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World Journal of Gastroenterology

Lian-Sheng Ma, Science Editor, Company Editor-in-Chief, Editorial Office

Dear Editors,

We are sending the revised version of the manuscript entitled "Association between oral contraceptives use and pancreatic cancer risk: a systematic review and meta-analysis", reference number ID 63990, by authors Milena Ilic, Biljana Milicic and Irena Ilic, as a clean copy and copy with each revision highlighted by using the track changes mode in MS Word, together with answers to your comments and those of the reviewer and Editors, and all of the requested accompanying documents.

Thank you again for the opportunity to publish our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

Prof. dr Milena Ilic

Answering Reviewers and Editors

We very much appreciate your valuable suggestions and kind advice, which were very useful for improving the manuscript.

1 MANUSCRIPT REVISION DEADLINE

We request that you submit your revision in no more than 14 days. Please note that you have only two chances for revising the manuscript.

Response: Thank you, we are submitting the revised version of our manuscript within the set timeframe.

2 PLEASE SELECT TO REVISE THIS MANUSCRIPT OR NOT

Please login to the F6Publishing system at <https://www.f6publishing.com> by entering your registered E-mail and password. After clicking on the “Author Login” button, please click on “Manuscripts Needing Revision” under the “Revisions” heading to find your manuscript that needs revision. Clicking on the “Handle” button allows you to choose to revise this manuscript or not. If you choose not to revise your manuscript, please click on the “Decline” button, and the manuscript will be WITHDRAWN.

Response: Thank you, we have carefully revised our manuscript.

3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report. Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and make point-by-point responses to the issues raised in the peer-review report(s), which are listed below:

Response: Authors are thankful to the Editor and the Reviewer for their careful reading of our manuscript and helpful comments which have helped us improve our manuscript.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Response: We are grateful to the Reviewer for their time and effort in reviewing our manuscript.

Specific Comments to Authors: This is a very intriguing study targeting the relationship between OCP and pancreatic cancer. I agree with the authors that this is the most comprehensive meta-analysis of observational studies which have investigated the association between the use of OCP and risk of pancreatic cancer to date. They found that ever use of OCP was associated with a decreased risk of pancreatic cancer in the present meta-analysis. My concerns are the bias of the healthy diet of some studies and the coffee consumption. The authors should address these two aspects in their investigation.

Response: We would like to thank the Reviewer for these comments and very useful suggestions. Following your advice, we have made changes in the revised manuscript. Namely, we have addressed the aspects of healthy diet of some studies and the coffee consumption. We have revised the section Discussion and added the following new sentences:

“While some of the included studies have adjusted for factors which refer to diet, this most often involved BMI^[9,10,21,25,26,28,30,33,34,36], with only two studies investigating nutrition variables such as green tea drinking and intake of dietary vitamin C^[21], and coffee and tofu consumption and dietary fat intake^[10]. Obesity is a risk factor for pancreatic cancer, however the mechanisms are not fully known and may involve sex hormones^[21]. High BMI might reflect high intake of dietary fat, although the findings regarding its association with pancreatic cancer risk are inconsistent^[21,34]. Notably, adipose tissue produces estrogens and might have a protective role^[34]. Therefore, dietary factors could confound the association between the risk for pancreatic cancer and the use of oral contraceptives^[10]. Similarly, studies investigating nutrition and pancreatic cancer risk should adjust for reproductive factors such as the use of oral contraceptives.”

In subsection Strengths and limitations in the Section Discussion, the following new sentence was added:

“Presence of bias due to the lack of confounding control cannot be excluded in included studies which have not considered dietary factors as possible confounding factors when investigating the association between the use of oral contraceptives and risk for pancreatic cancer.”

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript’s language will meet our direct publishing needs.

Response: Thank you, we have had our manuscript checked for clarity by a colleague whose native language is English.

5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes a meta-analysis of the association between oral contraceptives use and pancreatic cancer risk. The topic is within the scope of the WJG. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This is a very intriguing study targeting the relationship between OCP and pancreatic cancer. The questions raised by the reviewers should be answered; (3) Format: There are 2 tables and 4 figures; (4) References: A total of 39 references are cited, including 7 references published in the last 3 years; (5) Self-cited references: There is 1 self-cited reference. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade A. No language editing certificate was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by Ministry of Education, Science and Technological development, Republic of Serbia. The topic has not previously been published in the WJG. 5 Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (3) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text. 6 Recommendation: Conditional acceptance.

Response: We would like to thank the Science Editor for their thorough reading of our manuscript and very useful remarks which have helped us improve our manuscript.

We have answered the questions raised by the Reviewer and incorporated appropriate changes in the revised manuscript (please see above our response to the Reviewer).

Following Science Editor's comments, we have uploaded the funding document, provided the Figures in PowerPoint and added the Section "Article Highlights", which reads as follows:

"ARTICLE HIGHLIGHTS

Research background

Pancreatic cancer is the seventh most common cause of death among malignant tumours in women. It represents one of the deadliest types of cancer with overall five-year survival rate <10%.

Research motivation

Although the understanding of the etiology of pancreatic cancer has improved over the past decades and certain risk factors have been established, the causes of pancreatic cancer are still insufficiently known. Results of epidemiological studies show conflicting results regarding the association of the use of oral contraceptives and risk for pancreatic cancer.

Research objectives

The aim of this study was to evaluate the relationship between the use of oral contraceptives and risk for pancreatic cancer.

Research methods

A comprehensive literature search was performed based on defined inclusion and exclusion criteria. Quality of included observational studies was assessed and data was extracted. A meta-analysis of ever-use versus never-use of oral contraceptives and risk for pancreatic cancer was performed using Review Manager 5.3. In addition, the association between the duration of use of oral contraceptives and pancreatic cancer risk was also assessed, and a subgroup analysis was performed.

Research results

A total of 7700 cases of pancreatic cancer from 21 studies (10 case-control and 11 cohort) were included in this meta-analysis. A significant association was observed between the ever-use of oral contraceptives and pancreatic cancer risk (OR=0.85; 95% CI=0.73-0.98), while the duration of use (<1 year, <5 years, 5-10 years, >10 years) did not show a significant association. Subgroup analysis revealed a statistically significant decrease in pancreatic cancer and use of oral contraceptives in high quality studies, studies conducted in Europe and in postmenopausal women.

Research conclusions

This meta-analysis suggests a protective effect of the use of oral contraceptives and pancreatic cancer occurrence, however more epidemiological studies are necessary to fully elucidate this association.

Research perspectives

Further epidemiological studies are warranted to fully assess the association between the use of oral contraceptives and risk for pancreatic cancer. These future studies investigating the risk for pancreatic cancer should be well-designed and include detailed questions regarding the use of oral contraceptives.”

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors.

Response: We would like to thank the Company Editor-in-Chief for carefully reviewing our manuscript and relevant documents. We have revised the manuscript according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision.

6 STEPS FOR SUBMITTING REVISED MANUSCRIPT

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Step 2: Manuscript Information

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Step 3: Abstract, Main Text, and Acknowledgements

(a) Guidelines for revising the content: Please download the guidelines for Original articles; Review articles; and Case report articles for your specific manuscript type (Meta-Analysis) at: <https://www.wjgnet.com/bpg/GerInfo/291>. Please further revise your manuscript according to the guidelines for revising the content.

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If your manuscript has no “Video” or “Supplementary Material”, you don’t need to submit those two types of documents.

Response: The manuscript has been revised according to the STEPS FOR SUBMITTING REVISED MANUSCRIPT and relevant accompanying documents have been prepared and uploaded.

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Response: The Copyright License Agreement Form has been signed by all authors and uploaded.

8 CONFLICT-OF-INTEREST DISCLOSURE FORM

Please click and download the fillable ICMJE Form for Disclosure of Potential Conflicts of Interest (PDF), and fill it in. The Corresponding Author is responsible for filling out this form. Once filled out completely, the Conflict-of-Interest Disclosure Form should be uploaded to the file destination of ‘Conflict-of-Interest Disclosure Form’.

Response: The ICMJE Form for Disclosure of Potential Conflicts of Interest was filled completely and uploaded.

We would like to thank the Editors and Reviewer for their careful reading of our manuscript and the opportunity to revise our manuscript according to their very useful comments.