

Dear Editor,

The manuscript has been revised according to the suggestions and comments of the reviewers. Table 1 in the previous version has been renumbered as Table 2 and it has been revised to explain the putative mechanisms and the limitations of current studies as suggested by Reviewer 3 (00000663). Please kindly note that a new table and a figure have been added and the major revised parts are highlighted in red color for your convenience of re-reviewing.

Please also kindly note that the title of the manuscript has been changed to “Diabetes and gastric cancer: the potential links”.

The responses to the specific comments of the reviewers are as follows:

Reviewer 1 (00503540)

1. page 5, line 11: Need a table about the 4 references and explanations about the data source (Pubmed, for example) and how to select the references using a dendrogram.

Response: The text has been revised and a table (Table 1 in the revised manuscript) has been added accordingly. Because the process in selecting the references is not complicated and is easy to follow, it is described in the text instead of using a dendrogram in the revised manuscript (Page 5, third paragraph). The added Table 1 summarizes the main findings of the 4 references.

2. Table 1: Difficult to understand. I recommend a informative figure showing correlation between gastric cancer and diabetes instead of the table.

Response: A figure (Figure 1) has been added in the revised manuscript as requested. The original Table 1 is renumbered as Table 2 to provide a further summary of the explanations for the putative mechanisms shown in Figure 1.

Reviewer 2 (00038192)

Abstract: “Diabetes may share common risk factors with gastric cancer, including obesity, smoking, insulin resistance, hyperinsulinemia and smoking.” Please delete one of the “smoking.”

Response: Thank you. It has been deleted.

Page 3, 2nd line Helicobacter pylori, please add (HP)

Response: This has been added, but on Page 2, where it first appears in the Abstract.

Page 5, “pathophysiological mechanisms contributing to such a link remains mostly unknown” please correct.

Response: The sentence has been revised (Page 5, second paragraph).

Page 6, 1st paragraph, last sentence, please specify whether this observation is for men / women ?

Response: It is for both sexes. This has been added in the revised manuscript (Page 6, first paragraph, second line).

Page 7, “statistically significant” statistically has to be deleted because significant indicates statistics.

Response: Done.

Page 10, 3rd paragraph; “pro-inflammation” please rewrite. Diabetes is not always associated with obesity, please correct.

Response: The sentences in this paragraph have been rewritten (Page 10, second paragraph under “Shared risk factor”).

Page 12, 1st sentence, please correct grammatical errors.

Response: This paragraph has been revised and the sentence has been deleted in the revised manuscript (Page 11, second paragraph).

Page 16, please explain CagA

Response: This is explained in the revised manuscript (Page 16, first paragraph).

Page 18, the term proxy seem to be not appropriate, please replace.

Response: The sentence has been changed to “the use of insulin might indicate poor glycemic control.....” (Page 17, first paragraph).

Several statements are repeated throughout the manuscript, this has to be avoided to make the review more comprehensive.

Response: Thank you. The manuscript has been revised and some repeated statements have been deleted. The word count of the main text in the revised manuscript has been reduced by about 500 words.

Confounding effects in the studies reviewed may be summarized Table 1, please add references.

Response: In the revised manuscript, Table 1 shows the main findings from the four meta-analysis studies and the references were added. Limitations are also described. In the revised Table 2 (Table 1 in the previous version), some limitations have also been added.

A table summarizing risk for gastric cancer in diabetes may be helpful.

Response: This has been summarized in a new Table 1 in the revised manuscript.

Reviewer 3 (00000663)

The study revises the literature on the risk of gastric cancer in diabetes. Diabetes is known to increase the general risk of cancer, but several other factors may blur the evidence. The authors identify shared factors of obesity, salt intake, blood glucose helicobater pylori infection, antidiabetic drugs and comorbidities as possible confounders. Major problems 1. The review is difficult to read and needs to be supplied by figures/tables to facilitate reading. As an example, initially the authors discuss the 4 metaanalyses on diabetes and gastric cancer. It would be important to have a general table comparing the results of the reviews, to explain differences also related to the different studies included in metaanalysis.

Response: Thank you very much for your suggestion. A new Table 1 has been added to compare the findings and differences of the 4 metaanalyses.

2. The second part of the review addresses the possible pathogenic link between diabetes and gastric cancer. The possible links are summarized in the only table present in the review, in a way difficult to memorize. I would suggest itemize the possible pathogenic links for any possible cause, pinpointing the pro and cons of the proposed pathogenesis.

Response: Thank you. A new figure has been added to show the possible pathogenic link. Table 2 (Table 1 in the previous version) has been revised to explain the proposed pathogenesis and the limitations of current studies.

Best regards.

Sincerely yours,

Chin-Hsiao Tseng, MD, PhD