Author’s response to reviews

Title: Statin use and the risk of ovarian and endometrial cancers: A meta-analysis

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Dear Linda Gummlich, PhD

Editor BMC Cancer

Thank you very much for your comments and suggestions on improving our manuscript “Statin use and the risk of ovarian and endometrial cancers: A meta-analysis”. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made corrections which we hope meet with approval.

We highlighted the explanatory portions by marking in blue typein the manuscript. The main corrections based on reviewers in the paper and the responds to the editorial requirements are as follows:
Reviewer reports:

Ayelet Shai (Reviewer 1): This version of the manuscript is much better than the initial one.

Several comments:

1. There is still confusion as to the definition of "study population". To my understanding this is the entire population of women recruited to a certain trial, and the endpoint is incidence of ovarian/endometrial cancer. For example lines number 117, 165.

   Reply: Thanks for your kind suggestion. We are sorry for not clear statement. Yes, just as you said, population refers to the entire population of women recruited to a certain trial, and the endpoint is incidence of ovarian or endometrial cancer. And we also revise the manuscript as follows: “population: the entire population of women recruited to a certain trial, and the endpoint is incidence of ovarian or endometrial cancer.” These can be viewed in the methods section, line 118, page 6.

2. Line 126 - how can the authors be sure that patients in all the studies are not taking additional medications? In fact, it is likely (and stated in at least some of the trials) that many other medications were co administered. The authors should refer to this limitation of their study.

   Reply: Thanks for your kind suggestion. We agree with your suggestion totally that in some of the trials, other medications were co administered. When we analysed the studies we searched, we found that most of the patients who used statin were complicated with metabolic syndrome or cardiovascular disease. There were many menopausal women as well. In the selected studies, some other medications were administered such as antidiabetic medication, oral contraceptives or hormone drugs. As the studies can contribute a lot to the result of our meta-analysis, we can’t exclude these important studies. But as the other medication may be associated with the risk of cancer, for example, the use of metformin or oral contraceptives may lower the risk of gynecologic cancer, and hormone replacement therapy may influence the risk of gynecologic cancer, there was the possibility that our results had bias, which could be of concern. Hence, to confirm the conclusions of this meta-analysis, further RCTs enrolling larger populations to investigate the association between statin use and the risk of ovarian or endometrial cancer are needed.

   We are very grateful for your help in pointing out the deficiency, and we revise the exclusion criteria as follows: “(2) intervention: patients did not use statins;” These can be viewed in the methods section, line 128, page 6. And we also add the discussion in the limitation section: “Moreover, in some studies, patients were prescribed other medications in addition to statins. As other medications may be associated with the risk of cancer, for example, the use of metformin or oral contraceptives may lower the risk of gynecologic cancer [47, 48], and hormone
replacement therapy may influence the risk of gynecologic cancer [49], there was the possibility that our results had bias, which could be of concern. Hence, to confirm the conclusions of this meta-analysis, further RCTs enrolling larger populations to investigate the association between statin use and the risk of ovarian or endometrial cancer are needed.” These can be viewed in the discussion section, line 312, page 14.

We are very grateful for your help in improving the manuscript.

3. Line 346 - the discussion regarding interaction between statin use and metabolic syndrome is important and should be placed before the statistical discussion.

Reply: Thanks for your kind suggestion. We agree with your suggestion totally that the discussion regarding interaction between statin use and metabolic syndrome is important. So according to your advice, we placed this discussion before the statistical discussion. Now it is the first part of the discussion about limitation, which can be viewed in the discussion section, line 309, page 14.

5. The study by Lavie et al is a case-control trial, this is not stated or discussed.

Reply: Thanks for your kind suggestion. We agree with your suggestion totally. The study by Lavie et al is a case-control trial that all study participants (patients and controls) had similar basic health insurance plan and similar access to health services. Controls were individually matched to cases according to the year of birth, residence as defined by primary clinic location, and ethnic group. Therefore, the study excluded many confounding factors, which might lead to a more reliable result. We should take it into account seriously. According to your advice, we revise the manuscript as follows: “Among the included observational studies, the study by Lavie et al. [36] is a case-control trial in which controls were individually matched to cases according to age, sex, clinic and ethnic group. Therefore, the study excluded many confounding factors, which might lead to a more reliable result. As it has been reported that statin use could reduce the risk of endometrial and ovarian cancers, we cannot ignore the important finding. Although our pooled analysis was negative, the majority of the studies we included were retrospective, which may contain selection, information, and confounding bias. More RCTs or high-quality observational studies are needed to confirm or update our meta-analysis.” These can be viewed in the discussion section, line 322, page 14.

4. The manuscript needs language edition.
Reply: Thanks for your kind suggestion. We have made our manuscript edited by a professional English language editing company (American Journal Experts https://www.aje.cn/) and we have the certificate offered by the company.

Alan Richardson (Reviewer 2): The manuscript is now significantly improved.

Reply: We thank you for your kind and professional comment sincerely.

Research Square (Reviewer 3): "STATISTICAL REVIEWER ASSESSMENT:

Is the study design appropriate for the research question (considering whether the analyzed population accurately reflects the design and whether you see any problems with control/comparison groups, e.g., likely confounders)?

Yes - overall design, population, and control groups are appropriate

Are methodologies adequate and well implemented (considering whether assumptions are addressed and whether analyses are robust)?

Yes - methodologies are adequate and well implemented, assumptions are addressed, analysis is robust

Are the analyses adequately communicated (considering whether reporting details are adequate and whether figures and tables are well labeled and described)?

Yes - important reporting details are present, analyses are adequately communicated, figures and tables are well labeled and described

Does the interpretation accurately reflect the analyses without overstatement (considering whether limitations/bias are acknowledged and whether accurate descriptors, e.g., 'significant', are used)?

Yes - interpretation accurately reflects analyses, limitations/bias are acknowledged, accurate descriptors are used
Could an appropriately REVISED version of this work represent a statistically sound contribution?

Yes - current version has sound statistics

STATISTICAL REVIEWER COMMENTS:

The authors have addressed my statistical analysis concerns. The study was well conducted and the manuscript is easy to read.

REQUESTED REVISIONS:

No further revisions needed.

ADDITIONAL REQUESTS/SUGGESTIONS:

None.

Reply: We thank you for your kind and professional comment sincerely.

References


