Letter to the Editor

Cancer Epidemiology, Biomarkers & Prevention

Metformin, Diabetes, and Survival among U.S. Veterans with Colorectal Cancer—Response

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We appreciate the letter of Alam and colleagues, who underscore the point we made in our discussion section when we noted that time-related biases, such as immortal time bias, can threaten pharmacoepidemiologic studies of metformin as a potential chemotherapeutic agent (1). Vivid illustrations of this bias are available among prior metformin studies that defined exposure based on receipt of multiple prescriptions, with the interval of time between prescriptions being immortal, and discordant time zero definitions between comparison groups (2). Although using a time-varying analytic approach is one possible remedy to this bias, immortal time bias is likely best addressed through good study design. A recent framework recommends avoiding this "self-inflicted injury" by aligning start of follow-up, determination of study eligibility, and treatment assignment, in short, emulating the principles of a target randomized controlled trial (3). We similarly sought to maximize symmetry between groups in our own study by using an active comparator group for our primary analysis. Metformin-treated individuals were compared with those treated with another antidiabetic medication (with the same two prescription requirement), and time zero was set as date of cancer diagnosis in both groups. The majority of metformin treated (94%) and other diabetic drug-treated patients (90%) had initiated antidiabetic drug use before the date of cancer diagnosis, and among those who initiated antidiabetic drug use after diagnosis, the mean "immortal" time interval was the same in the two groups (74 vs. 69 days, respectively). Moreover, all estimates were unchanged in sensitivity analyses excluding subjects who initiated antidiabetic drug use after the cancer diagnosis date [for the comparison of metformin users with other antidiabetic drug users with respect to overall survival: main analysis HR_{adj}, 0.87; 95% confidence interval (CI), 0.79–0.95; $P = 0.003$ versus sensitivity analysis HR_{adj}, 0.88; 95% CI, 0.80–0.96; $P = 0.006$].

Alam and colleagues also expressed concern regarding our use of a multivariable regression model to adjust for confounding and suggested that a matched propensity score approach would have been preferable. The vulnerability of regression models to erroneous or unexplored assumptions regarding model specifications is a well-known limitation among epidemiologists. Yet, the superiority of propensity score approaches for confounding control has not been established (with matched studies in particular possibly suffering from compromised generalizability as results are conditional on ability to be matched). Despite strong support for propensity-based methods from rigorous theory and simulations, empirical comparisons to date show no clear improvement in agreement between propensity-adjusted studies and corresponding RCTs, relative to observational studies analyzed with conventional adjustment methods (4, 5). Although propensity scores are enormously popular tools in observational studies, we await forthcoming evidence that will inform methodologic choices regarding their use, how to best use them, and comparisons with "conventional" methods.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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