Author’s response to reviews

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

Authors:

Yizi Wang (wangyz3@sj-hospital.org)
Fang Ren (renf@sj-hospital.org)
Zixuan Song (songzixuan666@163.com)
Peng Chen (joyboy125@163.com)
Shuang Liu (fkzliushuang@126.com)
Ling Ouyang (ouyl@sj-hospital.org)

Version: 1 Date: 13 Jun 2019

Author’s response to reviews:

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

Dear Anne Menard

Editorial Board 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 type in the manuscript. The main corrections based on reviewers in the paper and the responds to the editorial requirements are as follows: 
Editor Comments:

1. Please note, the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared in the Funding section.

Reply: Thanks for your kind suggestion. According to your advice, we have noted in the Funding section that “The project was supported by National Natural Science Foundation of China (Grant number 81501235). The funding body had no role in the design of the study, collection, analysis, or interpretation of the data, or in the writing of the manuscript.” These can be viewed in the Funding section, line 385, page 17.

Reviewer reports:

Ayelet Shai (Reviewer 1):

1. Methods - it is unclear how many authors reviewed abstracts for inclusion. It is unclear whether studies looked at the incidence of epithelial OC only or other types as well and if borderline malignancies were included. There is no definition for "endocrine related malignancies". It would be better to simply address Ovarian and Endometrial cancer.

Reply: Thanks for your kind suggestion. According to your advice, we stated the authors who reviewed abstracts for inclusion and the types of ovarian cancer included in our manuscript. We revise the manuscript as follows:

“Two reviewers (YW and FR) reviewed and assessed each of the included studies. Data extraction was performed independently. The other authors (ZS, PC, and SL) reviewed the included studies as well for inclusion.” These can be viewed in the methods section, line 132, page 6.

The studies looked at the incidence of any histologic types of cancer, including ovarian borderline malignancies. We revise the manuscript as follows: “Studies were selected according to PICOS (population, intervention, comparison, outcomes, and study design) guidelines if they met the following inclusion criteria: (1) population: patients had ovarian or endometrial cancers. Any histologic types of cancer were included for ovarian and endometrial cancers, including ovarian borderline malignancies;” These can be viewed in the methods section, line 117, page 6.

And we are pleased to accept your advice that as the “endocrine related malignancies” is not defined, we revised the title and all the content, which simply addressed ovarian and endometrial cancers.
2. Studies included - the study by Rennert et al looked at bisphosphonate use and risk of OC and EC. Moreover, the population in this study is identical to the population of the study by Lavie et al. The study by Kabat et al looked at serum lipids and risk of cancer.

Reply: Thanks for your kind suggestion. The study by Rennert et al looked at bisphosphonate use and risk of OC and EC, and the study by Kabat et al looked at serum lipids and risk of cancer, but the studies also reported the number of patients that use statin and the incident of ovarian or endometrial cancer, from which we could extract the RR estimates as well.

However, we agree with your suggestion totally that the population the study by Rennert et al is identical to the population of the study by Lavie et al. According to your advice, we have removed the study by Rennert et al from our meta-analysis.

3. Studies done in Asia - no reference is given to these studies, and it appears that the 2 studies from Israel and 1 from China are those 3 studies. Israeli population is more similar to European population than Chinese population, and moreover one of the studies from Israel should be omitted from the analysis.

Reply: Thanks for your kind suggestion. According to your advice, we have labeled the references for each study location. We revise the manuscript as follows: “The studies were carried out in eight countries, which included North America [12, 13, 26, 27, 29, 30, 32, 34, 39, 40], Europe [14, 15, 28, 31, 33, 35, 36, 38], and Asia [37].” These can be viewed in the results section, line 167, page 8.

And we agree with your suggestion totally. Although Israel was next to Asia geographically, Israeli population is more similar to European. So we put Israel in the European group. At the same time, we have removed one of the studies from Israel (the study by Rennert et al) from our meta-analysis.

4. Tables - percentage of cancer cases should be noted in table 1

Reply: Thanks for your kind suggestion. According to your advice, we have noted percentage of cancer cases in table 1. Meanwhile, as you advise us to add the percentage of cancer, we think it is a good suggestion to add the subgroup analysis of percentage of cancer cases instead of the subgroup analysis of cases of cancer.

5. Why was 2013 chosen as a "cutoff"?
Reply: Our meta-analysis was an update study of the meta-analysis of Liu et al. in 2014, which had included studies published before 2013. So at the beginning, we just wanted to make a contrast of study before and after 2013. But thanks for your kind suggestion, and the “cutoff” may not be appropriate. Thus, we omitted the subgroup of publication year from our analyses.

6. Discussion - the authors do not discuss quality of studies and differences noted in percentage of cancer cases between different studies. Discussion regarding RCT's is unclear. Page 9 line 44 - what do the autors mean? did they look at other cancer types beside EC and OC? Why is longer statin use not associated with reduced risk? The authors do not discuss this puzzling finding.

Reply: Thanks for your kind suggestion. According to your advice, we add the subgroup analyses of quality of studies and percentage of cancer cases. We also discuss them respectively in the part of discussion. We revise the manuscript as follows: “We use the Jadad scale and NOS criterion to assess the quality of the RCTs and observational studies, respectively. The two RCTs were deemed to be of high quality, with Jadad total scores ≥3, and 14 observational studies had NOS scores ≥7, identifying them as high-quality. Subgroup analyses of the quality of studies indicated that no significant association between statin use and risk of endometrial cancer was observed in studies of high-quality or low-quality. The studies we included had different numbers of participants, most included large populations, and the percentage of cancer patients was low and varied. However, we found no significant differences in the association of statin use and the risk of ovarian or endometrial cancer in groups with percentages of cancer cases ≥ 1% versus groups with < 1%.” These can be viewed in the discussion section, line 246, page 11.

And regarding to RCTs, we are sorry for not clear statement. We have asked a native speaker of English to help us revise the manuscript: “Moreover, in these RCTs, statins were used to treat patients with coronary heart disease or hyperlipemia. Cancer was not a primary outcome. Hence, the results from the two RCTs were not powerful enough to conclude the outcome of cancers. Thus, further RCTs investigating statin use and the risk of ovarian or endometrial cancer will be required to confirm these results.” These can be viewed in the discussion section, line 340, page 15.

In our meta-analysis of the effects of long-term statin use, we combined the RR extracted from the studies and come to a conclusion that longer statin use was not associated with reduced risk. There are fewer studies reported the long-term statin use than the studies we have included. And at the beginning, the results were contradictory between the cancer risks in statin users and long-term statin users. But thanks for your kind suggestion, we simply addressed ovarian and endometrial cancers rather than "endocrine related malignancies" and omitted the study by Rennert et al, then we got a complete coincident result: “Our pooled analysis indicated that statin use did not reduce the risk of ovarian cancer (RR = 0.88, 95% CI = 0.76–1.03, p = 0.12)” These can be viewed in the results section, line 173, page 8. “There was no significant association
between the use of statins and the risk of endometrial cancer (RR = 0.88, 95% CI = 0.78–1.00, p = 0.05)” These can be viewed in the results section, line 185, page 9. “There was no association between long-term statin use (>5 years) and risk of endometrial cancer (RR = 0.79, 95% CI = 0.58–1.08, p = 0.14) or ovarian cancer (RR = 0.73, 95% CI = 0.51–1.04, p = 0.08)” These can be viewed in the results section, line 224, page 10.

We are very grateful for your help in pointing out the deficiencies of the methods we have applied, which improved our quality of study and made our results more rational. Thank you so much!

7. English - need extensive language editing.

Reply: Thanks for your kind suggestion. We have asked a native speaker of English to help us revise the manuscript.

8. It is often unclear if the authors refer to cancer patients or to the population of women studied.

Reply: Thanks for your kind suggestion. Yes, the cancer patients were from the population of women studied. And we also stated it in our manuscript. “Nine studies enrolled endometrial cancer patients, three enrolled ovarian cancer patients, and seven enrolled both. The cancer patients were from the population of women studied.” These can be viewed in the results section, line 165, page 8.

Alan Richardson (Reviewer 2):

1. Page 3 Line 29 "We postulated that metabolic syndrome may be related to ovarian or 2. endometrial cancer." I am unsure of the relevance of this sentence?

Reply: Thanks for your kind suggestion, and we are sorry for not clear statement. We have meant that metabolic syndrome may be related to ovarian or endometrial cancer, but the logic was a little confusing. Thus, we delete this sentence and use the result of meta-analysis conducted by Esposito et al. which reported that metabolic syndrome is associated with an increased risk of ovarian and endometrial cancers (Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D: Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes care 2012, 35(11):2402-2411.doi: 10.2337/dc12-0336). These can be viewed in the background section, line 75, page 4.
3. Page 3 Line 36 There are numerous studies reporting the activity of statins in preclinical cancer models. Rather than selecting just one or two to reference, the authors would do better to refer to a review of these.

Reply: Thanks for your kind suggestion. We agree with your suggestion totally. It is much better to cite a review than just a few reports. So we use a recently review to explain anti tumor effects of statins in experimental research (Iannelli F, Lombardi R, Milone MR, Pucci B, De Rienzo S, Budillon A, Bruzzese F: Targeting Mevalonate Pathway in Cancer Treatment: Repurposing of Statins. Recent patents on anti-cancer drug discovery 2018, 13(2): 184-200. doi: 10.2174/1574892812666171129141211). These can be viewed in the background section, line 78, page 4.

4. Page 3 Line 38 More effective than what? I don't understand the point the authors are making.

Reply: Thanks for your kind suggestion. We are sorry for not clear statement. We just wanted to express that the statins were found to be effective in female reproductive cancer. There was no comparison here. These can be viewed in the background section, line 80, page 4. At the same time we have asked a native speaker of English to help us revise the manuscript as well.

5. Page 6 line 7 and elsewhere P=0.000? Really? Use Scientific notation if necessary.

Reply: Thanks for your kind suggestion. We extracted relative risk (RR) from the included studies, and all analyses were performed using Stata software version 12.0 (2011; Stata Corp., College Station, TX, USA). As we have only taken the result to two decimal places, we just present the P value as P=0.00. And we present the original data as follow:

Risk of Endocrine-related gynecologic cancers among statin users:

Subgroup analysis based on cancer cite:

Ovarian cancer: RR=0.839, 95%CI 0.708–0.993, p=0.041.

Endometrial cancer: RR=0.882, 95%CI 0.777–1.001, p=0.051.

Subgroup analysis based on study type:

RCT: RR=0.583, 95%CI 0.174–1.953, p=0.382.

Cohort: RR=0.949, 95%CI 0.839–1.073, p=0.406.
Case-control: RR=0.789, 95%CI 0.674–0.925, p=0.003.

Subgroup analysis based on publication year:
≥ 2013: RR=0.816, 95%CI 0.711–0.938, p=0.004.
< 2013: RR=0.946, 95%CI 0.825–1.085, p=0.428.

Subgroup analysis based on cases of cancer:
≥ 120: RR=0.858, 95%CI 0.769–0.957, p=0.006.
< 120: RR=0.878, 95%CI 0.725–1.064, p=0.185.

Subgroup analysis based on study location:
North America: RR=0.892, 95%CI 0.764–1.042, p=0.149.
Europe: RR=0.985, 95%CI 0.917–1.059, p=0.690.
Asia: RR=0.499, 95%CI 0.388–0.642, p=0.000.

Risk of ovarian cancer among statin users:
Subgroup analysis based on study type:
RCT: RR=0.200, 95%CI 0.010–4.074, p=0.295.
Cohort: RR=0.977, 95%CI 0.773–1.236, p=0.848.
Case-control: RR=0.756, 95%CI 0.590–0.969, p=0.027.

Subgroup analysis based on publication year:
≥ 2013: RR=0.840, 95%CI 0.677–1.041, p=0.111.
< 2013: RR=0.820, 95%CI 0.661–1.017, p=0.071.

Subgroup analysis based on cases of cancer:
≥ 120: RR=0.800, 95%CI 0.644–0.995, p=0.045.
< 120: RR=0.883, 95%CI 0.717–1.086, p=0.238.

Subgroup analysis based on study location:
North America: RR=0.878, 95%CI 0.689–1.119, p=0.294.
Europe: RR=0.982, 95%CI 0.885–1.090, p=0.736.
Asia: RR=0.474, 95%CI 0.329–0.682, p=0.000.

Risk of endometrial cancer among statin users:

Subgroup analysis based on study type:
RCT: RR=0.716, 95%CI 0.191–2.677, p=0.620.
Cohort: RR=0.932, 95%CI 0.797–1.090, p=0.376.
Case-control: RR=0.798, 95%CI 0.615–1.034, p=0.088.

Subgroup analysis based on publication year:
≥ 2013: RR=0.773, 95%CI 0.617–0.968, p=0.025.
< 2013: RR=0.979, 95%CI 0.838–1.144, p=0.790.

Subgroup analysis based on cases of cancer:
≥ 120: RR=0.882, 95%CI 0.771–1.008, p=0.065.
< 120: RR=0.856, 95%CI 0.521–1.404, p=0.537.

Subgroup analysis based on study location:
North America: RR=0.897, 95%CI 0.726–1.107, p=0.311.
Europe: RR=0.966, 95%CI 0.849–1.098, p=0.592.
Asia: RR=0.523, 95%CI 0.369–0.743, p=0.000.

However, according for the advice of the Reviewer 1, we simply addressed ovarian and endometrial cancers rather than "endocrine related malignancies" and omitted the study by Rennert et al, and then we got some new results. We present the original data as follow:

Risk of ovarian cancer among statin users:

Subgroup analysis based on study type:
RCT: RR=0.200, 95%CI 0.010–4.074, p=0.295.
Cohort: RR=0.977, 95%CI 0.773–1.236, p=0.848.
Case-control: RR=0.822, 95%CI 0.653–1.035, p=0.096.

Subgroup analysis based on percentage of cancer cases:
≥ 1%: RR=0.760, 95%CI 0.550–1.050, p=0.096.
< 1%: RR=0.974, 95%CI 0.833–1.138, p=0.738.

Subgroup analysis based on study location:
North America: RR=0.878, 95%CI 0.689–1.119, p=0.294.
Europe: RR=0.897, 95%CI 0.717–1.122, p=0.341.

Subgroup analysis based on quality of studies:
High: RR=0.864, 95%CI 0.736–1.014, p=0.074.
Low: RR=1.240, 95%CI 0.723–2.128, p=0.435.

Risk of endometrial cancer among statin users:
Subgroup analysis based on study type:
RCT: RR=0.716, 95%CI 0.191–2.677, p=0.620.
Cohort: RR=0.932, 95%CI 0.797–1.090, p=0.376.
Case-control: RR=0.798, 95%CI 0.615–1.034, p=0.088.

Subgroup analysis based on percentage of cancer cases:
≥ 1%: RR=0.788, 95%CI 0.542–1.146, p=0.213.
< 1%: RR=0.896, 95%CI 0.776–1.036, p=0.139.

Subgroup analysis based on study location:
North America: RR=0.897, 95%CI 0.726–1.107, p=0.311.
Europe: RR=0.891, 95%CI 0.753–1.053, p=0.176.
Asia: RR=0.430, 95%CI 0.777–1.001, p=0.034.

Subgroup analysis based on quality of studies:
High: RR=0.885, 95%CI 0.778–1.006, p=0.061.
Low: RR=0.798, 95%CI 0.392–1.624, p=0.533.
6. Page 6 line 17 Were the subgroup analyses discussed on page 6 and onwards planned before the study or is this "p hacking" or was an appropriate statistical correction performed to correct for false discovery? (sorry but I don't know a more gentle way to say this). Without this, it is difficult to assess if results support the conclusions drawn. I also simply am mystified why 2013 was chosen as a cut-off year? This seems somewhat random

Reply: Thanks for your kind suggestion. And I’m so sorry to make you puzzled. To be honest, all analyses were performed using Stata software version 12.0, and we guarantee that the results were all true. And all the original data were presented above. However, when we considered your questions seriously, we realized the method of subgroup analyses might not be reasonable. And at the same time, according for the advice of the Reviewer 1, we have added the subgroup analyses of percentage of cancer cases instead of the subgroup analysis of cases of cancer.

Our meta-analysis was an update study of the meta-analysis of Liu et al. in 2014 which had included studies published before 2013. So at the beginning, we just wanted to make a contrast of study before and after 2013. But thanks for your kind suggestion, and the “cutoff” may not be appropriate. Thus, we omitted the subgroup of publication year from our analyses.

7. The authors should discuss in the discussion why a significant difference was only observed in case controlled studies and the significance of this

Reply: Thanks for your kind suggestion. Based on our subgroup analysis of study type, there was no significant association between statin use and risk of endocrine-related gynecological cancers in the RCTs and cohort studies, but a statistically reduced risk of endocrine-related gynecological cancers in the case-control studies. The most likely explanation is that the case-control studies were intended to help determine whether statin use is associated with a reduced risk of some cancers using an observational analytical non-experimental design usually in backward sense. Case and control groups are selected according to the presence or absence of the cancer, respectively, and statin use of the groups is compared to address their association with the risk of cancer. In comparison with cohort studies, case-control studies didn’t involve all the statin uses, which might induce selection bias.

At the same time, according for the advice of the Reviewer 1, we simply addressed ovarian and endometrial cancers rather than "endocrine related malignancies" and omitted the study by Rennert et al, and then we got a complete coincident result. We revise the manuscript as follows: “We conducted subgroup analyses of statin use and the risk of ovarian cancer based on study type, percentage of cancer cases, geographical study location (continent), and quality of studies. There was no significant association between statin use and risk of ovarian cancer in the RCTs (RR = 0.20, 95% CI = 0.01–4.07, p = 0.30), cohort studies (RR = 0.98, 95% CI = 0.77–1.24, p = 0.85), or case-control studies (RR = 0.82, 95% CI = 0.65–1.04, p = 0.10).” These can be viewed in the results section, line 181, page 8. And regarding to endometrial cancer, “There was no
significant association between statin use and risk of endometrial cancer in the RCTs (RR = 0.72, 95% CI = 0.19–2.68, p = 0.62), cohort studies (RR = 0.93, 95% CI = 0.80–1.10, p = 0.38), or case-control studies (RR = 0.80, 95% CI = 0.62–1.03, p = 0.09).” These can be viewed in the results section, line 205, page 9.

However, since the majority of the included studies are retrospective, there was the possibility that our results had recalling or selection bias, which could be of concern. 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 also mentioned these in the discussion section, line 309, page 14 and line 343, page 15.

8. The authors don't seem to have considered which different statins are used (which is very relevant given their different half-lives), and the dose of statin. All of these have been proposed to contribute to clinical outcome.

Reply: Thanks for your kind suggestion. We agree with your suggestion totally. Different statins which are used and the dose of statin have been proposed to contribute to clinical outcome. In the beginning, we have planned to conduct subgroup analysis base on different statins. However, the majority of studies we included didn’t report the specific drugs, the dose of statin and the duration of statin use as well. Thus, we could not combine the results from different studies for different statins or the dose of statin. According to your advice, we explained these aspects in the manuscript: “Second, we extracted RR data directly or indirectly, to represent the relationship between statin use and ovarian or endometrial cancer. However, each of the included studies utilized different study designs according to the different statins or different statin doses. Most studies observed the outcomes of overall statin use (rather than that of a particular drug) and cancer risk. Other studies classified statins as lipophilic or hydrophilic [13, 37] or separately observed different drugs [15, 33, 35, 39]. As different statins have different half-lives, the different types or doses of statin have been proposed to contribute differently to clinical outcomes. However, the results could not be combined because of such differences in the included studies.” These can be viewed in the discussion section, line 311, page 14.

And we agree with your suggestion totally, these aspects are so important, further RCTs investigating the association between different statins, different dose of statin and the risk of ovarian or endometrial cancer are needed to confirm or update the conclusions of this meta-analysis.
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)?

No - there are minor issues

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

No - there are minor issues

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

No - there are minor issues

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?

Probably - with minor revisions

STATISTICAL REVIEWER COMMENTS:

Can the authors calculate and present Number needed to treat for their main analyses results (results presented in the abstract)....so that readers can easily understand the extent of benefit with statins. These numbers can be presented in the results section of the main text. This would be especially useful as although p values barely reached significance......the clinical significance of this data would be much higher.
Reply: Thanks for your kind suggestion. According to your advice, we have presented the numbers of main analyses results in the abstract. And we presented all the numbers of our analyses results in the results section of the main text. These can be viewed in the results section, line 182, page 9, line 186, 188, 206, page 9 and line 210, 213, page 10.

Restricting publications to only English articles would lead to publication bias...especially on such an important research topic wherein there is likelihood of relevant publications in other languages.

Reply: Thanks for your kind suggestion. We agree with your suggestion totally that restricting publications to only English articles would lead to publication bias. However, to be honest, because of the limitation of languages we mastered, we could only read and understand the publications in English. And since mostly high quality studies were published in English, we just restricted publications to only English. Thus, there was the possibility that our results had publication bias, which could be of concern.

Search strategy should have included all statin names.....rather than just 'statin'.

Reply: Thanks for your kind suggestion. We agree with your suggestion totally. At the beginning, we conducted the search strategy included all statin names actually. But in consideration of the limited space, we didn’t list all the names. And according to your advice, we revise the manuscript as follows: “The following MeSH and main keywords were used: “hydroxymethylglutaryl-CoA reductase inhibitor,” “Reductase Inhibitors, Hydroxymethylglutaryl-CoA,” “Inhibitors, HMG-CoA Reductase,” “Reductase Inhibitors, HMG-CoA,” “HMG-CoA Reductase Inhibitors,” “Statins, HMG-CoA,” “Statins,” “Hydroxymethylglutaryl-Coenzyme A Inhibitors,” and associated terms; and “Ovarian Neoplasm,” “Ovary Neoplasm,” “Ovary Cancer,” “Ovarian Cancer,” “Cancer of Ovary,” “Endometrial Neoplasm,” “Endometrial Carcinoma,” “Endometrial Cancer,” “Endometrium Cancer,” “Endometrium Carcinoma,” and associated terms.” These can be viewed in the methods section, line 101, page 5.

In methods section, please mention how quality of the 2 included RCTs was assessed. NOS scale is not appropriate for RCTs.

Reply: Thanks for your kind suggestion. And according to your advice, we assessed the RCTs again using the Jadad scale. We revise the manuscript as follows: “The Jadad scale was used to assess the quality of the RCTs [16], and studies with 3 or more points were identified as high-quality [17]. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the observational studies [18], and studies with 7 or more points were deemed as high-quality.” These can be viewed in the methods section, line 138, page 7. “We use the Jadad scale and NOS criterion to assess the quality of the RCTs and observational studies, respectively. The two RCTs were deemed to be of high quality, with Jadad total scores ≥3, and 14 observational studies had
NOS scores ≥7, identifying them as high-quality.” These can be viewed in the discussion section, line 246, page 11.

In pooled analyses, describe how heterogeneity was assessed. Provide description (in methods section) of how the authors intended to explore sources of heterogeneity.

Reply: Thanks for your kind suggestion. And according to your advice, we revise the manuscript as follows: “Heterogeneity