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PAPER OF THE MONTH • MAY 2023

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Diabetes Care

Metformin and Cancer: Solutions to a Real-World Evidence Failure

Oriana Hoi Yun Yu and Samy Suissa.

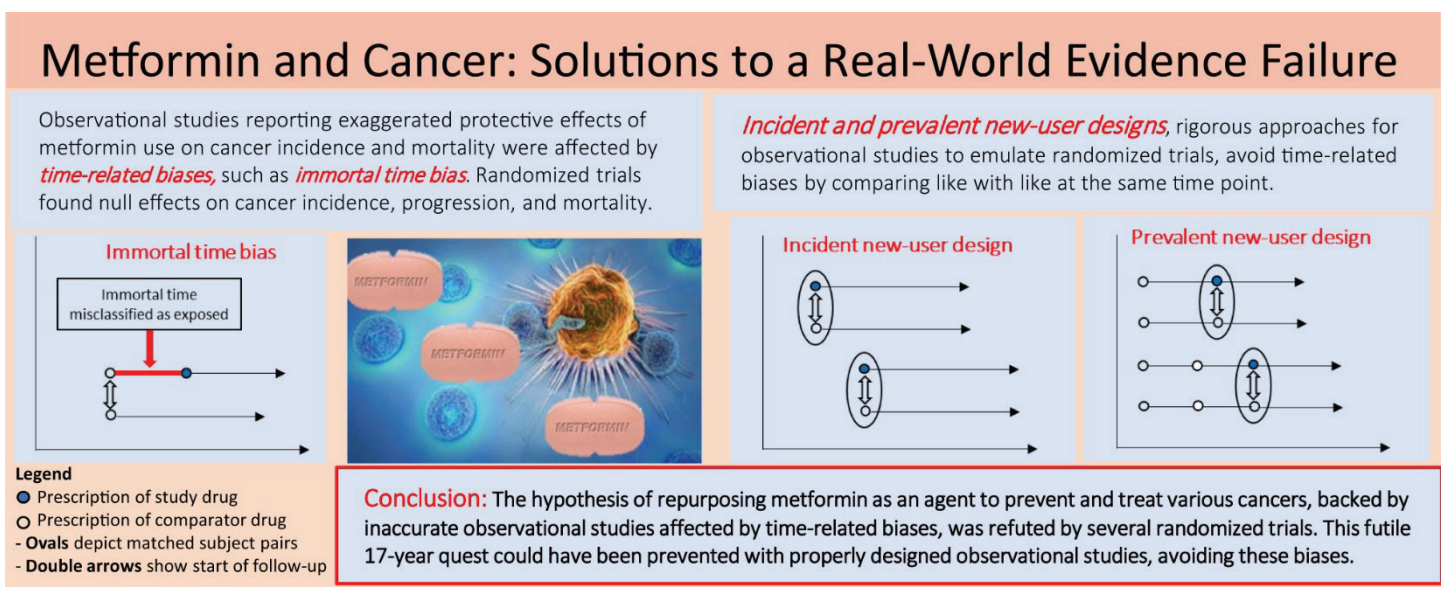
The quest to repurpose metformin, an antidiabetic drug, as an agent for cancer prevention and treatment, which began in 2005 with an observational study that reported a reduction in cancer incidence among metformin users, generated extensive experimental, observational, and clinical research.

Experimental studies revealed that metformin has anticancer effects via various pathways, potentially inhibiting cancer cell proliferation. Concurrently, multiple nonrandomized observational studies reported remarkable reductions in cancer incidence and outcomes with metformin use. However, these studies were shown, in 2012, to be affected by time-related biases, such as immortal time bias, which tend to greatly exaggerate the benefit of a drug. The observational studies that avoided these biases did not find an association. Subsequently, the randomized trials of metformin for the treatment of type 2 diabetes and as adjuvant therapy for the treatment of various cancers, advanced or metastatic, did not find reductions in cancer incidence or outcomes. Most recently, the largest phase 3 randomized trial of metformin as adjuvant therapy for breast cancer, which enrolled 3,649 women with a 5-year follow-up, found no benefit for disease-free survival or overall survival with metformin.

This major failure of observational real-world evidence studies in correctly assessing the effects of metformin on cancer incidence and outcomes was caused by preventable biases which, surprisingly, are still prominent in 2022. Rigorous approaches for observational studies that emulate randomized trials, such as the incident and prevalent new-user designs along with propensity scores, avoid these biases and can provide more accurate real-world evidence for the repurposing of drugs such as metformin.

In this article, we reviewed the evidence behind the metformin–cancer saga, focusing on the observational and randomized trials. We discuss reasons for the discrepancies in findings and describe some methods to better conduct future observational real-world evidence studies that can help reduce such discrepancies.

Finally, while the evidence to date suggests that metformin does not provide significant benefits in reducing cancer incidence and outcomes, further research should target specific promising phenotypic or genotypic subgroups.



https://doi.org/10.2337/dci22-0047