PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Diabetes mellitus and the risk of ovarian cancer – a systematic review and meta-analysis of cohort and case-control studies
AUTHORS	Wang, Li; Zhong, Lei; Xu, Bin; Chen, Min; Huang, Hong

VERSION 1 – REVIEW

REVIEWER	Dongyu Zhang Georgetown University, USA
REVIEW RETURNED	30-Jul-2020

GENERAL COMMENTS	The author synthesized epidemiologic evidence and explored association between diabetes and ovarian cancer risk. Overall, I have a few comments for this manuscript 1. Methods. The selection criteria are very vague. Please describe more details of the selection criteria. 2. Methods. Please describe more details about title/abstract screening and full-text review. How did you solve the inconsistency in these steps? 3. Methods. Publication bias should be described in section of statistical analysis. 4. Methods. Usually, we will use 0.05 as the cutoff for Cochran P-value. Why did you use 0.10? 5. Results. I suggest do not use section title like “assessment of study quality.” It looks like it is a section in methods. You can just report the resulting data without section title. 6. Results. I suggest you describe some strengths and limitations of included studies in your results section. Simply reporting NOS score is not enough. 7. Results. I think the association identified in case-control studies is almost null. Do you have any speculation why it is different from cohort studies? 8. Discussion. I think one limitation should be that many studies did not consider the interaction between anti-diabetic treatment and diabetes in relation to ovarian cancer risk. This may cause some bias in your analysis. 9. Discussion. The connection between diabetes and inflammation should be described with more details.

REVIEWER	Elina Urpilainen Oulu University Hospital and Oulu University, Finland
REVIEW RETURNED	03-Aug-2020

GENERAL COMMENTS	The manuscript ”Diabetes mellitus and the risk of ovarian cancer - a systematic review and meta-analysis of cohort and case-control studies” by Wang et. colleagues focuses on the important topic of diabetes and ovarian cancer risk. The manuscript is well executed

	but it needs a professional English proofreading. and some deeper discussion. In addition, I have some minor comments. Abstract 1. In a conclusion section, I would recommend to avoid dichotomous term “significant association”. 2. I would not raise the lack of histological subtypes of ovarian cancer as a major limitation of this study as the majority of ovarian cancers are epithelial carcinomas. Introduction 3. I would recommend replacing the reference (Zhou et al. 2018) for subtypes of diabetes mellitus to more appropriate as this reference mainly focuses to nephropathy and actual subtypes of diabetes. 4. Due the fact that this meta-analysis focuses on ovarian cancer risk, I would recommend discussing about the risk factors of ovarian cancer more deeply as only smoking, hormone replacement therapy and dietary factors are mentioned. How about protective factors as multiparity, oral contraceptives and breastfeeding? 5. Is high BMI undoubtedly considered as risk factor for ovarian cancer? 6. Have the previous studies presented conflicting results on the association between diabetes and ovarian cancer or are the results just variable? Results 7. “The follow-up period of cohort studies varied, ranging from 3.5 years to 18.01 years”. Is the two-decimal accuracy really needed in this sentence? 8. In my opinion, the p-value is not needed when reporting the confidence interval. Furthermore, I would avoid the term “significant” as the only p-value less than 0.05 would make the difference. Discussion 9. I would recommend discussing the possible role of different antidiabetic medication for ovarian cancer risk as a confounding factor. 10. I would recommend discussing more about the heterogeneity of previous studies. What are the main differences between the previous studies?

VERSION 1 – AUTHOR RESPONSE

Responds to the reviewer’s comments:
Reviewer #1:
Thank you very much for your efforts and valuable advices. We appreciate it that you have pointed out some shortcomings in our study, which is very helpful for revising and improving our paper. All corrections we have made following these comments are as below.

Comment 1:
Methods.
The selection criteria are very vague. Please describe more details of the selection criteria.
Response:
Thank you very much for pointing this out. We may have an inappropriate statement here. We have followed your advice and modified them.

Online databases, PubMed, Embase and the Cochrane library databases, were searched from the inception to 9 April 2020 for observational studies. The inclusion criteria were as follows: 1) original observational studies (cohort and case-control studies), 2) evaluating the association between DM and OC risk, 3) the risk estimates were reported, 4) human population, 5) without language restriction.
Thank you again for your comments!

Comment 2:
Methods.
Please describe more details about title/abstract screening and full-text review. How did you solve the inconsistency in these steps?
Response:
We appreciate the valuable suggestion and revise this section according to your comments.
First, two authors (WHL and ZL) excluded duplicates via a reference manager. Second, the two authors read the title and abstract to further screen the eligible studies. Finally, we included the studies by reviewing the full text. Any disagreements were solved by means of discussion.
Thank you very much again for your comments!

Comment 3:
Methods.
Publication bias should be described in section of statistical analysis.
Response:
Thank you for your suggestion. We may have an inappropriate statement here and revise it based on your comment (Line 173-177, Page 5).

Comment 4:
Methods.
Usually, we will use 0.05 as the cutoff for Cochran P-value. Why did you use 0.10?
Response:
Thanks for your good question!
A “Cochrane Handbook for Systematic Reviews of Interventions” by Higgins et al. in early 2008 has reported that the statistical heterogeneity of meta-analysis was measured by χ^2 (threshold p=0.10) and quantified by the I^2 statistic.
Meanwhile, the explanation is as follows: Care must be taken in the interpretation of the chi-squared test, since it has low power in the (common) situation of a meta-analysis when studies have small sample size or are few in number. This means that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity. This is also why a P value of 0.10, rather than the conventional level of 0.05, is sometimes used to determine statistical significance (Higgins JPT, Green S, Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. 2008).
Thank you again for your comments!

Comment 5:
Results.
I suggest do not use section title like “assessment of study quality.” It looks like it is a section in methods. You can just report the resulting data without section title.
Response:
We agreed to your advice and delete this section title in Result part.
Thank you again for your advice.

Comment 6:
Results.

I suggest you describe some strengths and limitations of included studies in your results section. Simply reporting NOS score is not enough.
Response:
Thank you for your comments. We do not understand the meaning of this sentence (I suggest you describe some strengths and limitations of included studies in your results section.). We hope you can give us a definite instruction. We are very sorry for the inconvenience that may have caused you. We're really looking forward to your suggestions and comments.
This meta-analysis was performed and reported based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE) protocol checklist and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.
A "Cochrane Handbook for Systematic Reviews of Interventions" by Higgins et al. in early 2008 has reported the tools for assessing methodological quality or risk of bias in non-randomized studies. The two most useful tools identified in this review are the Downs and Black instrument and the Newcastle-Ottawa Scale (Higgins JPT, Green S, Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. 2008).
The NOS contains eight items, categorized into three dimensions including selection, comparability, and—depending on the study type—outcome (cohort studies) or exposure (case-control studies). For each item a series of response options is provided. A star system is used to allow a semi-quantitative assessment of study quality, such that the highest quality studies are awarded a maximum of one star for each item with the exception of the item related to comparability that allows the assignment of two stars. The NOS ranges between zero up to nine stars (Stang, 2010, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses; PMID: 20652370).
The assessment of study quality is detailed in the Additional file 3.
We would appreciate it if you have some other improvement ideas.

Comment 7:
Results.
I think the association identified in case-control studies is almost null. Do you have any speculation why it is different from cohort studies?
Response:
Thank you for your comments.
Our systematic review and meta-analysis of 27 cohort and 9 case-control studies evaluated the association between DM and the incidence of OC and suggests that women with DM had a 20% elevated risk of OC, as compared to those without history of DM. Similar positive finding was observed when we analyzed by cohort studies (RR, 1.22; 95% CI = 1.11 to 1.33), however, no meaningful difference was noted when pooled by the case-control studies (RR, 1.08; 95% CI = 0.77 to 1.53).
Although this association was not statistically significant, a positive trend was observed in case-control studies group. A important problem concerns the assessment of DM in case-control studies, which was based on patients' self-reporting (5/9, 55%).
We are aware of this potential problem. Since the inherent nature of recall and select bias in case-control study, certain biases might lead to inaccurate reporting of causal relationship.
Thank you again for your comments!

Comment 8:
Discussion. I think one limitation should be that many studies did not consider the interaction between anti-diabetic treatment and diabetes in relation to ovarian cancer risk. This may cause some bias in your analysis.
Response:
Thanks so much for pointing this out. We appreciate the valuable suggestion. We agree with your opinion and added several sentences in our study.

Besides, several oral anti-hyperglycemic therapies (sulfonylureas) have been shown to increase risk of cancer development. However, metformin, as a insulin sensitizer, may reduce this risk via mediated by stimulation of AMP-activated protein kinase and inhibition of gluconeogenesis in the liver (Enhanced anti-proliferative and pro-apoptotic effects of metformin encapsulated PLGA-PEG nanoparticles on SKOV3 human ovarian carcinoma cells, PMID: 30892093).
Thank you again for your comments!

Comment 9:
Discussion. The connection between diabetes and inflammation should be described with more details.
Response:
Thank you for your suggestion. We may have an incomplete statement. We have made corrections based on your comments.
Studies have shown that the hyperglycemic state of patients with DM produces many of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-1β and IL-6, thereby facilitating a tumor-favorable microenvironment and potentially causing immune hyperactivation and tumor cells growth (Hyperglycemia, tumorigenesis, and chronic inflammation, PMID: 27931833; Association of biomarkers of inflammation and oxidative stress with the risk of chronic kidney disease in Type 2 diabetes mellitus in North Indian population, PMID: 24012111).
Thank you again for your suggestion.

We really appreciate your valuable advice！
Thank you again for your comments!
We would be glad to respond to any further questions and comments that you may have.

Reviewer #2:
We appreciate it that you have pointed out some shortcomings in our manuscript, which is very helpful for revising and improving our paper. Many thanks for those valuable suggestions.

Comment 1:
Abstract
In a conclusion section, I would recommend to avoid dichotomous term “significant association”.
Response:
Thank you for putting up such an important question. We may have an inappropriate statement here and revised it according to your valuable comments.

Comment 2:
I would not raise the lack of histological subtypes of ovarian cancer as a major limitation of this study as the majority of ovarian cancers are epithelial carcinomas.
Response:
Thanks so much for pointing this out. We have rethought this comment base on your requirement. Meanwhile, we read the relevant literatures again and delete this shortcoming.

Comment 3:
Introduction
I would recommend replacing the reference (Zhou et al. 2018) for subtypes of diabetes mellitus to more appropriate as this reference mainly focuses to nephropathy and actual subtypes of diabetes.

Response:
We are very sorry for this problem. Thanks so much for pointing this out. We agree on your advice and revise the reference (Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus; Report of the committee on the classification and diagnostic criteria of diabetes mellitus; PMID: 24843435) according to your valuable comments.
Thank you again for your comments!

Comment 4:
Introduction
Due the fact that this meta-analysis focuses on ovarian cancer risk, I would recommend discussing about the risk factors of ovarian cancer more deeply as only smoking, hormone replacement therapy and dietary factors are mentioned. How about protective factors as multiparity, oral contraceptives and breastfeeding?
Response:
Thank you very much for pointing this out. We are aware of this potential problem. Therefore, we once again read the relevant literatures and added a sentence in our study.
Besides, other immutable risk factors included age of menarche, age of natural menopause and endometriosis, etc.
Thank you again for your comments!

Comment 5:
Introduction
Is high BMI undoubtedly considered as risk factor for ovarian cancer?
Response:
Thanks for your good question!
Incidence of obesity and overweight is on the rise globally, potentially impacting worldwide cancer incidence and cancer-related mortality (PMID: 32793660).
A prospective study in reported that higher early-adult BMI was associated with higher risk of peritoneal, but not ovarian or fallopian tube, cancer (Fortner; 2020; Ovarian Cancer Risk Factor Associations by Primary Anatomic Site: The Ovarian Cancer Cohort Consortium; PMID: 32732252), which is further confirmed by other studies (PMID: 27325851, etc.).
However, these negative results were not validated by other studies. Indeed, the International Agency for Research on Cancer (IARC) established that there is convincing evidence that excess body fatness (i.e. highest BMI category evaluated versus normal BMI of 18.5-24.9 kg/m2) is associated with an increased risk of at least 13 different types of cancers (RRs ranging from 1.1 to 7.1), including endometrial, postmenopausal breast, colorectal, esophageal, renal/kidneys, meningioma, pancreatic, gastric cardia, liver, multiple myeloma, ovarian, gallbladder and thyroid (Friedenreich, 2020, Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms; PMID: 32741068). Several studies support this result (PMID: 32668472 and PMID: 32690459, etc.). Furthermore, in a study of ＞ 700 women with prospectively collected data on BMI and physical activity, higher pre-diagnosis BMI was associated with higher overall and ovarian cancer-specific mortality (PMID: 31383570).
Therefore, high BMI is considered as a potential risk factor for ovarian cancer.
Thank you again for your comments!

Comment 6:
Introduction
Have the previous studies presented conflicting results on the association between diabetes and ovarian cancer or are the results just variable?
Response:
Thanks for your advice. We have listed some pros and cons in the introduction section.

In recent decades, there are several epidemiological observational studies in this area since the first study investigating the association between DM and subsequent risk of OC in women was published. Several cohort studies and case-control have been reported that a history of DM is significantly associated with an augmented risk of OC, however, other relevant studies found a negative significant association.
Thank you again for your comments!

Comment 7:
Results
"The follow-up period of cohort studies varied, ranging from 3.5 years to 18.01 years". Is the two-decimal accuracy really needed in this sentence?
Response:
Thanks for your advice. We have rechecked and revised them carefully.

Comment 8:
In my opinion, the p-value is not needed when reporting the confidence interval. Furthermore, I would avoid the term "significant" as the only p-value less than 0.05 would make the difference.
Response:
Thank you for pointing this out. We all agreed to your advice and revised them.

Comment 9:
I would recommend discussing the possible role of different antidiabetic medication for ovarian cancer risk as a confounding factor.
Response:
Thanks so much for pointing this out. We appreciate the valuable suggestion. We agree with your opinion and added several sentences in our study.
Besides, several oral anti-hyperglycemic therapies (sulfonylureas) have been shown to increase risk of cancer development. However, metformin, as a insulin sensitizer, may reduce this risk via mediated by stimulation of AMP-activated protein kinase and inhibition of gluconeogenesis in the liver (Enhanced anti-proliferative and pro-apoptotic effects of metformin encapsulated PLGA-PEG nanoparticles on SKOV3 human ovarian carcinoma cells, PMID: 30892093).
Thank you again for your comments!

Comment 10:
I would recommend discussing more about the heterogeneity of previous studies. What are the main differences between the previous studies?
Response:
Thank you for your suggestion. We agree on your advice and revise it in our study.
To our knowledge, only three previous meta-analyses were published in this field. In 2013, Lee et al. performed a first meta-analysis with 7 case-control and 11 cohort studies and supported that DM patients have a 17% increased risk of OC, compared with non-DM patients. A subsequent meta-analysis carried out by Wang et al. in 2017 with 14 cohort studies exposed that DM is associated with a 19% raised risk of OC, which was further confirmed by a meta-analysis with 15 cohort studies (32%) later the same year. The overall heterogeneity of these three meta-analyses (cohort studies) is 27.0%, 43.8%,79.8%, respectively. The heterogeneity of our study (cohort studies) was also substantial (76.7%), mainly from the clinical or methodological diversity, or both, among the individual studies.
We would appreciate it if you have some other improvement ideas.

VERSION 2 – REVIEW

REVIEWER	Elina Urpilainen Oulu University
REVIEW RETURNED	18-Nov-2020

GENERAL COMMENTS	The authors have improved the manuscript and have satisfyingly answered all my previous questions. I have no further comments.