Reviewer's report

Title: Use of metformin or other antidiabetic drugs is not associated with a decreased risk of thyroid cancer: a case-control study

Version: 2 Date: 21 February 2015

Reviewer: jim yeung

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This manuscript reports a case-control analysis of potential associations of metformin and other antidiabetic drugs with the risk of thyroid cancer. They used data from the UK-based CPRD. They did not find any association of metformin or other antidiabetic drugs with an altered risk of thyroid cancer.

Major Compulsory Revisions:

1) The results presented in the manuscript do not support their conclusion that “metformin use was not associated with a decreased risk of thyroid cancer” and “none of the other antidiabetic drugs were associated with a change in risk of thyroid cancer”. They did not find any associations. Therefore, the null hypotheses cannot be rejected with a confidence level of 95%, but their sample size is relatively small, i.e., only 70 patients with both diabetes and thyroid cancer. Without a statistical power of >80%, one cannot conclude with sufficient confidence that there are indeed no associations. The conclusion on page 12, line 11-12 is not justified.

2) There are several distinct types of thyroid malignancies: papillary thyroid carcinoma, follicular thyroid carcinoma, anaplastic thyroid carcinoma, medullary thyroid carcinoma and thyroid lymphoma. All these distinct types of thyroid malignancies have unique pathogenic mechanisms and clinical behavior. It is not reasonable to assume they all respond to metformin and other antidiabetic medications in the same way. Although papillary thyroid carcinoma accounts for about 75 to 80% of all thyroid malignancies, the likelihood of being able to detect statistically significant differences will be compromised by the noise created by inclusion of a mixed bag of different malignancies affect the same anatomical site – the thyroid gland.

3) Page 3, line 27 and page 9, line 25: The PCCL3 cell line is not a thyroid cancer cell line. It is a clonal rat thyroid cell line that requires thyrotropin for growth. It is used in research on thyroid follicular cell function and iodide uptake. The paper by Andrade et al. (reference 24) reported a role of AMPK in the regulation glucose uptake in non-cancerous thyroid follicular cells. This paper is not relevant to thyroid cancer. The speculation that “AMPK activation by metformin could, in theory, lead to increased glucose uptake and thyroid cancer progression” (page 4, line 2) is not justified. The statement on page 9, line 25, “activation of AMPK has also been associated with increased GLUT1 expression in thyroid cancer cells”, is wrong.
4) Page 20, line 38 and page 21, line 44: Why the adjusted OR is adjusted only for BMI, smoking and diabetes but not alcohol consumption, hyperthyroidism and goiter, which have significant associations with thyroid cancer risk as shown in Table 1?

5) Page 20, Table 2 and page 21, Table 3: There are multiple discrepancies in the data:

Cases with any metformin use: 49 in table 2, but 47 in table 3.
Cases with 1-29 metformin prescriptions: 23 in table 2, but 21 in table 3.
Controls with any metformin use: 208 in table 2, but 254 in table 3.
Controls with 1-29 metformin prescriptions: 116 in table 2, but 129 in table 3.
Controls with =>30 metformin prescriptions: 92 in table 2, but 125 in table 3.
Number of diabetic patients in controls: 365 in table 1, but 419 in table 3.
Controls with any sulfonylurea use: 154 in table 2, but 188 in table 3.
Controls with 1-29 sulfonylurea prescriptions: 77 in table 2, but 97 in table 3.
Controls with =>30 sulfonylurea prescriptions: 77 in table 2, but 91 in table 3.
Controls with any insulin use: 87 in table 2, but 70 in table 3.
Controls with any TZD use: 41 in table 2, but 53 in table 3.

6) Page 9, line 12: “Similar to our findings, any use of sulfonylureas......was associated with an increased risk of thyroid cancer......” Yet the title of the manuscript and the abstract (page 2, line 20) are contradictory and state that none of the other antidiabetic drugs were associated with a change in risk of thyroid cancer.

7) Page 9, line 18: The statement, “These results are contradictory to the reported results of his first study [6]”, is wrong. In reference 6, no statistically significant association of metformin use with the risk of thyroid cancer was detected because of low statistical power. Not finding something does not necessarily mean that thing does not exist. Without sufficient statistical power, no conclusions can be drawn. There is no finding to contradict the finding in Tseng’s subsequent redesigned study. The authors are committing the same type of error in logic as described above in Major Concern 1.

Minor Essential Revisions:

1) Page 5, line 14: Why is alcoholism excluded and then alcohol intake is analyzed as a factor associated with thyroid cancer risk? How is “alcoholism” defined?

2) Page 10, line 6: TZDs do not inhibit DPP-4. The DPP-4 inhibitors are the gliptins.

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.