Comment on: Yang et al. (2010) Associations of Hyperglycemia and Insulin Usage With the Risk of Cancer in Type 2 Diabetes: The Hong Kong Diabetes Registry. Diabetes;59:1254–1260

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By analyzing data from the Hong Kong Diabetes Registry, Yang et al. (1) conclude that insulin use is associated with a reduced cancer risk in type 2 diabetes. The authors hypothesize that insulin treatment, by causing tighter glycemic control, less oxidative stress, and less inflammation, reduces the risk of cancer. We believe that the study presents serious methodological problems regarding patient matching as well as follow-up and that the conclusions are unrealistic.

From the original cohort of 4,623 diabetic patients, including 169 patients who developed cancer among insulin nonusers (4.6 vs. 3.3% among insulin users), a smaller new insulin user cohort, with 1:2 matched control subjects, was selected on the basis of the likelihood of initiating insulin therapy. When these new-user subcohorts were considered, a cancer-enriched population was selected from insulin nonusers (6.3%) but not from insulin users (which remained at 3.3%). After this selection, the two "matched" groups were significantly different for nearly all the variables considered, including the clinical, biochemical, and treatment parameters. This may indicate that the propensity score procedures had not allowed adequate case/control matching.

The number of cases of cancer development in the two cohorts was certainly influenced by the very different follow-up patterns, with the number of patients at risk dropping after 1 year to 39% (751/1,935) in insulin nonusers versus 83% (807/971) in insulin users. These cases had also a surprisingly abnormal time distribution: in insulin nonusers (111/120) cancer cases occurred in years 1 and 2, with a cumulative cancer rate of 9.9% in the first 2 years but of only 5.3% in the following 5 years.

The claim that insulin treatment might reduce cancer risk by avoiding hyperglycemia is contradicted by the observation that in insulin users, where fewer cancers were observed, A1C levels were significantly higher (8.1 vs. 7.1%, $P < 0.0001$) than in insulin nonusers. This casts serious doubts concerning the association between hyperglycemia and cancer and on the hypothesized mechanism of the anticancer effect of insulin via correction of hyperglycemia.

In summary, using sophisticated and complex statistical analyses of observational data in two unmatched subcohorts with different follow-up patterns, the authors come to the conclusion that insulin treatment reduces cancer risk in diabetic patients, which contradicts most previous studies, both clinical and experimental (2–4). Moreover, the reported effect of insulin is impressive—much larger and faster than any other known anticancer preventive therapy—in that the cancer incidence was reduced to one-fifth of the original (from 49.2 to 10.2 per 1,000 diabetic patient-years) in only 3 years after the initiation of insulin. Is this effect believable?

ACKNOWLEDGMENTS

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

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DOI: 10.2337/db10-1047