Reviewer's report

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

Version: 1 Date: 1 September 2014

Reviewer: Susan Jordan

Reviewer's report:

Major Compulsory Revisions
1. 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 stronger case for the rationale for this meta-analysis.

Minor Essential Revisions

Title
1. I think the fact that the meta-analysis includes studies of women with BRCA mutations should be mentioned in the title.

Methods:
2. 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.

3. 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 Does this mean that additional information (unpublished) was obtained/sought from the authors of the included studies?

4. 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.

Results
5. It would be useful if the studies mentioned from the third sentence on in the first paragraph were referenced.

6. 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.
7. 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.

Discussion

8. 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?

Discretionary Revisions

1. 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.

2. 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?

3. I would recommend that this paper be revised by an English language editor.

4. 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?

5. 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?

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 declare that I have no competing interests