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Response

Response to Khosrow-Khavar, Kurteva, and Douros

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We thank Khosrow-Khavar et al. for their letter that commented on our recent study on the chemopreventive effect of metformin on gastric cancer development in patients who had received *Helicobacter pylori* (HP) eradication therapy. The authors suggested several methods to further improve the robustness of our results, including defining drug exposure by the time-varying covariate instead of time-fixed method; implementation of a "lag-time period" because of the long time lag between cancer development and latency of drug effect; and a "new user" design by restricting the exposure cohort to new users of metformin.

In response to their suggestions, we first treated all medication uses including metformin as time-varying covariates, with the follow-up period split into 6 monthly intervals. Drug exposure was defined as at least 90 days of use in each interval (1). As there is no consensus on the optimal lag-time period after drug initiation (2), we arbitrarily used 1 year as the cutoff (1-year lag-time analysis). Sensitivity analysis was performed by using different cutoffs (2- and 3-year lag-time analysis). Concerning the last comment on new user design, this would result in more than 50% reduction in the number of patients from 7266 to only 3388. This may also introduce selection bias because of inclusion of mostly metformin users who were newly diagnosed with diabetes mellitus after receiving HP eradication therapy.

As previously described, propensity score regression adjustment was used as the primary method to derive the adjusted hazard ratio (aHR) of gastric cancer with metformin use. Covariates included age of receiving HP eradication therapy, sex, smoking and alcohol use, prior peptic ulcer disease, other comorbidities, and concurrent medication use.

In this reanalysis, there were 7266 patients with 37 gastric cancer cases (median duration of follow-up: 7.1 years; interquartile range [IQR] = 4.7–9.8 years). The median duration of metformin use was 5.5 years (IQR = 3.3–8.4 years). Among metformin users, the interval from first metformin use to gastric cancer development ranged from 2.9 to 10.4 years. On 1-year lag-time analysis, metformin use was associated with a reduced gastric cancer risk (aHR = 0.35, 95% confidence interval [CI] = 0.17 to 0.73). This association remains statistically significant on both 2-year and 3-year lag-time analysis (Table 1).

Table 1. Association between metformin use and gastric cancer (GC) risk using time-varying covariables and lag-time analysis

Lag-time analysis	Adjusted HR* of GC with metformin use (95% CI)	P†
1-year	0.35 (0.17 to 0.73)	.005
2-year	0.41 (0.18 to 0.91)	.03
3-year	0.37 (0.16 to 0.89)	.03

*Adjusted HR was calculated by propensity score regression adjustment. HR = hazard ratio; CI = confidence interval.
†Cox proportional hazards model was used to calculate the *P* values. A two-sided *P* value of less than .05 was used to define statistical significance.

Hence, the beneficial effect was not attenuated in this reanalysis using time-varying covariates and lag-time analysis as compared with our original analysis (aHR = 0.49, 95% CI = 0.24 to 0.98]). Although the lag-time analysis addresses the issue of latency of antineoplastic drug effect (2), the majority of our patients had a long period of follow-up and metformin use, which would not pose a biased effect on augmenting the potential chemopreventive effect of metformin.

Notes

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