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RE: Metformin Use and Gastric Cancer Risk in Diabetic Patients After *Helicobacter pylori* Eradication

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We read with great interest the article by Cheung et al. on the association between the use of metformin and the risk of gastric cancer in patients with type 2 diabetes following *Helicobacter pylori* eradication treatment (1). In their article, the authors reported that use of metformin was associated with a 51% reduction in the risk of gastric cancer (adjusted hazard ratio [HR] = 0.49, 95% confidence interval [CI] = 0.24 to 0.98) compared with non-use of metformin. Although this study addresses an important question given the proposed anticancer effects of metformin, we think that the observed beneficial effects may be the result of immortal time bias.

Immortal time refers to a period of follow-up during which, because of how the exposure is defined, the study outcome cannot occur (2). Indeed, the authors of the study defined metformin use as exposure to this medication for more than 180 days during follow-up, that is, the time between the index date (ie, *H. pylori* eradication treatment) and the end of the study period. Doing so, the authors gave exposed patients a "survival advantage" over the reference group, because they could not have experienced gastric cancer between the index date and the time point when they accumulated 180 days of metformin use. Importantly, immortal time bias has been previously examined in the specific setting of observational studies assessing the effects of metformin on the risk of cancer, where it was shown that it can lead to greatly exaggerated beneficial associations (3). Of note, immortal time bias tends to be augmented in analyses on cumulative duration of use or cumulative dose, because patients must remain event-free for even longer periods of time in order to reach longer durations of use or accumulate higher doses of the medication of interest. Accordingly, in this study, there was a 65% reduction in risk of gastric cancer in patients with 3 or more years duration of metformin use (HR = 0.35, 95% CI = 0.16 to 0.80) in comparison with a 25% statistically nonsignificant reduction in patients with less than 3 years duration of metformin use (HR = 0.75, 95% CI = 0.32 to 1.74). A similar trend was observed with cumulative dose.

Two further potential limitations need to be mentioned. First, the authors did not use a latency period between the onset of exposure and the occurrence of the study outcome. However, in studies assessing cancer as an outcome, "lagging" exposure is necessary for biological plausibility (4). Second, the authors did not restrict their population to new users. However, inclusion of prevalent users may lead to selection bias via differential inclusion of survivors by exposure category (5).

Thus, it would be informative if the authors could repeat their analysis by using a time-varying exposure definition instead of the time-fixed definition described above, introducing a latency period after the onset of exposure, and restricting their study population to new users. We believe that this reanalysis would yield a more realistic effect estimate of the association between metformin use and risk of gastric cancer.

Notes

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The authors have no conflicts of interest directly related to this correspondence.

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