Letter to the Editor

Cancer Epidemiology, Biomarkers & Prevention

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

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Paulus and colleagues (1) reported that "among colorectal cancer patients with diabetes, metformin users had a 13% improved overall survival . . .. . .." and proposed that these data lend "support to . . .. . .. . .randomized studies of . . .. . . metformin among patients with colorectal cancer." We strongly argue caution of this interpretation for two key reasons.

First, by defining metformin use as "at least two fills within the 6 months before and after colorectal cancer diagnosis," the authors tested the impact of both prevalent and new metformin use (rather than new users only, which better mimics a future trial setting). This approach is susceptible to immortal time bias, which occurs when drug use (exposure) may commence after the index date, so that individuals have to survive to start drug use. Individuals in the exposed group are then incorrectly assumed to be at risk before they become exposed. The net effect is invariably a survival advantage for those users of the drug of interest (2). Immortal time bias commonly leads to a lack of proportionality between survival curves, and this is evident in the first 6 months of metformin users versus nonusers from the Kaplan–Meier curves reported by Paulus and colleagues (1). This statistical pitfall is well recognized in pharmaco-epidemiology but perhaps less so in the cancer literature. It is equally applicable to the common (mis) perception that metformin use is associated with reduced cancer incidence. Suissa and Azoulay (3) convincingly demonstrated that immortal time bias is common in such studies, but when methods were used to avoid this bias [for example, time-dependent analyses in new users only, as advocated by the international Diabetes and Cancer Research Consortium (4)], no effect of metformin use on cancer risk was observed (3).

Second, comorbidity categories between metformin users and nonusers were substantially different (for example, 44.5% vs. 29% for zero comorbidities, respectively). Covariate imbalance is associated with model dependence, a term borrowed from social sciences, to describe that many causal estimates (including estimates in opposite directions) may be derived from the same data, depending on model specifications and functional forms used (5). In other words, despite adjustments for covariates, a range of causal estimates result, yet one is chosen to support a perceived hypothesis. Model dependence is corrected using balanced (matched) data (5).

Observational studies are important to inform future randomized trials in patients with cancer, but they need to be set within analytic frameworks, with appropriate design and analysis to reduce biases.

## Disclosure of Potential Conflicts of Interest

A.G. Renehan has received speakers bureau honoraria from Janssen and Novo Nordisk. No potential conflicts of interest were disclosed by the other authors.

Received October 26, 2016; accepted October 27, 2016; published OnlineFirst May 15, 2017.

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**doi:** 10.1158/1055-9965.EPI-16-0850



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