

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

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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,

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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.

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