

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77236

Title: Previous hepatitis B viral infection – underestimated cause of pancreatic cancer.

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03765308

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Doctor, Professor

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: Russia

Manuscript submission date: 2022-04-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-04-23 13:56

Reviewer performed review: 2022-04-26 15:33

Review time: 3 Days and 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Summary These investigators studied HBV genome and protein in 60 HBsAg negative patients with PDAC and 70 sex- and age-matched controls. They found that anti-HBc seropositive subjects were significantly higher in the case than in the control group. In addition, HBV genomes and HBx protein can be found in tumor tissues of the case group. They suggest that previous HBV infection may contribute to pancreatic carcinogenesis. Comments 1. PBI is not a common abbreviation. Please spell it out initially and replace it with anti-HBc-positive subjects or HBc-negative subject on subsequent text of abstract. 2. In the exclusion criteria section, please indicate how many HBsAg carriers were excluded from the case group. 3. In the Figure 1, please indicate when cases and controls were matched for age and sex. 4. From Table 3, it looks like that not all patients were examined for HBV pregenomic RNA, cccDNA, and HbxAg. Please describe how many and how these patients were selected for each study in the study procedure section. 5. In legend of Figure 2, please clarify the study samples were tumor or non-tumor part in case group. Please also describe how the control pancreas tissue was obtained. 6. In the result section, table 1 seems to be a description of Table 2. 7. In Table 2. Please remove Black race line. The HBV DNA in blood and pancreas should be separated in the two lines. Please indicate nil in the control pancreas HBV DNA. The percentage should be according to the number of anti-HBc-positive cases. 8. The first sentence of the discussion is not appropriate. Present of the HBV genome in cells does not indicate a direct relation to carcinogenesis. For example, HBV genomes are presented in hepatocytes, but not all of them developed HCC. 9. PC is the third leading cause of cancer-related deaths in the US, and fourth in the EU. These regions are not high HBV infection areas. On the



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other hand, those HBV endemic areas, such as Africa and East Asia, show relatively low pancreas cancer related death. This contrasts with previous HBV infection increase risk for pancreas carcinogenesis. Please discuss this discrepancy in the discussion.

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Peer-review model: Single blind

Reviewer's code: 05270042

Position: Editorial Board

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Viet Nam

Author's Country/Territory: Russia

Manuscript submission date: 2022-04-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-11 13:13

Reviewer performed review: 2022-05-18 12:48

Review time: 6 Days and 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statementsConflicts-of-Interest: [☐] Yes [☒] No**SPECIFIC COMMENTS TO AUTHORS**

This is a very interesting study with new ideas to find the association between previous HBV infection and pancreatic ductal adenocarcinoma (PDAC). 1. However, the author should mention factors such as NAFLD and diabetes. 2. In the PDAC group, with AntiHBc(+) patients, there were 2 cases detected HBVDNA/serum, and 6 cases detected HBVDNA in pancreatic tissue. Why were there total 9 cases instead of 8 cases in Table 3? 3. Why weren't pg RNA HBV and HBxAg performed for all 8 patients who were detected HBV DNA? 4. The research sample needed to be larger to be more convincing.

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Peer-review model: Single blind

Reviewer's code: 05755601

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Professor, Doctor

Reviewer's Country/Territory: Romania

Author's Country/Territory: Russia

Manuscript submission date: 2022-04-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-17 07:31

Reviewer performed review: 2022-05-28 11:32

Review time: 11 Days and 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors of the Case Control Study “Previous hepatitis B viral infection – underestimated cause of pancreatic cancer” have done a good job in assessing the implication of HBV infection and detecting the presence of HBV-DNA (cccDNA) and viral antigens in pancreatic tumor tissue. Some specific comments to authors include:

The original findings of this manuscript are of great importance due to the paucity of studies identifying the presence of HBV markers in PDAC tumor tissue; still, in Table 3, there is reported Patient no 3, who has a peculiar configuration of HBV markers, a detailed discussion about the absence of both pgRNA-HBV and cccDNA, together with the presence of HBV-DNA and HBxAg in the pancreatic tissue can be helpful. I think that some comments on the studies that did not report a positive association between HBV infection and PDAC, in large study groups after adjustment for age, sex, diabetes and smoking, can be provided by the authors (Chang MC, et al. Hepatitis B and C viruses are not risks for pancreatic adenocarcinoma. *World J Gastroenterol.* 2014;20(17):5060-5065. doi:10.3748/wjg.v20.i17.5060) Some questions can be consequently raised: What are the similarities and the differences between the studies?

Did the authors adjust diabetes as a risk factor? What is the incidence rate of pancreatic cancer in patients from their region? The limitation of the study, as the authors had already concluded, is the small number of the patients and samples of tumor tissues, that can decrease the statistical significance; if the number of study patients cannot be increased, the results remain an issue. I would also recommend the carefully correction for minor typos in the manuscript.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 05755601

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Professor, Doctor

Reviewer's Country/Territory: Romania

Author's Country/Territory: Russia

Manuscript submission date: 2022-04-20

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2022-07-09 05:39

Reviewer performed review: 2022-07-11 08:22

Review time: 2 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The authors have answered properly to all the questions.