Author's response to reviews

Title: No evidence for a decreased risk of thyroid cancer in association with use of metformin or other antidiabetic drugs: a case-control study

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Author's response to reviews:

Dear Dr Inoue,

Please find enclosed the revised version of the manuscript “Use of metformin or other antidiabetic drugs is not associated with a decreased risk of thyroid cancer: a case-control study” which we would like to re-submit to the BMC Cancer. We thank the reviewers 2 and 3 for their approval of our revisions. We again carefully addressed the concerns raised by reviewer 1 and hereby re-submit the second revision of the manuscript.

Reviewer 1

Major Compulsory Revisions:

1. Previous MCR 1: Please state the power (i.e., 1 - beta) for the statistical test that evaluate the significance of metformin as a factor associated with a decreased risk of thyroid cancer. Unless the power for the test is >80% (i.e., beta <0.2), one cannot conclude that “Use of metformin is not associated with a decreased risk of thyroid cancer”, and the title of the article should be "Lack of evidence that use of metformin is associated with a decreased risk of thyroid cancer". I just want to emphasize the logic that not being able to find "A" in a limited effort does not mean that "A" does not exist.

Beta for long-term metformin use is 0.0851 (model 1) and 0.0415 (model 2) and thus we think that we can conclude that “use of metformin is not associated with a decreased risk of thyroid cancer”. However, we certainly agree that our statement is based on the findings of this particular study population and that we were somewhat limited in terms of statistical power, ever though we used one of the largest and best-validated medical databases that is available for observational research and for pharmacoepidemiology. In order to slightly reduce the strength of our statement we propose to modify the title to “No evidence for a decreased risk of thyroid cancer in association with use of metformin or other antidiabetic drugs: a case-control study”

2. Previous MCR 2: The clinical behavior of thyroid cancer is not just divided
along the line of differentiated vs. poorly differentiated or anaplastic thyroid cancer. The biology, clinical behavior, treatment and prognosis of the differentiated thyroid cancers are all different. For example, medullary thyroid carcinoma arise from C cells of the thyroid and they do not uptake iodine. The majority of the thyroid cancer cases are papillary thyroid carcinoma. If it is impossible to identify the type of thyroid cancer in the data set, the word "differentiated" (page 11 line 26) should be replaced by "papillary thyroid".

We agree and we changed the wording on page 12, lines 2-3, as suggested by the reviewer.

3. Previous MCR 3: The authors only presented one side of the story. The following publications should also be cited and discussed:

Plews et al. J. A Novel Dual AMPK Activator/mTOR Inhibitor Inhibits Thyroid Cancer Cell Growth. Clin Endocrinol Metab. 2015; 100(5):E748-56.


It was certainly not our intention to just present one side of the story. We always pay a lot of attention to a balanced discussion and to construct a solid hypothesis which is based on all available literature. In our manuscript we clearly state that “our results are somewhat surprising given that available evidence suggests a possible antitumor effect of metformin or in thyroid cancer cell lines”. However, we agree with this reviewer that this part of them manuscript could be improved and we elaborated this section in more detail in the revised manuscript by adding some of the suggested references (page 10, lines 1-3). Please note that it is not the purpose of this manuscript to discuss all evidence from mechanistic and basic science studies in depth; our discussion is intended to focus on the results which we found in light of other observational evidence.

4. Previous MCR4: Hyperthyroidism and goiters are known risk factors for thyroid cancer. The a priori models were deficient by not including them. After reporting the results of the a priori models, what are the obstacles that will prevent analyzing a new model postpriori (post hoc) as long as the models are reported as such with appropriate control for the type I error rate?

We did not consider hypothyroidism and goiter as covariates in the a priori model because these variables are most likely not confounding the association of interest. They could only confound the association if they were not only associated with an altered risk of thyroid cancer (which we agree that this may be the case), but also with an altered likelihood of being exposed to a particular
antidiabetic drug, which is unlikely. However, we ran additional analyses to support our decision. As expected, inclusion of these two additional variables did not meaningfully change our results. We now included the results for the multivariate models with the variables for hyperthyroidism and goiter as “Model 2” in Tables 2 and 3 (page 20 and 21). We also commented in the Methods section on this post hoc analysis (page 7, lines 22-24), and we added a sentence to the Discussion (page 11, lines 4-7).

5. Previous Minor Essential Revision 2: The reference on page 10 line 17 (reference 40) is a review article. A reference with primary data to support that statement that "TZD inhibit proteolytic activity of dipeptidyl peptidase (DPP) IV" needs to be cited. Although TZDs may lower the circulating DPP IV level, I am not aware of any data showing that TZDs can inhibit DDP IV in intact thyroid cancer cells at concentrations reachable pharmacologically in humans.

We agree with the reviewer in that TZDs are not competitive DPP-4 inhibitors per se but rather reduce serum DPP-4 activity as a result of reduced DPP-4 secretion (Lenhard et al. Biochem Biophys Res Commun 2004). We therefore modified the statement on page 10, lines 15-16 accordingly.

We hope we were able to address the concerns to your satisfaction, and we would be pleased to see our study published in BMC Cancer.

Sincerely,

Christoph R. Meier, PhD, MSc (corresponding author) on behalf of all authors