

## COMMENTS AND RESPONSES

### Comment: Analyses Using Time-Dependent Pioglitazone Usage in Cox Models May Lead to Wrong Conclusions About Its Association With Cancer

We read the two articles published in a recent issue of *Diabetes Care* by Lewis et al. (1) and Ferrara et al. (2) with interest. The first study tested a time-dependent use of pioglitazone for the risk of bladder cancer among 193,099 diabetic patients in the Kaiser Permanente Northern California Diabetes Registry and concluded that use of the drug over 24 months was associated with an increased risk of bladder cancer (hazard ratio 1.4, 95% CI 1.03–2.0). The second study tested a time-dependent use of pioglitazone for the risk of cancer among 252,467 diabetic patients aged  $\geq 40$  years from the Kaiser Permanente Northern California Diabetes Registry and found that ever use of pioglitazone was not associated with cancer risk. Although the two studies have large sample sizes, analysis of time-dependent use of pioglitazone may cause great concern over reliability of their findings and conclusions about the associations between pioglitazone usage and cancer.

In our previous analysis of the associations between insulin usage and cancer risk, we tested the relative credibility of some common statistical methods such as non-time-dependent and time-dependent use of drugs in Cox regression by examining the known effects of statins on cardiovascular disease (CVD) in the Hong

Kong Diabetes Registry (3). We found that time-dependent use of statins was associated with increased risk of CVD (hazard ratio 1.37, 95% CI 1.03–1.82) after adjusting for age, sex, BMI, smoking status, alcohol use, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, systolic blood pressure, A1C, estimated glomerular filtration rate, and urinary albumin-to-creatinine ratio (3). Conversely, the non-time-dependent use of statins led to a hazard ratio of 0.55 (95% CI 0.42–0.73) after adjusting for the same group of covariates (3). Thus, it is evident that the analysis of time-dependent use of statins has introduced a substantial bias, which has changed the conclusion regarding the effect of statins on CVD from “reducing risk” to “increasing risk.”

Initiation of statin therapy is often associated with high LDL-C and other CVD risk factors. Thus, the wrong conclusion about statins' effect on CVD is likely due to the confounding by high LDL-C and other CVD risk factors at the time of initiation of statin therapy. Such bias cannot be removed by adjustment for non-time-dependent LDL-C levels. In that case, analysis of a non-time-dependent use of statins in Cox regression may introduce less bias than a time-dependent use of the drug. We have previously reported a linear positive association between hyperglycemia and cancer (4). In support of our findings, in the Emerging Risk Factors Collaboration consisting of 97 prospective cohorts, diabetes was associated with 1.3-fold increased risk of cancer mortality, which was attenuated by adjustment for fasting plasma glucose (5). In diabetic patients, initiation of pioglitazone therapy was most likely to be associated with hyperglycemia. Given the drug use indication, likely due to hyperglycemia over time, which, however, was not available in the data analysis, the analysis of time-dependent pioglitazone usage in Cox models might lead to misleading conclusions regarding its risk associations with cancer.

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#### References

- Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011;34:916–922
- Ferrara A, Lewis JD, Quesenberry CP Jr, et al. Cohort study of pioglitazone and cancer incidence in patients with diabetes. *Diabetes Care* 2011;34:923–929
- Yang X, Ma RC, Chan JC. Response to comment on: Yang X, Ko GTC, So WY, Ma RWC, Yu LWL, Kong APS, Zhao H, Chow C-C, Tong PCY, Chan JCN. 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. *Diabetes* 2010;59:e19–e22
- Yang X, Ko GT, So WY, et al. 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
- Seshasai SR, Kaptoge S, Thompson A, et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364:829–841