fallopian tube cancer. In order to state that these patients were early stage- please describe how many patients underwent staging. If this information was not available please let the reader know that as well.

5. I have a hard time understanding the "IMPLICATIONS OF FINDINGS" section. Are you now introducing your own case report in this manuscript? I am not sure what this section is doing and maybe a side authors personal thoughts on microinvasive disease.

6. The paper describes a significant rage of patients - stage I, StageIB, microinvasive disease and patients with STIC lesions. Please clean this up- the title states "Very early" diagnosis. The more I read the more confused I get as to what patients are you describing in the text. Stage IB patients and microinvasive patients as well as STIC patients are not going to get treated the same way. Also when having a stage IB lesion- were those patients staged- Are they truly Stage IB?

7. Additionally- the description of the patient with microscopic disease on lines 252-256 makes no sense clinically. Why do you have microscopic disease at RRSO- then you state you gave her neoadjuvant chemotherapy_ Why? Then you state you debulked a stage IB- what did you debulk? Or did you stage her and she was a stage IB after chemotherapy so you do not really know her stage? Please clarify this patient.

8. In figure 3 can the authors comment on how many patients underwent surgical staging?

9. The authors should review this data and comments with in the discussion- "What is currently understood is that STIC may be found in 80-100% of RRSO specimens but lead to malignant transformation in only 5-10% of cases, although it is possibly too embedded in tumor to isolate. Therefore, care should be taken to separating the tube and analyzing it in its entirety 31." In reviewing this paper I am not sure if the data to support that 80-100% of patients with RRSO who have a BRCA mutation will have a STIC lesion. This paper focused on evaluating patients with pelvic serous carcinoma and attempted to identify STIC lesions in the fimbria.

STATISTICAL EDITOR'S COMMENTS:

1. General and Abstract: Should include CIs for (1) the prevalence of occult tubal ca, (2) the recurrence rate among that subset and (3) the prevalence of post-RRSO peritoneal ca, to put the risk and recurrences in context.

2. line 93: Should include range for the median of 17 months.

3. line 195: Should label the stats test as log-rank, rather than LR, lest it be confused with likelihood ratio. Should separately cite the median (range) follow-up for the BRCA1 and BRCA2 cohorts.

4. lines 200-201: Although each of these factors were associated with more frequent diagnosis of occult tubal ca, the

overall number of cases in this series (86 out of 6425) does not appear sufficient to state whether these are independently associated with occult tubal ca. Is there data available to construct a Table for the 86 vs the remainder in terms of counts for advanced age, BRCA status, previous breast ca and extensive sampling of the fimbriated end? It appears that the incidence of occult tubal ca (~ 1.3%) is low, and therefore the factors, although they may be statistically associated with dx of occult tubal ca, would not be useful in absolute terms for prediction of occult tubal ca. That is, the overall rates of 0/1605 for BRCA2 has a non-zero 95% CI upper bound of 0.23%, while the 13/2963 for BRCA1 had a rate o 0.43%, so there would be poor sensitivity to utilize BRCA status in an attempt to predict occult tubal ca.

5. Fig 3: Should include the N remaining at risk for the BRCA1 and BRCA2 patients at the time increments along the x-axis.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. As of January 1, 2020, authors of systematic reviews must prospectively register their study in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), an international database of prospectively registered systematic reviews. Please refer to the PROSPERO registration number in your submitted cover letter and include it at the end of the abstract.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

6. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

8. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Reviews, 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

14. The Journal's Production Editor had the following suggested changes for the figures in your manuscript

"Figure 1: Please upload as a figure file on Editorial Manager.
Figure 2: Please upload a high resolution figure file to Editorial Manager (eps, jpeg, tiff). Please add an in-text citation to this figure.
Figure 3: Please upload a high resolution figure file to Editorial Manager (eps, jpeg, tiff)."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 07, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

_____

Montreal, November 8 2019

To the editors of Obstetrics and Gynecology,

Please find attached the revised manuscript for our systematic review titled **OCCULT TUBAL CARCINOMA FOLLOWING RISK-REDUCING SALPINGO-OOPHORECTOMY IN BRCA PATIENTS: A SYSTEMATIC REVIEW.**

We have responded to the reviewers below and included the new additions in the text, with line numbers. A track changes version of the manuscript has also been submitted. In summary, we have removed low quality studies and those without pathological protocol, resulting in 27 papers retained for qualitative and quantitative analysis. We restructured the results and discussion sections to better reflect flow of ideas, and removed one of the figures.

We hope this edited version will satisfy criteria for publication in your journal.

Kind regards,

Sabrina Piedimonte, MDCM MSc.
On behalf of Dr. Walter Gotlieb, corresponding author, and co-authors Ms. Cairina Frank, Dr. Claudie Laprise and Ms. Andrea Quiattiani

RESPONSE TO REVIEWER COMMENTS:

Reviewer 1 Comments:
Comments:
1) Why did you query articles as far back as 1946 - so much has changed with management, diagnosis, treatment - it doesn't seem like the data from that long ago would be relevant or allow for adequate comparison

Response: Based on expert librarian search and epidemiologist analysis, authors felt using the oldest time limit of the databases would be appropriate, although most of the papers were post 1999. Therefore we have added to the methods section (line 146-147):

> *The time period was from 1946 to March 2019; papers retained were between 2002-2019.*

2) I am not sure the 1st paragraph of the background with the emphasis on size of tumor and doubling is the most appropriate start to this manuscript. Especially because tubal cancer in BRCA patients behaves high a high grade tumor and is perhaps different than tumors that are not associated with this mutation.

- **Response:** Thank you for your comment, the purpose of this section is to indicate that 'detectable early cancers', such as ovarian tumors visible on ultrasound or detectable by CA125, are actually not early at all. We agree that this is more a section that belongs in the discussion, and have modified it and moved it to the discussion.

3) should patients with BRCA really be compared to patients with "high risk" based on family history? It seems like these are 2 distinct groups with separate risks and should be evaluated separately.

- **Response:** Thank you for your comment, they are indeed 2 distinct groups with different risks but the similarities are more striking than the differences, and separating them would dilute the findings too much. To address your relevant comment, we have included the variations in definition of "high risk" in the discussion section.

4) Quality score is reviewed, but what score were these studies given? Were studies of poor quality eliminated?

- **Response:** Please see table one, MINORS score was used. All scores were over 8. Low quality papers(MINORS <6), which were mostly case reports have now been excluded in the quantitative analysis (see figure 1, table 1) but will be mentioned in the discussion. We included a quality assessment to conform with the standard requirements of a systematic review, but all papers retained for qualitative and quantitative analysis responded to our exclusion criteria.

We have added the following statement in the methods section (lines 160-161):

> *Papers were excluded if these reported only ovarian or peritoneal carcinomas, were of low quality (MINORS <6) , or lacked a standardized pathological protocol.*

5) Results section - the reasons for exclusion of studies is mentioned, but the exclusion criteria was already addressed and doesn't need to be repeated.

- **Response:** Thank you- the following sentence in the results section was moved up to complement the "inclusion criteria" section (lines 155-158):

> *Reasons for rejection after screening of titles included irrelevant to research question, incorrect study group, no report of fallopian tube cancers (only ovarian or primary peritoneal), discussion of pathogenesis, clinical trials without results or papers related to parp-inhibitors.*

6) Under Implications - I don't understand the relevance or role in a systematic review for an in-depth discussion of 1 or 2 particular cases

- **Response:** The relevance of this systematic review is to characterize poor outcomes in patients, despite early (pre-clinical) diagnosis in patients with no evidence of disease prior to risk reducing surgery. The motivation to perform this review came following an unexpected poor clinical outcome in a patient with only microscopic disease at the time of RRSO despite the most comprehensive treatment available today. We have now added this case to an addendum. This review shows the existence of other cases of occult tubal carcinoma found in the literature with recurrence and some cases of post RRSO peritoneal cancer diagnosed in absence of disease at initial surgery. We have rearranged the implications of findings to better highlight the findings of the included studies in a more organized fashion, reduced the discussion of STIC and placed our case report as an addendum explaining how it motivated the present study.

7) **Under Implications - cases with out complete removal or without complete sampling of pathology shouldn't be considered**

- **Response:** Thank you, we have now removed the papers from Colgan and Carcangiu in which this was a problem.

8) Under Implications - if there was a change in pathological protocol, doesn't this affect the ability to compare data. it seems that the review should be limited to evaluation of studies that occurred after the pathological protocol was implemented as the inconsistencies in pathological reporting would make a systematic review inaccurate

- **Response:** We agree that this staging protocol could affect the detection of invasive tubal carcinomas and number of subsequent cases of post RRSO peritoneal carcinoma We have reviewed all papers description of pathologic protocol and the papers included had already incorporated a pathologic protocol as described in their methods section. Two studies with non-uniform pathologic protocol were excluced **(Colgan 2001, Carcangiu 2006)** in the reviewed version of the manuscript.

9) There is mention of incomplete data - if there is incomplete data and studies of poor quality, these should be eliminated

-Response: It is not that the data is incomplete, however some studies do not comment on the treatments or long term outcomes. Keeping these cases add to the pool of patients with this rare outcome and eliminating them would lead to reporting a false prevalence. The primary outcome of the study is the prevalence of invasive tubal carcinomas at the time of RRSO in BRCA or high-risk patients. We have

performed a sub-analysis on the 18 studies with treatment outcomes in order to properly report the prevalence of recurrence and post RRSO peritoneal cancers. We have added this in the methods section. Lines 226-236 now read:

> *A sub-analysis was performed on the 18 studies reporting on follow-up, including recurrence and post-RRSO peritoneal carcinoma. Prevalence of recurrence was obtained by dividing the number of recurrences by the number of cases of invasive tubal carcinoma and post RRSO peritoneal cancers divided by the total number of patients undergoing RRSO within these 18 studies.*

10) There is a discussion of STIC but if this is different than micro invasive disease it should not be considered in the same review as micro invasive disease

Response: We agree with this statement and have toned down this section in the discussion. We left a sentence discussing that STICS might explain why some of the cases developed post RRSO peritoneal carcinoma. In addition, we have removed the following paragraph:

> *Given inconsistencies in pathological protocol and data reporting, it is difficult to extrapolate an accurate estimation of STIC transformation to peritoneal carcinomas. What is currently understood is that STIC may be found in 80-100% of RRSO specimens but lead to malignant transformation in only 5-10% of cases, although it is possibly too embedded in tumor to isolate. Therefore, care should be taken to separating the tube and analyzing it in its entirety* [31].

11) If some patients had prophylactic oophorectomy while others had BSO, these 2 groups cannot be compared due to the risk of tubal cancers

-Response: This is a valid point, and we have excluded the study where the description between performing a BSO and a BO was unclear (Carcagiu, 2006). This section was also removed from the interpretation section

12) If the quality of the studies is poor it doesn't warrant a systematic review so please address the quality and limit study to only good quality studies

-Response: Thank you for this point- MINORS criteria was used to grade quality on a variety of important points. The quality of studies was assessed using MINORS criteria. All very low quality studies were now excluded in the revised manuscript, including case reports as they were all prior to 2009, had variations in pathological protocol and surgical approach.

13) **Limit study to good quality studies after similar pathological protocol in BRCA patients and you would have a more meaningful review**

-Response: Thank you for this valid recommendation to strengthen our study. We have now excluded 3 poor quality studies without pathological protocol and 5 case reports. The new forest plot and prevalence rates can be found in Figure 1. Overall, this modification did not lead to a significant decrease in total number of patients undergoing RRSO or cases of tubal carcinoma, therefore similar rates are reported in the manuscript. Based on the recommendations, the reviewed manuscript now features a more homogenous population of patients allowing some inferences.

Reviewer #2: Background
1. Information in the first paragraph does not add to the primary focus of your study.

- **Response:** Thank you, we moved it to the discussion.

Statistical analysis
2. Data from Kaplan Meier calculations to assess progression free-survival in BRCA 1 patients versus BRCA 2 patients is suspect as these patients were not uniformly treated with adjuvant chemotherapy.

- **Response:** We have now removed this graph.

Results
3. Why did you separate out patients with fallopian tube/ovarian cancer from patients with peritoneal cancer in your analysis?

- **Response:** Thank you, the cases of peritoneal cancers reported were following RRSO and thus believed to arise from remnant tubal cells or STIC transformation. The initial prevalence calculation was on the cases of invasive tubal carcinoma found at the time of risk reducing surgery.

Reviewer #3: Review: Microinvasive tubal carcinomas: cases of poor outcome despite 'very early' diagnosis. A systematic review of the literature

Overall: This is an interesting literature review project focusing on evaluating the prognosis of patients with early stage tubal carcinoma. The authors have performed a great deal of work with the literature search and have done a very nice job of describing studies that were screened, reviewed, and then ultimately included in this review. This is a large study on a very rare disease that has recently been described. The issue with many of these thorough reviews on rare topics is that the time frame of included studies is quite large.

Additionally, including many small studies to make a large study does not eliminate all of the potential confounders with in small study. Simple questions such as pathology review and were all patients surgically staged with early tubal carcinoma? This review paper is well written and concise for such a large amount of data. I congratulate the author on completing this important work. Table 1 is an excellent summary for the reader. However,the average age of a patient in this review is 53- patients with BRCA mutations are recommended to undergo risk-reducing surgery prior to this age. Therefore we have already incorporated some these findings into treatment guidelines to help prevent the development of cancer. These data strengthen these RRSO recommendations. I find the results interesting and helpful. However, I do have some questions concerning this work. Please see list of specific concerns below

Specifics

1. The authors quote STIC as serous tubal epithelial carcinoma- it really should be serous tubal intraepithelial carcinoma- stage O cancer.

- **Response:** Thank you for pointing this out- we haved corrected this in the manuscript

2. Obstetrics & Gynecology is a scientific journal- I am not sure what "very early diagnosis" is or means? I would change the title.

- **Response:** Thank you we have modified the title to accurately reflect the work reported:

OCCULT TUBAL CARCINOMA FOLLOWING RISK-REDUCING SALPINGO-OOPHORECTOMY IN BRCA PATIENTS; A SYSTEMATIC REVIEW

3. Microinvasive tubal carcinoma and STIC lesions are 2 very different diagnosis- microinvasive disease is invasive cancer and STIC is no invasion. Please be clear in your review and discussion that these are separate entities.

- **Response:** Thank you, we have now clarified this in the edited version of the manuscript

4. A recurrence rate of 15% is very high for early stage fallopian tube cancer. In order to state that these patients were early stage- please describe how many patients underwent staging. If this information was not available please let the reader know that as well.

- **Response:** Thank you for pointing out this nuance. In fact, as per table 1, some of the cases were initially Stage II or III, which accounted for most cases of recurrence. We have added the following sentence in the discussion section (lines 306-307):

Three recurrences occurred in Stage I or microinvasive tubal carcinomas[6,16,20]; the other cases were Stage II or III.

5. I have a hard time understanding the "IMPLICATIONS OF FINDINGS" section. Are you now introducing your own case report in this manuscript? I am not sure what this section is doing and maybe a side authors personal thoughts on microinvasive disease.

- **Response:** Thank you, please see the reply to comment number 6 of Reviewer One.

6. **The paper describes a significant rage of patients - stage I, StageIB, microinvasive disease and patients with STIC lesions. Please clean this up- the title states "Very early" diagnosis. The more I read the more confused I get as to what patients are you describing in the text. Stage IB patients and microinvasive patients as well as STIC patients are not going to get treated the same way. Also when having a stage IB lesion- were those patients staged- Are they truly Stage IB?**

- **Response:** As per response in point #3, we understand this concern and the answer can be found in table 1. Some of the initial cases were stage II or III at time of initial surgery and this was mentioned in the table and clarified in the text. The table also indicates all published data on the treatment the patients had received. In absence of treatment information, the authors of each paper were contacted and the information added when available. In order to be more precise, we have renamed “microinvasive tubal carcinoma” to “occult tubal carcinoma”.

7. Additionally- the description of the patient with microscopic disease on lines 252-256 makes no sense clinically. Why do you have microscopic disease at RRSO- then you state you gave her neoadjuvant chemotherapy. Why? Then you state you debulked a stage IB- what did you debulk? Or did you stage her and she was a stage IB after chemotherapy so you do not really know her stage? Please clarify this patient.

- **Response:** The case was removed from the main manuscript and placed as an addendum. The microscopic invasion was diagnosed after RRSO. The value of this case report is that if one assumes that early detection could improve outcome, one would never be able to find disease earlier than in this patient. Nevertheless,

she recurred despite the fact that she was treated with the best and most complete treatment we give to patients with stage IIIc disease. This suggests that finding high grade serous cancers even at the stage of only microinvasion does not change the outcome, at least in some cases.

8. In figure 3 can the authors comment on how many patients underwent surgical staging?

- **Response:** Figure 3 has now been removed (see other reviewers comments above)

9. The authors should review this data and comments with in the discussion- "What is currently understood is that STIC may be found in 80-100% of RRSO specimens but lead to malignant transformation in only 5-10% of cases, although it is possibly too embedded in tumor to isolate. Therefore, care should be taken to separating the tube and analyzing it in its entirety 31." In reviewing this paper I am not sure if the data to support that 80-100% of patients with RRSO who have a BRCA mutation will have a STIC lesion. This paper focused on evaluating patients with pelvic serous carcinoma and attempted to identify STIC lesions in the fimbria.

- **Response:** Thank you, we have removed this line, and have rearranged the results and discussion to better reflect the key findings of our paper. We have moved discussions on age, BRCA and previous breast cancer into the discussion section.

STATISTICAL EDITOR'S COMMENTS:

1. General and Abstract: **Should include CIs for (1) the prevalence of occult tubal ca, (2) the recurrence rate among that subset and (3) the prevalence of post-RRSO peritoneal ca, to put the risk and recurrences in context.**

-Response: Thank you we have now added confidence intervals to all the prevalence rates.
The abstract and results section now read:

> *After a pooled median follow-up of 52.45 months (range 12-150), 10 recurrences (18.7%, 95% CI 7.5-53%) and 24 cases of post-RRSO peritoneal cancer (0.54%, 95% CI 0.4-1.9%) were reported in 18 studies.*

2. Line 93: Should include range for the median of 17 months.
- **Response:** Thank you this was added to line 100 and reads as follows:

After a pooled median follow-up of 45.6 months (range 24-100), 10 recurrences (18.7%) and 24 cases of post-RRSO peritoneal cancer (0.54%) were reported in 18 studies.

3. Line 195: Should label the stats test as log-rank, rather than LR, lest it be confused with likelihood ratio. Should separately cite the median (range) follow-up for the BRCA1 and BRCA2 cohorts.
Response: We have removed figure 3 following the comments of the reviewers.

4. lines 200-201: Although each of these factors were associated with more frequent diagnosis of occult tubal ca, the overall number of cases in this series (86 out of 6425) does not appear sufficient to state whether these are independently associated with occult tubal ca. Is there data available to construct a Table for the 86 vs the remainder in terms of counts for advanced age, BRCA status,

previous breast ca and extensive sampling of the fimbriated end? It appears that the incidence of occult tubal ca (~ 1.3%) is low, and therefore the factors, although they may be statistically associated with dx of occult tubal ca, would not be useful in absolute terms for prediction of occult tubal ca. That is, the overall rates of 0/1605 for BRCA2 has a non-zero 95% CI upper bound of 0.23%, while the 13/2963 for BRCA1 had a rate o 0.43%, so there would be poor sensitivity to utilize BRCA status in an attempt to predict occult tubal ca.

-Response: Thank you for this analysis – this interpretation was based on qualitative analysis of the studies descripted in the discussion section, rather than a quantitative analysis for which we did not have sufficient data.

5. Fig 3: **Should include the N remaining at risk for the BRCA1 and BRCA2 patients at the time increments along the x-axis.**
We have now removed figure 3

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.: confirmed

3. As of January 1, 2020, authors of systematic reviews must prospectively register their study in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), an international database of prospectively registered systematic reviews. Please refer to the PROSPERO registration number in your submitted cover letter and include it at the end of the abstract.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250

words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.
-Total number of pages 22, word count 2 853

6. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.
- We have edited the title to comply to the character limitation

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

8. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.
- Systematic review of occult tubal carcinoma

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Reviews, 300 words. Please provide a word count.
-Abstract was double checked with results section. Abstract word count: 297

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of

an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.
-We have now reported confidence intervals everywhere appropriate.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.
-not applicable

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").
-done

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.
-done

14. The Journal's Production Editor had the following suggested changes for the figures in your manuscript

"Figure 1: Please upload as a figure file on Editorial Manager.
Figure 2: Please upload a high resolution figure file to Editorial Manager (eps, jpeg, tiff). Please add an in-text citation to this figure.
Response: We have done so- on line 447: Evaluation of complete papers yielded 27 that met criteria for quantitative analysis and were included in this systematic review (Figure 2).

Figure 3: Please upload a high resolution figure file to Editorial Manager (eps, jpeg, tiff)."

- We have removed this figure

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.