Letter to the Editor

Is it Time to Test Metformin in Breast Cancer Prevention Trials? a Reply to the Authors

To the Editor: We read with great interest the article by Cazzaniga et al. (1) on the potential use of the insulin sensitizing agent metformin for therapeutic and chemopreventive purposes in breast cancer. We found that the safety profile of metformin was inadequately elicited and poorly supported by the cited references. This was particularly striking with regard to lactic acidosis, defined by the authors as "the only potential adverse event in metformin therapy." The authors further refer to this condition in terms of a rare event, which primarily occurs in patients with renal and hepatic disorders. The reported evidence was not exhaustive and the only cited reference was taken from an article published in 1996 (2). Given the current use of metformin in several common pathologic conditions associated with insulin resistance (e.g., type 2 diabetes and polycystic ovary syndrome) as well as the great potential of this drug in breast cancer therapy and prevention, the relation between metformin use and lactic acidosis in both diabetic and non diabetic patients is in urgent need of clarification particularly in light of much more recent and comprehensive scientific evidence.

The Cochrane Collaboration has conducted a systematic review evaluating the risk of fatal and nonfatal acidosis attributed to metformin use compared with placebo and other agents in type 2 diabetes patients. Salpenter et al. (3) pooled data for a total of 59,321 patient-years of metformin use and 51,627 patient-years in the nonmetformin group. They found no evidence of the association between metformin use and risk of lactic acidosis.

In nondiabetic patients, lactic acidosis occurs in association with pathologic conditions leading to tissue hypoxia, such as infections, heart failure, liver failure, and renal failure. In these cases, mortality is predicted by the severity of the underlying hypoxia and does not correlate with metformin accumulation (4, 5).

In conclusion, when referring to the association between this drug use and lactic acidosis in an evaluation of the timeliness of testing metformin in breast cancer prevention trials, the following message should be clearly conveyed: although circumstantial evidence has linked metformin treatment with lactic acidosis, no causal relationship has been shown thus far, either in patients with type 2 diabetes or in nondiabetic patients. Conversely, this drug has been proven to reduce cardiovascular mortality in type 2 diabetes patients and, when considered in a preclinical setting, to possess anticarcinogenic properties on breast, colon, and prostate (1).

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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