

# 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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**Y**ang et al. (1) recently reported that insulin usage is associated with a reduced cancer risk. It contrasts with evidence from epidemiological surveys in healthy populations and from pharmaco-epidemiological studies in diabetic patients, suggesting that hyperinsulinemia and growth factors play a key role in the association—maybe causal relationship—between diabetes/hyperglycemia and cancer, as we reviewed recently (2). In the accompanying editorial (3), Johnson and Gale state “pearl of wisdom often taught in introductory epidemiology courses is that one should be wary of implausibly low (or high) risk estimates” and that “this prompts further exploration of the study design and data for alternative explanations including the selection of the comparison groups, matching and residual confounding.” To go further than their suggestion that differences in time exposure to treatments could have introduced bias, a major confounding factor, namely BMI, should have been taken into account. Indeed, increased body weight is associated with an increased risk of cancer incidence (4) and cancer mortality (5). This led to adjust for BMI in most of the studies reporting association between diabetes/hyperglycemia and cancer (2). As clinicians are reluctant to prescribe insulin treatment in overweight and obese type 2 diabetic patients, it is surprising that BMI did not reach the *P* level of 0.30 required in the forward stepwise algorithm to be included in the propensity score (1). If BMI had been

included, it may have prevented the observed significantly higher BMI in insulin nonusers compared with insulin users ( $24.8 \pm 4.8$  vs.  $24.5 \pm 5.1$  kg/m<sup>2</sup>, *P* = 0.0070 with the cohort design and  $24.9 \pm 4.9$  vs.  $24.5 \pm 5.1$  kg/m<sup>2</sup>, *P* = 0.0014 with the new-user cohort design) (1). Given the relatively low BMI in Asian diabetic populations (6), 0.3 or 0.4 kg/m<sup>2</sup> makes a big difference to increase the cancer risk in insulin nonusers. Thus, at least adjustment for BMI should have been performed to compare the two treatment groups. The difference in BMI may explain the very controversial findings by Yang et al. (1).

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## REFERENCES

1. Yang X, Ko GT, So WY, Ma RC, Yu LW, Kong AP, Zhao H, Chow CC, Tong PC, Chan JC. Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong Diabetes Registry. *Diabetes* 2010;59:1254–1260
2. Simon D, Balkau B. Diabetes mellitus, hyperglycaemia and cancer. *Diabetes Metabolism* 2010;36:182–191
3. Johnson JA, Gale EA. Diabetes, insulin use, and cancer risk: are observational studies part of the solution—or part of the problem? *Diabetes* 2010;59:1129–1131
4. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569–578
5. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625–1638
6. Chan JCN, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009;301:2129–2140

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