COMMENT ON BORDELEAU ET AL.

# The Association of Basal Insulin Glargine and/or n-3 Fatty Acids With Incident Cancers in Patients With Dysglycemia. Diabetes Care 2014;37:1360–1366

*Samy Suissa and Laurent Azoulay*

*Diabetes Care 2014;37:e216 | DOI: 10.2337/dc14-1075*

In their report of the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial on the effects of glargine insulin on cancer incidence, Bordeleau et al. (1) also examined the association between metformin and cancer, finding a null effect. In the discussion of this null finding, the authors state that "metformin . . . has been associated with a reduced risk of cancer . . . and cancer mortality . . . in a number of observational human studies" (1). Such a statement should now be considered obsolete as over 20 of these observational human studies have been shown to be incorrect, as they were subject to serious time-related biases (2). Instead, more properly conducted observational studies, which correctly accounted for metformin exposure as a time-related exposure to avoid these vexing biases, have not found a reduction in the incidence of several cancers with metformin use (3,4).

With several ongoing trials assessing the preventive effects of metformin in certain cancer populations, it is important to recall that improperly conducted observational studies have previously been used to support large trials with disappointing results. Examples include the cardiovascular benefits of hormone replacement therapy reported in several observational studies in the 1990s and 2000s that were debunked in the large Women's Health Initiative randomized trial. A more recent example is the Selenium and Vitamin E Cancer Prevention Trial (SELECT) that randomized over 35,000 men to assess whether vitamin E and selenium can reduce the incidence of prostate cancer (5). After a median follow-up of 7 years, vitamin E was in fact associated with a 17% increased risk of prostate cancer (5). Such trials are a reminder that assessing the cancer preventive effects of pharmacological agents is not without risk and also can raise ethical concerns when the evidence to support them is based on flawed observational studies.

In the case of metformin, we believe the time has come to seriously reconsider the assertion that it is associated with a decreased risk of cancer incidence and mortality, certainly at least if the claim is based on the observational human studies. The analysis by Bordeleau et al. (1) of the ORIGIN trial, which properly considered metformin as a time-varying exposure, provides additional evidence of no such association.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

## References

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*Centre for Clinical Epidemiology, Jewish General Hospital, and the Departments of Epidemiology and Biostatistics and of Medicine, McGill University, Montreal, Canada*

*Corresponding author: Samy Suissa, samy.suissa@mcgill.ca.*