COMMENTARY

Metformin and Cancer: Mounting Evidence Against an Association

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Metformin, a biguanide derived from the French lilac, has become the preferred first-line therapy for the treatment of type 2 diabetes (1). This drug is inexpensive, has an excellent safety profile, and can be safely combined with other antidiabetes agents (2). As a result, it has become the most widely prescribed antidiabetes drug worldwide.

In addition to metformin's well-established antidiabetes effects, there has been considerable interest in its antitumor properties. Such interest started from a short report of an observational study published in 2005 that suggested that the use of metformin was associated with a 23% decreased risk of any cancer (3). Since then, a large number of observational studies have been published with several "corroborating" a possible decreased incidence of cancer with this drug (4). In parallel, several laboratory studies have also suggested that metformin has antineoplastic activity, although doses used in such experiments were typically higher than the conventional doses used in the treatment of type 2 diabetes (5). Nonetheless, this apparent convergence of evidence from both observational and laboratory studies has led some to call for large randomized clinical trials (RCTs) of metformin in cancer prevention and treatment (6–9). However, a careful assessment of the observational studies conducted to date point to some important time-related biases that systematically exaggerated the reported antitumor effects of metformin (10).

Time-related biases, such as immortal time bias, time window bias, and time lag bias, have been previously described in studies of diabetes treatment (10) and in other therapeutic areas (11–14). These biases result from not properly classifying exposure during the follow-up of a cohort study or from measuring exposure over unequal time intervals in case-control studies, which can produce spurious risk reductions. For example, a cohort study that compares users of metformin with "nonusers" of metformin on the time to cancer incidence will necessarily have to be careful about "time." Indeed, the time span between diagnosis and metformin treatment initiation, which could span a few years during which nonpharmacologic therapies could have been used, is necessarily "immortal" in the sense that the patient could not have developed cancer during this period; the ones who do develop cancer are necessarily in the "nonuser" group. This will result in an overestimation of cancer incidence in the nonusers and an underestimation in the metformin user group. A variation of this bias is when multiple prescriptions of metformin are used to define exposure (14). For example, in the study using the Taiwanese National Health Insurance data, the cohort included 12,005 patients who received at least two prescriptions of metformin during 2000–2007 and 4,597 who received one prescription of another oral agent during this period as the comparator (15). The use of metformin was associated with a highly significant 88% reduction in the incidence of any cancer (hazard ratio 0.12; 95% CI 0.08–0.19). This finding is, however, subject to immortal time bias introduced from the definition of metformin exposure, which required at least two prescriptions of metformin during 2000–2007. Indeed, as depicted in Fig. 1, the time between the first and second metformin prescriptions during follow-up is immortal, as the patient must be cancer-free to have received the second metformin prescription. On the other hand, the comparator group needed only a single prescription of another oral antidiabetes drug and did not have such a condition of a second prescription. Thus, the concern with the analysis that computed the astonishing hazard ratio of 0.12 was that the yet unexposed immortal person-time was misclassified as exposed, thus leading to immortal time bias.

In this issue, Mamtani et al. (16) assessed whether the use of metformin monotherapy in comparison with

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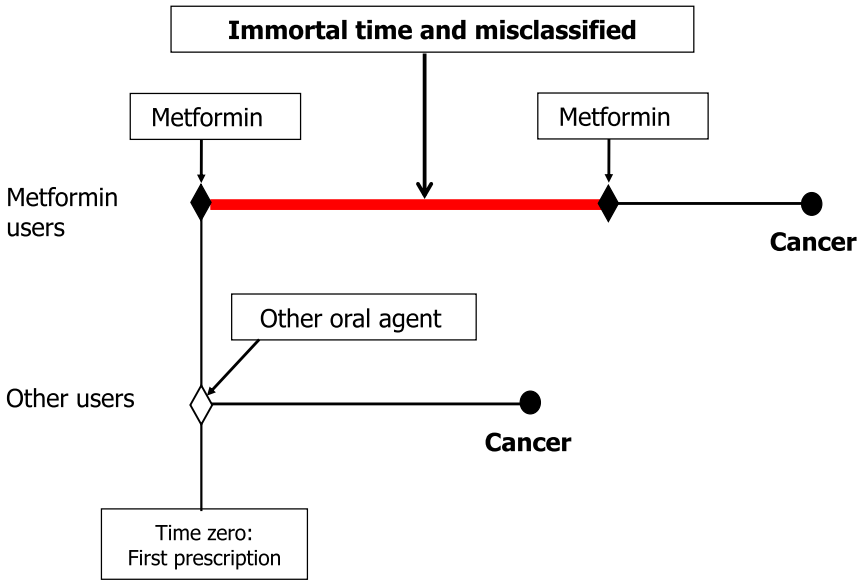

Figure 1—The concept of immortal time bias is depicted schematically using the cohort study from the Taiwanese National Health Insurance data during 2000–2007: 12,005 patients who received at least two prescriptions of metformin were compared with 4,597 patients who received one prescription of another oral agent during this period (15).

sulfonylurea monotherapy is associated with a decreased risk of bladder cancer. Using The Health Improvement Network (THIN) database, the authors extracted a large cohort of 87,600 new users of metformin or sulfonylureas. Overall, when compared with sulfonylureas, metformin was not associated with a decreased risk of bladder cancer, along with no duration-response relationship. This study is notable in several key respects. First, this study also defined exposure by two prescriptions of metformin or two prescriptions of sulfonylureas, but properly avoided immortal time bias by defining cohort entry as the date of the second prescription. Second, by comparing new metformin monotherapy users to new sulfonylurea monotherapy users, time lag bias was minimized as these patient groups were at similar stages of their disease. Moreover, the authors considered metformin and sulfonylurea durations as time-dependent variables in the models, providing a form of cumulative dose-response analysis as well in the process. Finally, the authors conducted a number of sensitivity analyses, which included applying a 1-year lag period after initiation of the drugs and additional adjustments for potential confounding factors.

While the current study successfully avoided these vexing time-related biases, it does have some limitations that require certain attention. First, as acknowledged by the authors, this study had a short 2-year median follow-up, which was in part imposed by censoring patients at the time of a switch or add-on to one of the study drugs. Such censoring, however, does not only truncate the follow-up but is problematic in that it assumes that there are no residual effects of the drugs after a switch or add-on of one of the study drugs, which is inconsistent with the known latency of bladder cancer. Furthermore, it is common for patients on metformin monotherapy to add-on or switch to a sulfonylurea, as is the add-on of metformin to sulfonylurea monotherapy users. Thus, censoring patients at the time of the crossover ignores bladder cancers occurring during times when patients remained exposed to the drugs in question. A hierarchical exposure definition, with first identifying metformin users and then sulfonylurea users, coupled with matching on important potential confounding factors, such as duration of treated diabetes, would have resolved this issue.

The study conducted by Mamtani et al. (16) joins a growing set of observational studies reporting null effects of metformin use on cancer prevention and treatment (17–21). Because of their observational nature, these studies may have been affected by other biases, but are generally free of major time-related biases that are known to potentially exaggerate the benefits of drugs. Indeed, observational studies with time-related biases have reported extraordinary effects ranging from 20 to 94% reductions in the risk of cancer (10), suggesting that metformin may be more effective at preventing or treating cancer than preventing the cardiovascular complications of diabetes. Moving forward, it will be essential to critically appraise the current scientific literature, and conduct rigorous studies using designs and methods of analysis that avoid these vexing biases. It is well accepted that properly conducted observational studies can contribute significantly to the knowledge base on the effects of drugs and that computerized health databases can play a major role in providing this important information quickly and accurately.

With the study by Mamtani et al. (16), the evidence is now mounting against an association between metformin and cancer, so that a careful reassessment is now warranted before more RCTs of metformin as a treatment for cancer are initiated. Similar quests for the potential cardiovascular benefits of hormone replacement therapy and the mortality benefits of inhaled corticosteroids in chronic obstructive pulmonary disease based on flawed observational studies resulted in large RCTs disproving these time-related biased findings (22). We should strive to avoid repeating such missteps in diabetes and cancer.

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