**Author’s response to reviews**

**Title:** Tubal Ligation and Endometrial Cancer Risk: A Global Systematic Review and Meta-Analysis

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**Author’s response to reviews:**

BCAN-D-18-01785R1
Tubal Ligation and Endometrial Cancer Risk: A Global Systematic Review and Meta-Analysis
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BMC Cancer

Dear Editor,
Thank you for your and reviewers comments regarding our manuscript (BCAN-D-18-01785R1). We tried to revise all comments in the manuscript.
Regards
Almasi-Hashiani Amir
Technical Comments:

Author contributions

- We note that two authors have the same initials (MS). To distinguish between them in the Authors’ Contributions section please designate them as MS1 and MS2, with MS1 corresponding to Mahdi Sepidarkish, chosen because this name is furthest up the author list.

It is right. MS1 stands for Mahdi Sepidarkish and MS2 for Maryam Shokrpour.

Declarations

- Please note that all manuscripts must contain all the following sections under the heading 'Declarations'. The Declarations should follow the Conclusions section, and be before the References.

All the following sections were included in the manuscript.

Abbreviations

Ethics approval and consent to participate

Consent for publication

Availability of data and material

Competing interests

Funding

Authors' contributions

Acknowledgements

PRISMA guidelines

- In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/submissions/editorial-policies#standards+of+reporting), could you please ensure your manuscript reporting adheres to PRISMA guidelines (http://www.prisma-statement.org/) for reporting systematic reviews. This is so your methodology can be fully evaluated and utilised. Can you please include a completed PRISMA checklist as an additional file when submitting your revised manuscript. Please complete the checklist in full by inserting the page number/paragraph and section of your manuscript which reports the information that meets the criteria of the checklist. For example, “Methods, paragraph 2”. If a criterion is not applicable for your particular manuscript/study, we can accept “N/A”. Please note that checklists completed incorrectly will be returned for revision as we cannot progress your manuscript to peer review until the checklist has been completed.

The revised version of PRISMA was prepared.

Editor Comments:

Reviewer reports:

Shailesh Advani, MD, PhD (Reviewer 1): Abstract:

Needs scientific editing throughout.

a) Give brief idea of previous results in abstract. A systematic review and meta-analysis was performed…

We add a brief idea regarding previous results.

b) Results: Summarize the entire search strategy. What was the Cohen-s Kappa for interrater reliability? Why was random effects model not used? What were I2 values of heterogeneity?

We added a summary of search process in the results.

The percent agreement was reported in the abstract and main body of manuscript.

We used random effect model because of heterogeneity. It was revised.

The I2 values of heterogeneity were reported in Table 2, and also the overall I2 was added to the abstract.
c) Why was first 8 studies pooled than 10? How many studies were used to measure adjusted ORs? What factors did these studies adjust for?
We find ten related studies but the raw data were reported just in eight studies and also the adjusted OR was reported in eight studies. We pooled these studies separately. And in an analysis, we pooled crude and adjusted ORs together which include all ten studies. The adjusted factors for each study were reported in Table 2 in detail.

Background:
a) Lines 1 and 2: are these statistics for all cancers or Endometrial cancer?
These statistics are for all cancers. It was clarified.
b) In accordance with the report, endometrial cancer is the most frequent gynecological malignancy and the sixth most frequent malignancy among women in the world and its incidence is increasing—Seems contraindicating: When you state that it is most frequent gynecology malignancy, how can it be 6th?
Endometrial cancer among women is the sixth most frequent malignancy and also it is most frequent gynecological malignancy (Which only includes woman's reproductive tract cancers).
c) Combine paragraphs 1 and 2
It was done.
d) With no metastatic……u mean no metastases?
It was revised.
e) Primary prevention of this disease should be a priority, since part of the new cancer cases can be prevented- Please expand. This does not give clear idea of the message. Plus provide references.
It was a general idea regarding all cancers that primary prevention can reduce the new cases of cancers. Because it was a general idea that was not only related to endometrial cancer, it was removed.
f) Lines 71-73: Need clarification.
It was revised.
g) There seems to be no background on TL and Endometrial cancer, Add these Statistics of TL: do these match with rates of Endometrial Cancer.
We added some statistics regarding prevalence of TL in the US and worldwide and also we revised and provided some evidences concerning the link of TL and endometrial cancer.
i) Need scientific editing throughout
It was done.

Methods and Results:
a) What was the start date of search?
It was revised. As stated in the manuscript, the start date of search was May 30, 2018.
b) Who did the search? Please elaborate.
The search was performed by the corresponding author and it was checked by an epidemiologist (MS1).
c) Was an interrater reliability test done? Describe in detail
The percent agreement between the two researchers was calculated in this study and it was added to the manuscript.
d) These data were entered into the Excel software for preparation and cleaning and finally they entered into the Stata software for meta-analysis.--- They entered?
It was revised.
e) Describe in more detail the demographic characteristics of studies included. Add a paragraph.
The needed items were added to the manuscript.
f) Line 151: Report I2
It was reported.
g) Line 152: Give refs for 2 studies
They were added.
h) Line 152-153: Provide reference and basis for same
It was done.
i) Line 156: provide I²
It was done.
j) How many studies reported adjusted odds ratio? References needed
Eight studies. Their references were added to the manuscript.
k) Add I² everywhere with ORs and 95% CI.
It was added.
l) In methods: describe steps involved in meta-regression. How was bias assessed using meta-regression? Outputs needed in form of tables if possible.
It was added to the methods and the output was reported in the results section but not in the form of tables.
m) Show Newcastle Ottawa scale output as figures
It was done for both case control and cohort study separately.
n) In tables: add country from which study was conducted.
The name of countries was added to Table 1.

Discussion:

a) The results of the current systematic review and meta-analysis suggest that tubal ligation is related with significantly reduced risk of endometrial cancer by approximately 14-42%—Consider rephrasing, as this was based on 3 different meta-analysis, and one effect size is important. Please consider which should the readers follow.
We focused on the main results of meta analysis and the results of adjusted analysis was considered as an additional analysis.

b) In results: especially when including adjusted analysis, describe what factors were your study results adjusted for.
We added this issue to the discussion that “In case of adjusted analysis, it should be noted that the results of the studies were adjusted for various confounder variables; the list of these variables for each study is shown in Table 1.”

c) Line 221: How were these year periods defined? Based on??
We placed the published studies in the last 10 years (which were relatively new) in one group and the other studies in the second group. Also, for us, the number of studies in each group was also important and we tried to have enough articles in each category. And also, in the sample size, we divide the studies in two groups, less or more than median.
d) Metaregression: Why not try and assess if age was a main source by doing subgroup analysis based on age group inclusion.
This is a very interesting idea, but because of the overlap between studies in terms of age, and because most studies were similar in age, it is not possible to divide them into two age groups. Therefore, we were not able to perform sub-group analyzes based on age groups.

Reviewer 2 (Reviewer 2):
PEER REVIEWER ASSESSMENTS:
OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective.
Thank you for your confirmation.

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
No - there are major issues.
We revised the manuscript based on the reviewer comments. And it should be noted that in design and report the results of this systematic review and meta-analysis, we followed the standard guideline of “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” and the Cochrane Handbook for Systematic Reviews of Interventions.

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
No - there are minor issues
We revised the manuscript based on the reviewer comments.

STATISTICS - Is the use of statistics in the manuscript appropriate?
Yes - appropriate statistical analyses have been used in the study.
Thank you for your confirmation.

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
No - there are minor issues
We revised the manuscript based on the reviewer comments.

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Maybe - with major revisions.
We completely revised the manuscript based on the two reviewers and also editorial comments.

PEER REVIEWER COMMENTS:

GENERAL COMMENTS:
The quality of information provided is adequate and could be interesting for the researchers and stimulate further investigation.
Thank you for your confirmation.

Despite the statistical analysis is accurate, I have some concerns about the inclusion/exclusion criteria that should be cleared by the authors (conversely, the data analysis would not allow to a firm conclusion about the main questions of the study).
In method, we clarified that, any kind of tubal ligation including mono-lateral or bi-lateral salpingectomy, tubal coagulation with or without cut, tubal ligation by stitches with or without cut were included in the meta-analysis.
In particular, authors should declare whether they included women who underwent monolater/bilateral salpingectomy, tubal coagulation with/without cut, tubal ligation by stitches with/without cut? It is clear that these represent six different conditions and should not be evaluated in the same analysis (authors should perform *at least* a subanalysis).
This is quite true, since the kind of tubal ligation was not specified in the included studies and was not included in the separate analysis; there was no possibility for sub-group analysis. This issue was added to the discussion as study limitation.

In addition, authors did not declare whether their work followed the Cochrane Handbook for Systematic Reviews of Interventions. Since the Cochrane Handbook is the main source of design and conduct meta-analysis studies, authors of the study also followed this Handbook. Therefore, we revised the manuscript as: “In this systematic review and meta-analysis, we followed the standard guideline of “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” and the “Cochrane Handbook for Systematic Reviews of Interventions”.

Finally, it is not clear why authors did not register their work in PROSPERO database before to start the search. Unfortunately, we did not register in the PROSPERO previously, and we tried to register now, but this possibility was not available on this site to retrospectively register.

REQUESTED REVISIONS:
I hereby list the most important points to address:
- All the text needs a careful review by an English native speaker, in order to correct grammar and improve style.
  The manuscript was edited by an English native speaker.

- In the pdf I received for evaluation, line numbers were doubled (probably ones were added by authors before submission, the others were added by the submission system during the pdf creation). We removed the line number to avoid duplication in the manuscript.
- When citing other groups, authors should use "Surname et al. [x]" without the indication of the name of the first author (until it is not directly suggested by the guidelines for authors of the Journal). It was revised in all cases.
- Introduction: authors should discuss, at least briefly, the current knowledge about the role of salpingectomy to decrease the risk of epithelial ovarian cancer. They may refer to: PMID: 30913193; PMID: 26513872.

Thank you for your suggestion. We added a paragraph regarding the role of salpingectomy to decrease the risk of epithelial ovarian cancer and referred to PMID: 30913193.

- Methods: did author follow the Cochrane Handbook for Systematic Reviews of Interventions, beside the PRISMA? If they did not, they should explain why.
  Since the Cochrane Handbook is the main source of design and conduct meta-analysis studies, authors of the study also followed this Handbook. Therefore, we revised the manuscript as: “In this systematic review and meta-analysis, we followed the standard guideline of “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” and the “Cochrane Handbook for Systematic Reviews of Interventions”.

- Methods: inclusion/exclusion criteria are absolutely not clear. Did authors include women who underwent monolater/bilateral salpingectomy, tubal coagulation with/without cut, tubal ligation by stitches with/without cut? It is clear that these represent six different conditions and should not be evaluated in the same analysis (authors should perform *at least* a subanalysis).

  This is quite true, since the kind of tubal ligation was not specified in the included studies and was not included in the separate analysis; there was no possibility for sub-group analysis. This issue was added to the discussion as study limitation.
Methods: did author register the systematic review and meta-analysis on PROSPERO? If they did not, they should explain why.
Unfortunately, we did not register in the PROSPERO previously, and we tried to register now, but this possibility was not available on this site to retrospectively register.

Discussion: authors should stress, at least briefly, the current management of endometrial cancers, especially in early stages in women of reproductive age, referring to: PMID: 28188573; PMID: 29544706; PMID: 28108938.
We revised the manuscript and added a paragraph regarding the fertility management of endometrial cancers.

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Editorial Policies
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For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must state that data will not be shared, and provide reasons for this in the manuscript text. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page - http://www.biomedcentral.com/submissions/editorial-policies#availability+of+data+and+materials.

All the following sections were included in the manuscript.

Declarations
- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions

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