

Metformin and Malignant Tumors: Not Over the Hill [Response to Letter]

Weiling Leng^{1,*}

Juan Jiang^{2,*}

Bing Chen¹

Qinan Wu³

¹Endocrinology Department, The First Affiliated Hospital of the Third Military Medical University (Army Medical University), Chongqing, People's Republic of China; ²Endocrinology and Nephrology Department, Chongqing University Cancer Hospital and Chongqing Cancer Institute and Chongqing Cancer Hospital, Chongqing, People's Republic of China;

³Endocrinology Department, Dazu Hospital of Chongqing Medical University, The People's Hospital of Dazu, Chongqing, People's Republic of China

*These authors contributed equally to this work

Dear editor

Thank you for Dr Rastmanesh's comments on our manuscript,¹ which we reviewed the anti-tumor effect and also increase the sensitivity of malignant tumors to chemotherapy of metformin, analysed its possible mechanism, and identified possible research hot spots, we also put forward some valuable researches and hypothesis on metformin in many type of malignant tumors.

First of all, we agree with what the author mentioned in question 1: retrospective analysis is not the best evidence. This is what we have repeatedly mentioned in the manuscript: There were many biases in the retrospective analysis on the anticancer effect of metformin, such as only diabetes patients recruited in some researches of breast cancer and liver cancer, and in colorectal cancer, prostate cancer and gastric cancer, lots of retrospective studies have confounding or public biases. We will also make a summary review in our manuscript: However, Srivastava et al proposed that these studies potentially exaggerate the tumor-related benefits of metformin.² In 2012, a systematic review and collaborative meta-analysis of randomised clinical trials did not support the hypothesis that metformin had a significant beneficial effect of metformin on cancer prognosis.³ Seven years later, Oh and Song conducted a nationwide sample cohort study to analyze the relationship of metformin use and cancer in diabetes patients. They found a lack of association between metformin treatment and the risk of cancer among diabetes patients, even in the high daily dosage groups (>1 g/day).⁴ However, there might be some confounders or time bias in this study. Thus, further prospective, large population-based cohort studies are needed to confirm these findings. It suggested that we still hold that some researches were not enough to prove the metformin has anti-cancer effect. At the same time, we have analyzed these studies, so there is a dispute or controversy on whether metformin really has anti-cancer effect, which we have mentioned many times in this manuscript.

Secondly, as you said in question 2, some studies have indicated that metformin has anticancer effect. Since this viewpoint is more accepted by the public, we did not cite the original literature at here, but replaced it by some reviews and also their viewpoint, such as the reference.⁴⁻¹²

About the question 3, it is that the main reason for we choosing these cancers is that these cancers leading the highest incidence rate and mortality rate in Chinese population, or it has the closely relationship to metformin. Although the pathogenesis of cancer is common, it is a heterogeneous disease. There are great differences between different kinds of cancer and even every cancer patient. For example,

Correspondence: Qinan Wu
Endocrinology Department, Dazu
Hospital of Chongqing Medical University,
The People's Hospital of Dazu, Chongqing
Email wqn11@126.com

diabetes can promote the incidence of many kinds of cancer, but it is lower for prostate cancer.¹³

About the question 4, there are large number of signal pathways and hypotheses of the cancer. We just summarized some signal pathways and hypotheses that are more closely related to metformin, more recognized and more thoroughly studied. Unfortunately, some valuable hypotheses may be omitted for our limitation.

At last, many thanks for the supplement and reminder, we are glad to consider the advices in future investigations.

Disclosure

Weiling Leng and Juan Jiang are co-first authors for this communication. The authors declare no conflicts of interest in this communication.

References

- Leng W, Jiang J, Chen B, et al. Metformin and malignant tumors: not over the hill. *Diabetes Metab Syndr Obes.* 2021;14:3673–3689. doi:10.2147/DMSO.S326378
- Srivastava SP, Goodwin JE. Cancer biology and prevention in diabetes. *Cells.* 2020;9(6):1380. doi:10.3390/cells9061380.
- Stevens RJ, Ali R, Bankhead CR, et al. Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. *Diabetologia.* 2012;55(10):2593–2603. doi:10.1007/s00125-012-2653-7.
- Oh TK, Song IA. Metformin use and the risk of cancer in patients with diabetes: a nationwide sample cohort study. *Cancer Prev Res.* 2020;13(2):195–202. doi:10.1158/1940-6207.CAPR-19-0427.
- Simon D, Balkau B. Diabetes mellitus, hyperglycaemia and cancer. *Diabetes Metab.* 2010;36(3):182–191. doi:10.1016/j.diabet.2010.04.001
- Wolf I, Sadetzki S, Catane R, et al. Diabetes mellitus and breast cancer. *Lancet Oncol.* 2005;6(2):103–111. doi:10.1016/S1470-2045(05)01736-5
- Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med.* 2002;137(1):25–33. doi:10.7326/0003-4819-137-1-200207020-00009
- Chan AT. Metformin for cancer prevention: a reason for optimism. *Lancet Oncol.* 2016;17(4):407–409. doi:10.1016/S1470-2045(16)00006-1
- Samuel SM, Varghese E, Varghese S, et al. Challenges and perspectives in the treatment of diabetes associated breast cancer. *Cancer Treat Rev.* 2018;70:98–111. doi:10.1016/j.ctrv.2018.08.004
- Goodwin PJ, Ligibel JA, Stambolic V. Metformin in breast cancer: time for action. *J Clin Oncol.* 2009;27(20):3271–3273. doi:10.1200/JCO.2009.22.1630
- Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: a meta-analysis and systematic review. *World J Gastroenterol.* 2015;21(19):6026–6031. doi:10.3748/wjg.v21.i19.6026
- Dilokthornsakul P, Chaiyakunapruk N, Termrungruanglert W, et al. The effects of metformin on ovarian cancer: a systematic review. *Int J Gynecol Cancer.* 2013;23(9):1544–1551. doi:10.1097/IGC.0b013e3182a80a21
- Handelsman Y, Leroith D, Bloomgarden ZT, et al. Diabetes and cancer—an AACE/ACE consensus statement. *Endocr Pract.* 2013;19(4):675–693. doi:10.4158/EP13248.CS

Dove Medical Press encourages responsible, free and frank academic debate. The content of the Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

Dovepress

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion

and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-targets-and-therapy-journal>

<https://doi.org/10.2147/DMSO.S336807>