ANSWERING REVIEWERS

January 16, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 1359-review.docx).

Title: ABO blood type, long-standing diabetes, and the risk of pancreatic cancer

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

Revision has been made according to the suggestions of the reviewers

To the first reviewer (00057780)

(1) We did not have data on ABO blood type and other cancers. According to published literature, ABO blood type is associated with various cancers, including pancreatic cancer, skin cancer, oesophageal cancer and hepatocellular carcinoma. We described these facts in the introduction as follows: "although an association between the ABO blood type and various disease was proposed 50 years ago, the ABO blood type has recently been confirmed to be associated with malignant tumors, including skin cancer, esophageal cancer, hepatocellular carcinoma and pancreatic cancer."

(2) Yes, we do not have any data regarding mechanism. We reported the distribution of ABO blood type in pancreatic cancer patients based on a retrospective examination. In fact, the mechanism underlying the association between ABO blood type and pancreatic cancer has not been clarified. We added some sentences about tumor necrosis factor alpha and the plausible but still equivocal explanation to the contents of the discussion as follows (The part of highlight is added sentences.). "The association between the ABO blood type and diabetes is controversial. Advances in genome-wide sequencing have provided novel insights into the pathogenesis of diabetes mellitus. A recent GWAS showed that genetic variants in the ABO locus were associated with not only diabetes risk, with blood group B showing a decreased risk compared with blood group O, but also the plasma levels of soluble intercellular adhesion molecule 1 and soluble E selectin, both of which are markers of inflammation and are thought to be related to the risk of type 2 diabetes mellitus. In addition, a SNP at the ABO locus was reported to be strongly associated with serum tumor necrosis factor alpha, which is a pro-inflammatory cytokine that modulates rates of pancreatic ductal cell apoptosis and an adipocytokine that has been implicated in the development of insulin resistance. Although the mechanism underlying the association between ABO blood type, diabetes and pancreatic cancer has not been clarified, these findings suggest interactions among ABO blood types, inflammatory markers, type 2 diabetes and pancreatic cancer."

(3)The reviewer is correct. Previous studies, including both epidemiologic and genome-wide association studies, have shown an association between ABO blood type and pancreatic cancer. What is

new in our study? The new finding is that our retrospective examination of a large cohort of pancreatic cancer patients showed that the distribution of ABO blood type seemed to differ between the patients with long-standing type 2 diabetes and those without, with the former showing a higher frequency of blood type B. In addition, when we divided the former into 3 subgroups according to the duration of diabetes, we found that there may be several subgroups that are associated with a specific blood type and characterized by the duration of diabetes. These findings suggest that long-standing type 2 diabetes and other underlying factors, such as blood type and period of diabetes, may play a role in predisposing diabetic patients to pancreatic cancer. Although our results should be replicated in prospective studies, they would be useful to define a subset of diabetics that is associated with increased susceptibility to pancreatic cancer.

The contents mentioned above have been already contained in the draft.

To the second reviewer (00039529)

We thank the reviewer for the positive comments on our study. Also we appreciate the reviewer's concern about marginal clinical relevance. We acknowledge this limitation. This is also the problem that confronts many epidemiologic studies. Many findings may lack sufficient clinical relevance. Even genome-wide association studies produce findings that are difficult to be readily used in the clinical setting. So far, the findings in our study are not still beneficial for further enrichment of the population of the pancreatic cancer to allow cost-effective screening. Nonetheless, by combining our findings with other known factors and novel biomarkers from prospective studies of GWAS, it is probable to detect more early-stage cancers, leading to a better prognosis.

To the third reviewer (00159396)

To major comments;

(1) We agree with the reviewer. The lack of appropriate control group is the major limitation of our study. We have already mentioned it in the Discussion. Because the Japanese is ethnically almost homogeneous, we referred to Nakao's article and the general Japanese population, which we believe may provide indirect evidence on the association between blood type and pancreatic cancer.

(2) We agree that variables such as HbA1c, glucose level are important biomarkers that can be used to predict the development of diabetes or pancreatic cancer. Unfortunately, these data were not available in our study. Other retrospective studies might also have been limited by the insufficient data on biomarkers. Furthermore, prospective studies are the best design to address the predictive values of these biomarkers. Further prospective studies incorporating these biomarkers are warranted.

To minor comments;

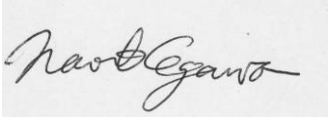
(1) According to the reviewer's comment, we have revised the abstract.

(2) A control group is necessary when quantifying the association of pancreatic cancer risk with the duration of diabetes or ABO blood type. Because our subjects were only pancreatic cancer cases, we did not perform the statistical analyses the reviewer indicated.

(3) As shown in Table 1 and Table 3, no difference was seen in localization of the tumor among the groups. The data were lacking on staging, grading, or metastasis.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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