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Letter to the Editor

Comments on "Use of metformin and risk of kidney cancer in patients with type 2 diabetes", Chin-Hsiao Tseng, Eur J Cancer, 2016, No. 52, pp. 19–25

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Dear Editor,

We have read with great interest the article by Chin-Hsiao Tseng, Use of metformin and risk of kidney cancer in patients with type 2 diabetes, which appeared in the *European Journal of Cancer* issue of January 2016 [1]. We have noted, however, that the results of this study may have been affected by selection bias.

Using the Taiwanese National Health Insurance reimbursement database, Tseng performed a retrospective population-based cohort study of incident type 2 diabetic patients who either received metformin as the first antidiabetic drug (ever users of metformin) or other antidiabetic drugs as first treatment without receiving metformin during follow-up (never users of metformin). To estimate the risk of kidney cancer, the author performed a Cox regression analysis and adjusted for imbalance between baseline characteristics by applying inverse probability treatment weighting of the estimated propensity scores (PSs). Subsequently, a hazard ratio (95% confidence interval) of 0.279 (0.254–0.307) was

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estimated for the risk of kidney cancer in ever users of metformin compared to never users. Unfortunately, the PS approach incorporated in the statistical model cannot completely correct for any selection bias that may have occurred during the formation of the study population. For example, the history of any cancer excluding kidney cancer was 1.4-fold higher in never users of metformin (26.88%) versus ever users of metformin (19.32%).

Based on the methodology section of the paper and the results in Table 2, we believe a significant selection bias may have occurred during the allocation process of individuals to the treatment group of never users of metformin. Patients using other antidiabetic drugs before they start with metformin were excluded from the study population (n = 200,785). Therefore, possible follow-up time designated for the group of never users of metformin is wrongfully excluded from the analysis. This can also be seen in Table 2, where the amount of follow-up time in the never users of metformin is much shorter than that in the ever users of metformin (433,005.63 vs. 1,144,982.82 person-years). In addition, this selection bias might partly explain the significant baseline differences as seen in Table 1.

Within the scientific community, there is ongoing debate concerning the protective effect of metformin on cancer development in patients with type 2 diabetes mellitus, with studies showing conflicting results for various cancers. Earlier studies concluded metformin could decrease cancer risk but were afflicted by time-related biases, such as immortal time bias. More recent studies that used methods to avoid these biases reported no effect of metformin use on cancer incidence [2,3]. Based on this, we are currently not convinced that metformin has a clinically relevant protective effect on cancer development. Costly trials based on methodologically inaccurate studies should also not be encouraged. Therefore, we kindly ask Dr. C.-H. Tseng to reanalyse the risk of kidney cancer in users of metformin compared to non-users of metformin without the currently potential selection bias.

Conflict of interest statement

None declared.

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