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Comment on: Risk of Pancreatic Cancer in Relation to ABO Blood Group and Hepatitis C Virus Infection in Korea: A Case-Control Study

To the Editor:

The quality of each analysis is dependent on the background knowledge, and to be bound to our knowledge on the same time when we are applying our awareness for example during analysis and reporting the results. Maybe authors of the paper about the association between pancreatic cancer and ABO blood group (1) are aware from the below mentioned comments; but, usually a third person may observe some hints from outside which persons involved in the work cannot see.

This paper (1) consolidate previous literature in this filed. However, I am interested to know why authors did not use conditional logistic regression while they have paired match their controls for age, gender and date of admission or visit? The analysis should be matched (Paired t-test and conditional logistic regression) when our controls are paired matched with our cases.

Authors have only studied 34% of eligible cases who had available data about ABO blood group. For preventing selection bias, it is recommended to compare cases with missing data (66%) and the others (34%) specifically when the percentage of missing data is high. Any results can be distorted in these situations. We are not aware are there any differences between participants and non-participants in this study? According to the mentioned information about data gathering, it seems that such data are available but have not analyzed or reported. Usually, we have not easy access to such data.

About control group, were there selected from the base of the cohort (case-cohort) or from the persons with similar time of exposure which are enrolling at the time of selecting cases (nested case-control)? They have mentioned that cases and controls were matched for date of admission/visit; but, it is not determined if they are matched for duration of follow up (nested case-control) or not. It can determine type of study, the strength of association and many other details.

As mentioned in methods, "multivariate logistic regression analyses, including age, gender, smoking history and diabetes, were performed to estimate the adjusted odds ratios (AOR)." Such sentence dictates me that they have entered all these variables in the model and have run the logistic regression once. So, ORs are adjusted not only for age and gender; but also, for other variables which are included in the model. For example, in table 2, Non-O blood group OR in comparison with O blood group has an OR which is adjusted for age, gender, smoking history and diabetes. However, they have mentioned it is age- and gender-adjusted OR. They do not mean that these are variables that they have analyzed separately in different logistic models. If they want to mention which variables are evaluated in multivariable logistic regression, they should also express HBsAg and anti-HCV, as well. Therefore, according to the text, we should consider these ORs adjusted for all mentioned variables entered the model.

Results show that AORs for pancreatic cancer in subjects with blood types A is 1.36 (1.09-1.71; $P = 0.08$). It should be significant based on confidence interval, because it has not covered the number one. However, according to P value, it seems non-significant (higher than usual cut off point for P value which is 0.05). Is there any explanation by authors? It is not unusual for borderline values. However, it is some more far to be considered borderline.

When we pooled data, subgroup differences may be obscured. The log-rank test can detect differences between two different groups like AB and O. Here, the authors have compared all four groups (A, B, AB, and O) at once which may hide the underlying significant difference.

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The Author Response:

We appreciate the kind and incisive comments related to our manuscript titled "Risk of Pancreatic Cancer in Relation to ABO Blood Group and Hepatitis C Virus Infection in Korea: A Case-Control Study"(1). When the case-control data is frequency

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matched, which was the case for the current study as described in the second paragraph of the MATERIALS AND METHODS, one generally do not need to use a matched-pair analysis. However, the controlling of the matched variables is recommended since the matching will bias the association (e.g. OR) toward the null (2). We therefore performed age and gender adjusted logistic regression, and regarded this as age and gender adjusted "univariate" analysis for the target explanatory variable. When variables other than age and gender are adjusted, we termed this as "Adjusted OR" (AOR) for the target explanatory variable. i.e. AOR is not the OR adjusted only for age and gender, and the definition of AOR can be found in the method section.

We totally agree that the mechanism of the missing should be carefully monitored in all research. However, one of the explicit inclusion criteria of the current study was availability of the ABO blood type information. Data on pancreatic cancer patients with missing ABO blood type information were not collected as part of the study because of the explicit inclusion criteria. Post-hoc analysis found that some demographic variables were not significantly different between patients with missing ABO blood type and those without. Cases and controls were frequency matched only for age and sex, and not for the date of admission and visits except that those admitted during 2001-2011 were included in the study.

We apologize for this misstatement, and it will be corrected. We sincerely apologize for the wrongfully reported *P* value. When an explanatory variable has more than 2 categories, there are different ways to put a contrast between different levels of the variable. To estimate the OR of A, B and AB blood types over O blood type, we should have used a contrast 1 for A, B and AB, and 0 for O blood types. Instead, we used 1 for A, B and AB, and -1 for O. The estimated ORs and confidence intervals remain the same but by doing so, the *P* values are reported wrong. The corrigendum will be sent to the journal.

The odds ratios in univariate analysis were determined as 1.36 (1.10-1.68; P = 0.005) for blood type A, 1.21 (0.91-1.60; P = 0.20) for type AB, and 1.15 (0.92-1.44; P = 0.23) for type B, compared with blood type O after adjusting for age and gender. The AORs for pancreatic cancer in subjects with blood type A, AB and B were 1.36 (1.09-1.71; P = 0.007), 1.29 (0.96-1.74; P = 0.09), and 1.20 (0.94-1.52; P = 0.14), respectively.

The comparisons between each of A, AB and B blood types and O blood type were already performed, and the results were not significant. One should however note that this invokes multiple testing and the significance should not be evaluated at 0.05 level. The log rank test can test whether there is any difference between 4 groups, and when there is a difference in general by log rank test, one may be able to test each comparison separately.

There has been increasing evidence of the involvement of ABO gene variability and pancreatic cancer risk. Further research is warranted to describe the mechanisms by which ABO blood type or closely linked genetic variants influence pancreatic cancer risk.

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