

Dear Editor:

We greatly appreciate your letter and reviewers' comments concerning our manuscript entitled "**Pancreatic cancer: a review of epidemiology, trend and risk factors**" (Manuscript NO.: 64017, Review). All comments are valuable and helpful for improving our manuscript. Based on all reviewers' suggestions, we have carefully revised the manuscript and underline it in red, and we hope that the revised manuscript will meet the journal's standard. Below you will find our point-by-point responses to the reviewers' comments.

The corresponding author is Chengfei Zhao, and his address and other information are as follow:

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Thanks very much for your attention to our manuscript.

We are looking forward to hearing from you at your earliest convenience.

Sincerely yours

Chengfei Zhao and Jianxiong Hu

The itemized responses to all reviewers' comments are as follows:

Reviewer #1:

Specific Comments to Authors: This is a review of epidemiology, trend and risk factors of pancreatic cancer. The paper is interesting, comprehensive of good literature's review, and well-written. Minor point: The Introduction is too long with redundant anatomical description and the part regarding endocrine cancer is not appropriate.

Reply: First of all, we sincerely thank you very much for your recognition and guidance of our work. And thanks very much for your suggestions. According to your suggestion, we have rewritten the Introduction. The corrected INTRODUCTION in the revised manuscript is as follows:

Page 3, line 2-24:

“The pancreas is an about 6-inch-long, spongy, tube-shaped organ located in the back of the abdomen between stomach and spine ^[1]. The normal pancreas consists of digestive enzymes-secreting acinar cells, bicarbonate-secreting ductal cells, centro-acinar cells that are the geographical transition between acinar and ductal cells, hormone-secreting endocrine islets and relatively inactive stellate cells ^[2]. Pancreatic cancer occurs when pancreas cells develop abnormal DNA mutations that make them grow and divide out of control, forming a tumor ^[3]. Pancreatic cancer is characterized as a fatal disease and one of the most aggressive and lethal malignancies ^[4,5]. By the time of diagnosis, pancreatic cancer often presents at an advanced stage, and has often spread to other parts of the body. Clinically, common pancreatic cancer is the general term for tumor formed in the epithelial cells of glandular structures in the pancreatic ductal cells, referred to as adenocarcinoma ^[6], and pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic cancer ^[7]. Due to the poor survival outcomes, PDAC is the seventh leading cause of global cancer death despite being the 10th most common incident cancer ^[8]. Other less common exocrine pancreatic cancers include: adenosquamous carcinoma, squamous cell carcinoma, giant cell carcinoma, acinar cell carcinoma, and small cell carcinoma. At present, pancreatic cancer remains a devastating disease whose prognosis has remained largely

unchanged over the last two decades^[9]. Improvement in patient outcomes will depend on clear knowledge of epidemiology, reasonable prevention and scientific regulation of early detection^[4]. Therefore, it is necessary to understand the epidemiological characteristics, development trends and risk factors of pancreatic cancer in detail, which will eventually establish rational prevention approaches for clinical benefit.”

We hope that the revised manuscript will meet the requirements of the journal. And we cordially hope that you will give us guidance if the revised manuscript still has deficiency. Thank you very much again!

Reviewer #2:

Specific Comments to Authors: I read the invited manuscript entitled "Pancreatic cancer: a review of epidemiology, trend and risk factors" with a great interest. The authors well reviewed the tremendous papers about pancreatic cancer with latest information. Comments: First, the authors reviews the several risk factors for pancreatic adenocarcinoma, however, they refer to the endocrine tumors in the introduction. I did not find any description of endocrine tumors in the text. It is better to delete the sentence about endocrine tumor in the introduction. Additionally, endocrine pancreatic cancer is not exact nomenclature. It is better to use neuroendocrine neoplasm (NEN) or neuroendocrine carcinoma according to the WHO classification, if they remain the sentence of endocrine tumor. Second, though the authors well reviewed the many papers about pancreatic cancer, they also discussed some controversial risk factors. But they affirmed the screening and prevention in the conclusion. I recommend to replace these phrase "can screen..., can provide" to "may screen..., or possibly, etc..."

Reply: Firstly, we sincerely thank you very much for your guidance and suggestions. According to your suggestion, we have delete the sentence about endocrine tumor in INTRODUCTION. And we have rewritten the INTRODUCTION. We hope that the revised manuscript will meet the requirements of the journal. The corrected INTRODUCTION in the revised manuscript is as follows:

Page 3, line 2-24:

“The pancreas is an about 6-inch-long, spongy, tube-shaped organ located in the back of the abdomen between stomach and spine ^[1]. The normal pancreas consists of digestive enzymes-secreting acinar cells, bicarbonate-secreting ductal cells, centro-acinar cells that are the geographical transition between acinar and ductal cells, hormone-secreting endocrine islets and relatively inactive stellate cells ^[2]. Pancreatic cancer occurs when pancreas cells develop abnormal DNA mutations that make them grow and divide out of control, forming a tumor ^[3]. Pancreatic cancer is characterized as a fatal disease and one of the most aggressive and lethal malignancies ^[4,5]. By the time of diagnosis, pancreatic cancer often presents at an advanced stage, and has often spread to other parts of the body. Clinically, common pancreatic cancer is the general term for tumor formed in the epithelial cells of glandular structures in the pancreatic ductal cells, referred to as adenocarcinoma ^[6], and pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic cancer ^[7]. Due to the poor survival outcomes, PDAC is the seventh leading cause of global cancer death despite being the 10th most common incident cancer ^[8]. Other less common exocrine pancreatic cancers include: adenosquamous carcinoma, squamous cell carcinoma, giant cell carcinoma, acinar cell carcinoma, and small cell carcinoma. At present, pancreatic cancer remains a devastating disease whose prognosis has remained largely unchanged over the last two decades ^[9]. Improvement in patient outcomes will depend on clear knowledge of epidemiology, reasonable prevention and scientific regulation of early detection ^[4]. Therefore, it is necessary to understand the epidemiological characteristics, development trends and risk factors of pancreatic cancer in detail, which will eventually establish rational prevention approaches for clinical benefit.”

According to your suggestion, in CONCLUSIONS AND PERSPECTIVES, we have replace these phrase “can screen..., can provide” to “may screen..., may provide”, etc...” The corrected text in the revised manuscript is as follows:

Page 30, line 5-19:

“Over the next 10 to 20 years, an increase in pancreatic cancer is inevitable. At the same time, in the face of the characteristics of high mortality and difficult early

diagnosis of pancreatic cancer, early prevention of pancreatic cancer through understanding the risk factors of pancreatic cancer is an economical and effective means, which is to prevent pancreatic cancer in advance. In view of the non-modifiable factors affecting pancreatic cancer, we may screen the susceptible population of pancreatic cancer, and provide reliable screening strategies and reasonable diagnostic ideas for the early diagnosis of pancreatic cancer. By studying the modifiable risk factors that affect pancreatic cancer, we may provide earlier interventions to prevent pancreatic cancer so that it can be possibly blocked in its early stages of canceration, thus significantly reducing the incidence of pancreatic cancer. Globally, a comprehensive prevention and control strategy for pancreatic cancer should include effective tobacco-control policy, recommendations for healthier lifestyles, and enlarging coverage of screening, education and vaccination programmes to better improve public awareness of the need to take precautions.”

We hope that the revised manuscript will meet the requirements of the journal. And we cordially hope that you will give us guidance if the revised manuscript still has deficiency. Thank you very much again!

Science editor:

1 Scientific quality: The manuscript describes a reivew of the pancreatic cancer. The topic is within the scope of the WJG. (1) Classification: Grade B and Grade C; (2) Summary of the Peer-Review Report: The authors well reviewed the tremendous papers about pancreatic cancer with latest information. It is interesting and well-written. However, the introduction is too long with redundant anatomical description and the part regarding endocrine cancer is not appropriate. The questions raised by the reviewers should be answered; and (3) Format: There are 2 figures. (4) References: A total of 154 references are cited, including 48 references published in the last 3 years; (5) Self-cited references: There are 2 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove 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 recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

Reply: we firstly thank you very much for your guidance and suggestions. According to reviewers' suggestion, we have rewritten the INTRODUCTION in the revised manuscript.

The 2 self-cited references in the manuscript are reasonable self-citations and are closely related to the topic.

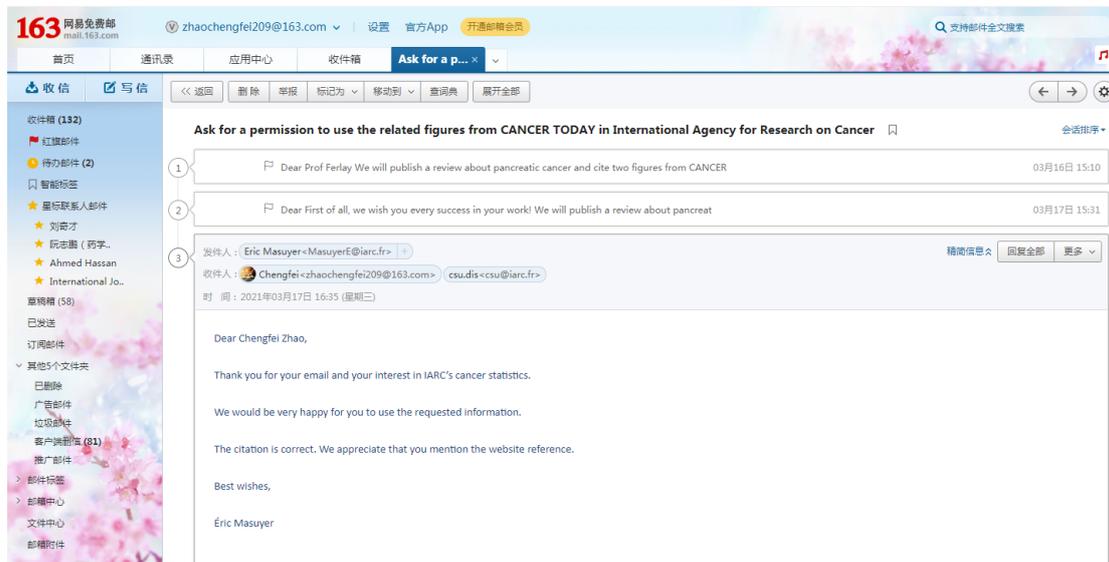
The reviewers did not recommend any references.

2 Language evaluation: Classification: Grade B and Grade B. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by 2 grants. 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; and (3) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu

MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc [6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

Reply: We have uploaded the funding agency copy of approval documents.

Figure 1 is from CANCER TODAY in International Agency for Research on Cancer (<https://gco.iarc.fr/today>). We sent email to International Agency for Research on Cancer, and have receive the permission to use the two figures, as shown in following figure. We do not find the corresponding entry in the F6Publishing system, and could not upload the PDF version of the screenshot of the email. We will send you an email if required.



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International Agency for Research on Cancer

 World Health Organization
 Cancer Research for Cancer Prevention

From: Chengfei [mailto:zhaochengfei209@163.com]
Sent: mercredi 17 mars 2021 08:32
To: csu.dis
Subject: Ask for a permission to use the related figures from CANCER TODAY in International Agency for Research on Cancer
Importance: High

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From: Chengfei [mailto:zhaochengfei209@163.com]
Sent: mercredi 17 mars 2021 08:32
To: csu.dis
Subject: Ask for a permission to use the related figures from CANCER TODAY in International Agency for Research on Cancer
Importance: High

Dear

First of all, we wish you every success in your work!

We will publish a review about pancreatic cancer and cite two figures from CANCER TODAY in International Agency for Research on Cancer (as shown in the following figure). The citation information is as follows: **Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.fr/today>, accessed [15/1/2021].**

Here, would we like to ask you whether the related figures from CANCER TODAY can be cited? These two figures are only for the dissemination of academic knowledge, not for any commercial purposes. We would appreciate it if you would give us your permission.

The URL of the two figures are as follows: https://gco.iarc.fr/today/online-analysis-map?v=2020&mode=population&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=13&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmssc=1&include_nmssc_other=1&projection=natural-earth&color_palette=default&map_scale=quantile&map_nb_colors=8&continent=0&show_ranking=0&rotate=%255B10%252C0%252D

We are looking forward to hearing from you soon.

With kind regards,
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 Putian University
 E-mail: zhaochengfei209@163.com



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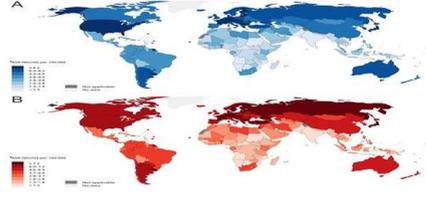
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We are looking forward to hearing from you soon.

With kind regards,
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Thank you very much for your guidance to improve our manuscript. We

sincerely hope that the revised manuscript meet the requirements of the journal. If there are still deficiencies in the revised manuscript, we will endeavor to improve it.

We sincerely thank you for your guidance again! Wish you success in your work!