Author's response to reviews

Title: Benign prostatic hyperplasia increases bladder cancer risk in diabetic patients: a population-based cohort study using the National Health Insurance in Taiwan

Authors:

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Author's response to reviews: see over
Dear Editor,

The manuscript has been revised taking into account all the comments and suggestions from the editor and the reviewers. Please kindly note that in the revised manuscript the title has been modified to fit the requirement of the Journal. Furthermore, the age subgroup analyses have been restricted to those aged 60 years or older as suggested by the reviewer Takayuki Sugiyama. A new table 5 has been added to show the hazard ratios for bladder cancer for diabetes duration and medications used for diabetic control in BPH men, as suggested by the reviewer Tetsuto Kanzaki.

The format of the manuscript has been revised in accordance with journal’s style. Furthermore, the major parts revised are shown in red color for your convenience of re-reviewing.

Please find the responses to the specific comments of the reviewers as follows.

Sincerely yours,

Chin-Hsiao Tseng, MD, PhD
Reviewer: Tetsuto Kanzaki

1. In introduction (last paragraph), the author stated bladder cancer risk associated with pioglitazone. This is not enough to explain why the author started to investigate bladder cancer risk in BPH patients, especially in diabetes. Is BPH highly prevalent in diabetes?

Response: Thank you for your kind suggestions. More information has been added in the Introduction, especially on the relationship between diabetes and BPH (Page 4, last paragraph to Page 5).

2. Are diabetic duration and diabetic control related with bladder cancer risk in BPH men? The author should show it, if data is available.

Response: As indicated, additional models were created to analyze the hazard ratios for bladder cancer in BPH men with regards to diabetes duration and the medications used for diabetic control. However, we did not have information on blood glucose levels for analyses. It was noted that diabetes duration was not significantly predictive for bladder cancer in BPH men; and that among all anti-diabetic drugs metformin was significantly associated with a lower risk of bladder cancer in the BPH men. A new Table 5 was added to show the results of these findings, and the text has been revised accordingly with regards to these additional analyses.

3. The author should show bladder cancer risk in BPH of non-diabetic Taiwan male inhabitants, and compare with diabetic patients, if data is available.

Response: For the analyses of this manuscript, we could only retrieve partially the reimbursement databases of all diabetic patients diagnosed within the period from 1996 to 2009, because of the regulations restricting data retrieve from the whole databases to a certain percentage. To retrieve the reimbursement information of non-diabetic subjects simultaneously would have exceeded such a restriction. Therefore, we did not have data for BPH in non-diabetic subjects for analysis. This was considered as a limitation of the study (Page 14, second paragraph).

4. In discussion, the author must discuss the significance of diabetes in relation with BPH and bladder cancer risk.

Response: The significance of diabetes in relation with BPH and bladder cancer risk was discussed in more detail in the revised manuscript (Pages 12-14).
Reviewer: Takayuki Sugiyama

In this article, the authors describe one of their limitation is the lack of the details of the bladder cancer. I assume that the sub-analysis of the “malignant level of the bladder cancer” if the database have the information of the "operation maneuver of the bladder cancer". Cause of the “total cystectomy may be surrogate marker of the “Invasive bladder cancer”.

Response: For the analyses of this manuscript, we could only retrieve partially the reimbursement databases of all diabetic patients diagnosed within the period from 1996 to 2009, because of the local regulations restricting data retrieve from the whole NHI datasets to a certain percentage. Asking for the detailed information regarding the surgical procedures for bladder cancer at the stage of data request might have exceeded such an allowance. Therefore, we could not perform the sub-analysis as indicated. This was considered as a limitation of the study in the revised manuscript (Page 14, second paragraph).

In Table4, it is thought that the element of "age" is corrected, but if the target age groups are 60 years old or older, I think that the difference of the risk of bladder cancer show much clearly.

Response: Thank you for this suggestion. In the revised manuscript the age subgroup analyses have been restricted to age 60 years or older. Please kindly note that Tables 2-4 have been changed accordingly.