COMMENTS AND RESPONSES

Comment on: Suissa and Azoulay. Metformin and the Risk of Cancer: Time-Related Biases in Observational Studies. Diabetes Care 2012;35: 2665–2673

We agree with Suissa and Azoulay (1) that observational studies, particularly those of drug effects, can be subject to biases and that "time-related" biases must be carefully controlled in these types of studies. In their recently published article (1), Suissa and Azoulay have attempted to "show that several of the observational studies investigating the association between metformin and cancer incidence and mortality are affected by these time-related biases." Since several of our studies have been so charged, we have carefully considered their concerns in relation to our own research (2–5).

In their article, Suissa and Azoulay criticized four of our studies (three case-control [2–4] and one nested case-control [5]; by the way, they are not all nested as claimed). Their concerns about our articles were restricted to "time window bias," known to others as bias due to differential exposure opportunity, which is an important potential bias that indeed should be controlled for. In our studies we either matched on length of time in the database (2–4), or we carefully assessed the comparability of exposure opportunity between cases and controls (5). In fact, in the breast cancer study we did adjust for length of time in the database, which we reported to be similar between cases and controls. Thus, there is no reason to suspect that controls would have had longer records than cases, possibly accounting for the decreased risk associated with long-term exposure to metformin observed in our study. There were, however, cases and controls in that study with long-term exposure to various other oral hypoglycemic drugs that were not associated with the risk of breast cancer. It seems implausible that the exposure opportunity was equal between cases and controls for all other hypoglycemic drugs while it differed only for patients with long-term use of metformin, the group of patients yielding the only decreased relative risk estimate in our analysis. Thus we believe that there was no evidence for exposure opportunity bias in our study, and the speculation by Suissa and Azoulay about what in theory may or may not have happened is not founded.

There are particular methodological concerns in studies of drugs in relation to diabetes where published guidelines prescribe a stepwise treatment approach usually starting with metformin. In such studies, matching cases and controls on length of diabetes history invariably matches on duration of diabetes treatment, which will bias the observed measure of association toward no effect. Suissa and Azoulay commented on selected results from our studies without providing scientific evidence for a significant role of differential exposure opportunity bias. Furthermore, they ignored (null) results from the same studies that did not fit their assertion, raising the question of whether their choice of articles and findings to review was perhaps subject to its own bias.

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