

# Metformin and Malignant Tumors: Not Over the Hill: A Short Comment [Letter]

Reza Rastmanesh <sup>1,2</sup>

<sup>1</sup>The Nutrition Society, London, UK;

<sup>2</sup>The American Physical Society, College Park, MD, USA

## Dear editor

I applaud Leng et al<sup>1</sup> for their brilliant review paper.

I, however, have some major comments. Having a glance over the reference list of sources cited, one acknowledges that the review synthesis suffers some problems. The authors have cited eight retrospective studies plus many systematic papers/meta-analyses, including some of the same retrospective studies, possibly leading to double bias. Retrospective studies may better fall within the scope of the third level of hierarchy of evidence,<sup>2</sup> but definitely are not the best evidence for mechanistic reviews.

Second, there are currently many published studies – easily accessible via online medical sources – from clinical trials, controlled clinical trials, and randomized Phase I and II studies on possible anticancer effect of metformin – which are not cited in this review paper by Leng et al.<sup>1</sup> One could certainly question whether the conclusions would have been the same if the authors had included results of these clinical trials, rather than retrospective analyses.

Third, the authors have discussed limited types of cancers and have left others unsolved. It would be an efficient strategy to revisit the main mechanisms of action of metformin in light of the emerging views on tumor heterogeneity. Most cancers/tumors share common pathologic pathways. It could be an efficient strategy if they could prepare a list of common tumorigenesis pathways in an attempt to facilitate generalization of metformin's anticancer effect to other types of cancers. This might also facilitate the discovery of better preventive measures and therapeutic agents for the treatment/management of cancers and lead to better choice of first-line medicines in the treatment of diabetes.

Lastly, there are novel anticancer mechanisms of metformin (such as those that inhibit DNA replication machinery, suppression of cancer progression through calmodulin-like protein 3, aryl hydrocarbon receptor-interacting protein (AIP) silencing novel pathway, and cell cycle arrest at the G0/G1 phase, suppression of cell migration, and alteration of cytoskeleton distribution, just to mention a few) which are not mentioned within their updated review and could be easily found in online sources such as PubMed, Scopus, etc.

These comments apply not only to the review by Leng et al,<sup>1</sup> but more generally to all reviews and systematic reviews of metformin and its potential anticancer effects.

I suggest three feasible approaches to diminish/avoid such controversies and non-inclusive conclusions for future reviews:

Correspondence: Reza Rastmanesh  
Private Clinic, #6, Physicians Building,  
Sarshar Alley, Vali Asr Street, Tajrish,  
Tehran, 1961835555, Iran  
Email: r.rastmanesh@gmail.com

(i) To select the best evidence in order to specifically answer mechanistic questions.

(i) Meta-analyzing causal mediation analysis of all related factors and data which combines evidence from multiple sources and improves power.<sup>3</sup>

(iii) To adjust for rescue treatment which complicates result interpretation in clinical trials,<sup>4</sup> randomized clinical trials,<sup>5</sup> longitudinal clinical trials and in failure-time settings with competing events by choosing appropriate estimands. For proper references, see statistics textbooks such as the Wiley Encyclopedia of Clinical Trials which is available online.

I hope that my short comment will open up further discussion, and maybe help Leng et al<sup>1</sup> to enrich their magnificent diagrams by including newly-discovered mechanisms and adding a list of common tumorigenesis pathways.

## Disclosure

The author has no competing or conflicts of interest in this communication.

## References

1. 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
2. Gulpinar O, Guclu AG. How to write a review article? *Turk J Urol.* 2013;39(Suppl 1):44–48. doi:10.5152/tud.2013.054
3. Zhu Y, Centorrino F, Jackson JW, et al. Meta-analysis of total effect decomposition in the presence of multiple mediators: the example of schizophrenia treatment. *Epidemiology.* 2021;32(1):120–130. doi:10.1097/EDE.0000000000001269
4. Ratitch B, Bell J, Mallinckrodt C, et al. Choosing estimands in clinical trials: putting the ICH E9(R1) into practice. *Ther Innov Regul Sci.* 2020;54(2):324–341. doi:10.1007/s43441-019-00061-x
5. Michiels H, Sotto C, Vandebosch A, et al. A novel estimand to adjust for rescue treatment in randomized clinical trials. *Stat Med.* 2021;40(9):2257–2271. doi:10.1002/sim.8901

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.S335574>