Author's response to reviews

Title: Is Prior Oral Contraceptive Use Associated with Improved Survival in Ovarian Cancer Patients?

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Version: 3
Date: 23 July 2015

Author's response to reviews: see over
July 22, 2015

Professor Sophie F. Derchain  
Editorial Offices  
BMC Cancer

RE: Is Prior Oral Contraceptive Use Associated with Improved Survival in Ovarian Cancer Patients? (now re-entitled)

Dear Professor Derchain,

Thank you for your recent review of our manuscript, as referenced above.

We are grateful for the thoughtful comments from both reviewers and have done our best to revise the manuscript based on their comments. Changes to the manuscript are highlighted in yellow.

Below please find a point-by-point response to each comment.

Reviewer: Salma Butt

COMMENT: This is a manuscript of great scientific importance and the aim and conclusion is of great interest.

REPLY: Thank you for this comment.

COMMENT: The title is stated as a question. I personally like titles with questions however the use of these on research papers gives a somewhat populistic impression. Consider revising.

REPLY: Based on this comment, we have now changed the title.

COMMENT: The abstract starts with stating the aim instead of information on background. Moreover, the aim is stated in a very long sentence that could be somewhat difficult to comprehend. Consider revising.

REPLY: We have made these changes, as suggested.

COMMENT: The Methods in the abstract is described in past tense. Consider revising.

REPLY: Although we had tried to change the tense, the manuscript ended up sounding very awkward in its wording. For this reason, we have not revised the manuscript along these lines. If the editor wishes us to truly make this change, we will remain receptive to revising further.
COMMENT: Background - in second paragraph, line 65, a referral to another research group is done and then the results are discussed. Consider saving that discussion to the discussion part. The same comment for the next paragraph starting on line 79.

REPLY: We have now shifted this information to the discussion section of the manuscript.

COMMENT: Line 93, "Our main goal...", consider revising to "aim".

REPLY: Thank you -- change made.

COMMENT: Methods - what is the background to inclusion of peritoneal cancer with epithelial ovarian and fallopian tube cancer? Please explain in the manuscript.

REPLY: We apologize for the omission and have revised the manuscript to now include this rationale.

COMMENT: Study endpoints - this paragraph is a bit difficult to understand. What does "/.../external medical record review /.../ mean? Where were the death-certificates retrieved from?

REPLY: Thank you -- we have now revised the manuscript to provide further clarity.

COMMENT: Line 117, consider revising the word "examined" to "studied"/"analysed".

REPLY: Done.

COMMENT: Definition of covariates - the grouping within the parous women, please explain if women with one and two children were included in the same group in order to gain statistical power or for some other reason.

REPLY: We have now clarified.

COMMENT: Analyses - please do explain left truncation in the methods section in order to make it clearer for the reader why this method was used.

REPLY: We have now done this – thank you!

COMMENT: Please explain why the multivariate models were constructed as they were -and please do discuss limitations under discussion.

REPLY: We have now done this.

COMMENT: Results - very clearly written.

REPLY: We are grateful for this favorable comment.
COMMENT: Conclusions - revise title to Discussion. Add more discussion about the former studies (that are approached in the background of the manuscript) and discuss limitations of the multivariate analyses.

REPLY: We appreciate this guidance; our revised manuscript reflects the above.

COMMENT: Tables - Table 1 - very easy to follow. Table 2 - easy to follow, however then on-significant data should also be published. Consider adding in an appendix table.

REPLY: We apologize but we are having some trouble in understanding what is being requested here. We have provided all data in these 2 tables.

COMMENT: Figures - add box explaining what the different lines represent. Change the title on Y-axis to overall survival and progression-free survival. The figure legends should not add more statistical results. Revise.

REPLY: We have made these changes. Please note that the figure legends are only explaining what is in the figure and that the results are already described in the manuscript.

COMMENT: Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I have no competing interests.

REPLY: We appreciate the above.

Reviewer: Patricia Moorman

COMMENT: Lines 66-67 - This statement is contradictory and doesn’t make sense as written “… previous OC use was associated with a lower risk of death within three years of cancer diagnosis (five-year increase in relative risk 0.69…”

REPLY: Thank you. We have revised this line by deleting the “three years” portion of the sentence.

COMMENT: The description of the previous studies on oral contraceptive use and ovarian cancer mortality needs to make a distinction between the study designs used and hence the interpretation of the findings. For example, Hannaford, et al. and Vessey et al. used a cohort design of OC users and non-users and then looked at the outcome of death from ovarian cancer. In contrast, the Nagle study was a cohort of women with ovarian cancer and looked at the survival experience of
cancer patients who were OC users and cancer patients who were OC non-users. In the former study design, the lower ovarian cancer mortality among OC users could reflect both lower incidence of ovarian cancer and improved survival after diagnosis, whereas the latter study design only addresses survival after diagnosis. The statement made in line 75 that these studies (Hannaford, Vessey, Collaborative Group) reported “decreased overall mortality among ovarian cancer patients who had used oral contraceptives prior to their cancer diagnosis” implies the comparison group is ovarian cancer patients who had not used oral contraceptives and does not accurately reflect the study design used. The discussion of the studies of ovarian cancer mortality related to OC use needs to more precisely describe the findings taking into account the different study designs used and acknowledge that the inconsistency in findings between the Nagle study and the other studies could be due to the study designs addressing slightly different research questions. Finally, the Hannaford paper that is referenced (ref 5) addresses ovarian cancer risk, not mortality. The more appropriate reference would be Hannaford’s 2010 BMJ paper “Mortality among contraceptive pill users…”

REPLY: Thank you for all these insightful comments; we have made changes as directed above.

COMMENT: The rationale for censoring follow-up at five years for those with unknown vital status (line 119) needs to be described. If vital status was known at some point beyond 5 years, why would that patient be censored at 5 years?

REPLY: We apologize for omitting this rationale from the paper and have now included it in the revised manuscript.

COMMENT: Related to comment 3 above regarding censoring at five years, line 174 describes the number of deaths and recurrences that had occurred to date. Follow-up time for the cohort apparently ranged from 1 to 14 years, yet the survival curves only depict outcomes through 60 months. This needs to be explained.

REPLY: We apologize for the confusion. We censored at 5 years and for this reason, our survival curves go to 60 months. Please tell us if the manuscript remains unclear on this point, and we are happy to revise further.

COMMENT: Although the statement in lines 201-202 that the protective association was observed in univariate analysis is true, it is misleading because the univariate analysis does not take into account the obvious confounding by age and possibly other factors such as debulking status and receipt of chemotherapy.

REPLY: This reviewer raises an important point. We believe it is understood that a univariate analysis is not adjusting for other confounded, but, given this reviewer’s perspicuous comment directly above, we have stated this assumption clearly in the revised version of the manuscript.

COMMENT: Another limitation of the study that should be mentioned is that there
apparently was no information regarding what age or how recently OCs were used. If there is in fact an association between OC use and ovarian cancer survival, the timing of OC use would likely have an important impact on the strength of the association.

REPLY: This is a good point. We have now described this limitation in the revised manuscript.

COMMENT: The figure legends report large differences in the number of OC users (793 in Figure 1 and 700 in Figure 2) suggesting that different populations were used in these univariate analyses. An explanation should be included of why some women were excluded from the univariate progression-free survival analyses as compared to the overall survival group.

REPLY: Yes, this is an important point, and we have now revised the manuscript to explain that all data were not available for all patients. In essence, some patients were followed only for vital status and not for disease status.

COMMENT: Minor Essential Revisions. References are needed for several statements made in the introduction including line 49 (effect of OCs in BRCA carriers) and lines 49-52 (mechanisms related to continuous ovulation).

REPLY: We have added more references to substantiate these comments.

COMMENT: The statement in lines 52-54 about numbers of ovarian cancer cases and deaths that could be prevented is not accurate – the numbers are not for the US, but for the world.

REPLY: We appreciate that this reviewer picked up this error and have corrected this.

COMMENT: It would be useful to describe the completeness of vital status ascertainment.

REPLY: We believe we have done this under “study endpoints” but would be happy to expound further if provided with further direction on how to do so.

COMMENT: What was the rationale for using 48 months as the cutpoint for OC use categories?

REPLY: We used the 48 month cutoff because numerous other questionnaires that reported on oral contraceptive use had used a similar cut off.

COMMENT: Please clarify if the 656 recurrences include some or all of the deceased patients.

REPLY: Thank you for the question. The 656 events include both deaths and recurrences. We have provided more clarity in the revised manuscript.

COMMENT: Statements such as “the more numerous the DNA mutations, the more aggressive the cancer” need to be supported with appropriate references.

REPLY: Thank you; we have now provided a reference.
COMMENT: The figures should include a legend that indicates that the solid lines are OC users and the dotted lines are OC non-users.

REPLY: Done.

COMMENT: Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

REPLY: We appreciate the comments above.

Finally, although the reviewer immediately above considered the quality of our written manuscript as acceptable, the first reviewer suggested some editing. We have edited the manuscript in areas to improve readability.

In summary, we are most grateful for all the comments from the reviewers. We hope that the extensive editing to our manuscript will enable it to be published in your journal.

Sincerely,

Aminah Jatoi, M.D.