Author’s response to reviews

Title: Prophylactic salpingo-oophorectomy: a meta-analysis on ovarian cancer risk and all cause mortality

Authors:

Claudia Marchetti (clamarchetti@libero.it)
Francesca De Felice (fradefelice@hotmail.it)
Innocenza Palaia (innocenza.palaia@uniroma1.it)
Giorgia Perniola (claudia.marchetti@uniroma1.it)
Daniela Musio (daniela.musio@libero.it)
Ludovico Muzii (ludovico.muzii@uniroma1.it)
Vincenzo Tombolini (vincenzo.tombolini@uniroma1.it)
Pierluigi Benedetti Panici (pierluigi.benedetti@uniroma1.it)

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Author’s response to reviews: see over
Manuscript Submission: Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers

Dear Editor,

Thank you for considering our manuscript for publication in “BMC Women’s Health”. We have really appreciated the suggestions and corrections made by the Editor and by the two reviewers and we have modified the paper consequently. We are convinced that with the modifications recommended the paper has been significantly improved and we strongly hope it will be considered for publication in your Journal. Please find enclosed a revised version of the manuscript, modified on the basis of the reviewers criticisms, and a point-to-point reply to reviewers comments. Thanks again for your availability and consideration.

Yours Sincerely,

Claudia Marchetti
Department of Gynecological and Obstetrical Sciences and Urological Sciences, University of Rome “Sapienza”, Viale del Policlinico, 155 - 00161 - Rome - Italy
E-mail: clamarchetti@libero.it
Tel.: + 39-3384652744
Fax.: + 39-0649972564
Response to reviewers

LEGEND:
RC: REVIEWER’S COMMENT
AR: AUTHOR RESPONSE

REVIEWER 1.

Dear reviewer,
thank you for your precious suggestions needed to improve our manuscript.
We have corrected it accordingly with your suggestions as follows:

Reviewer #1:
Major Compulsory Revisions
RC: My major concern about this manuscript is whether it actually contributes
anything new to our understanding of the effects of PSO in women with BRCA
mutations. The results of the meta-analysis published by Rebbeck, et al in 2009
are very similar to this and I can’t see that the results of this paper are any more
robust than those published in that previous meta-analysis. In my view the type
of study design is not in itself a guarantee of research quality. I think the authors
need to present a much strong

AR: We thanks the reviewer for this comment. In our view our meta-analysis has seve ral differences
and improvement compared with that by Rebbeck et al.. Firstly, the number of patients has
significantly raised (from 2840 to 9192), giving more power to final conclusions. Secondly, they do
not analyze the overall mortality risk reducing, that is of great interest in the light of controversial
data recently published which suggest that RRSO in women younger than age 45 may be associated
with an increased mortality. Finally we try to identify the ovarian cancer risk reduction accordingly
with specific BRCA1 or BRCA2 mutation We clarify this on the text.

Minor Essential Revisions
RC: Title. I think the fact that the meta-analysis includes studies of women with BRCA
mutations should be mentioned in the title.
AR: We have modified the title accordingly

RC: Methods: I found the use of some terminology confusing. The studies included in this
meta-analysis seem to be prospective cohort studies but they are consistently referred to as
trials. Trials would generally involve an intervention being imposed by the investigators but
this is not the case in these studies. Additionally, the participants in the studies are not cases
and controls but rather women who have been exposed (to PSO) or not exposed.
AR: We have modified the paper accordingly

RC: Methods: The last sentence of the third paragraph states that “Update information on
survival and date of last follow-up were requested.” Does this mean that
additional information (unpublished) was obtained/sought from the authors of the included studies?
AR: We thank the reviewer for this comment. We don't consider unpublished data. The sentence has been removed

RC: Methods: The boxes on the forest plots represent the weight that the study contributes to the meta-analysis, not the confidence interval. The confidence interval is represented by the horizontal line that goes through the box
AR: We thank the reviewer for this comment. We correct the paper accordingly

RC Results: It would be useful if the studies mentioned from the third sentence on in the first paragraph were referenced.
AR: References have been added.

RC Results: As well as the hazard ratios it would be informative to see the actual number of events in each group. This sort of information can be useful for both women and their health care providers in decision making.
AR: We agree with this observation. Nonetheless the absolute number of patients were no published in each article, differently from HR; therefore we prefer to not mentioned

RC: Results: The HR for ovarian cancer in the BRCA1 group was 0.20 and the HR in the BRCA2 group was 0.21, i.e., essentially identical, so to say that there was no benefit in the BRCA2 group seems odd. In fact, biologically speaking, it would be expected that PSO would prevent ovarian cancer in women with BRCA2 mutations. The association was not statistically significant but this relates to the much smaller numbers of women with BRCA2 mutations and perhaps the smaller number of events. In the discussion, the effect of PSO among the BRCA1 women is described as being larger than that in the BRCA2 women. There is no evidence that the effect is larger in BRCA1 women. These results in fact suggest that the effect in the two groups may be very similar.
AR: We thank the reviewer observation. Nonetheless in our point of view, the broader confidence interval of the cancer risk reduction in BRCA2 patients suggests a less convincing evidence of reduction. Nonetheless we agree that this may be due to the smaller numbers of patients, therefore we modified the text in order to not assume incorrect deductions.

RC: Discussion: A reference should be provided at the end of the first paragraph of the discussion. Is the role of PSO in reducing risk in women with BRCA mutations still debated or is it the role of PSO in women without an elevated risk of ovarian cancer that is debated?
AR: We added references

Discretionary Revisions
RE: I would suggest providing a reference for the statement that significant heterogeneity is indicated by an I2 >50%; or at least a justification for using the 50% figure.
AR: A reference has been added

RC: If women have both their ovaries and fallopian tubes removed and they are microscopically normal, how do they subsequently develop ovarian cancer? Are the women actually developing primary peritoneal cancer? Should this be clarified in the paper?
AR: This topic is of great interest. Nonetheless in the majority of studies it is not specified and several authors describe incidence of ovarian and primary peritoneal cancer, without distinction.
We modified the title and the text of the manuscript, from “RRSO of ovarian cancer” to “RRSO of ovarian, tubal and primary peritoneal cancer in order to homogenize results.

ER: I would recommend that this paper be revised by an English language editor.
AR: the paper has been revised by a native English speaker

RC: Table 1 would benefit from the addition of information about where the studies were conducted and the numbers of events observed in the exposed and unexposed groups. Is the follow-up time mean or median years of follow-up?
AR: Table has been modified accordingly

EC: Some discussion of the relatively short period of follow-up might be beneficial as well. Do we know anything specifically about how these women do in the longer-term (10-20 years) given that the relatively young age at PSO?
AR: A sentence has been added

REVIEWER 2.

Dear reviewer,

thank you for your precious comments and requests needed to improve our manuscript. We have corrected it according your indications as follows:

Reviewer #2:

RC Replacement of word study (for e.g. in abstract) by meta-analysis
AR: As you suggest we modified the paper accordingly

RC The primary end-point used was the risk of developing OC. It needs to be clarified as to how occult cancers that were detected at surgery were dealt with – were these excluded or were prevalent cancers included in the risk reduction calculation
AR: We clarified this issue in the text.

RC: Important to clarify that the outcome measure is not primary ovarian but primary ovarian, tubal and peritoneal cancer. This is what has been included correctly in the statistics though the outcome measure has not been described.
AC: We modified the text accordingly

RC Reference 5 and 14 are the same.
AC: We modified the text accordingly

Discretionary Revisions
RC: Would suggest use of risk reducing rather than prophylactic salpingo-oopherectomy as the former better describes what can be achieved and reflects the growing understanding of ovarian cancer origins. Words like
prevention/prophylactic tend to over exaggerate the impact and set unrealistic expectations in patients, the lay public and nonspecialist clinicians.

AC: As suggested by the reviewer we modified the text accordingly

RC: PSO is not an abbreviation that is in use and would suggest it is replaced by more common abbreviations such as RRSO or prophylactic BSO (bilateral salpingo-oopherectomy), if authors wish to persist with use of the term prophylactic salpingo-oopherectomy.

AC: As suggested by the reviewer we modified the text accordingly

RC: The title does not describe what was done - would suggest ‘- a meta-analysis on impact on ovarian cancer risk and all-cause mortality’ or some variation of this.

AC: As suggested by the reviewer we modified the title accordingly