COMMENTS AND RESPONSES

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

XILIN YANG, PHD[1,2]
JULIANA C.N. CHAN, MD, FRCP[1,2,3]

From the [1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China; the [2]Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China; and the [3]Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China.

Corresponding authors: Xilin Yang, yang.xilin@cuhk.edu.hk or yxl@hotmail.com, and Juliana C.N. Chan, jchan@cuhk.edu.hk.

DOI: 10.2337/dc11-0627

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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 ≥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.

Acknowledgments—J.C.N.C. is an investigator of clinical trials supported by Takeda, a member of the GlaxoSmithKline (GSK) advisory board, and an invited speaker and faculty member of GSK education programs. No other potential conflicts of interest relevant to this article were reported.

References

1. 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
2. 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
3. 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
4. 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
5. 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

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We thank Yang and Chan (1) for their interest in our articles (2,3). They propose that our studies may be biased by use of time-varying exposures in Cox regression models.

If more severe hyperglycemia is associated both with increased cancer risk and with use of pioglitazone, and it is also affected by pioglitazone therapy (i.e., hyperglycemia is both a confounder and an intermediate variable), we agree that our use of the time-dependent Cox model may have led to an over-estimate of our hazard ratios for pioglitazone use (4).

Although current evidence suggests that diabetes is weakly to modestly associated with increased risk of cancer and cancer mortality in the general population (5), the data on an association between levels of hyperglycemia and cancer risk among patients with diabetes are more limited and less clear (5,6).

Several of our findings also suggested that hyperglycemia was not a risk factor for cancer within our cohort of diabetic patients. First, we did not see an association between increasing HbA_{1c} levels at baseline and increasing risk of cancer at any site or an association between other diabetes medications and cancer risk. We also did not observe an increased risk of any cancer associated with ever versus never use of pioglitazone. Finally, we did not see an association with longer duration of pioglitazone use and risk of cancer at any site other than bladder.

We therefore believe that our use of time-varying Cox models was appropriate and that our hazard ratios for pioglitazone use are unlikely to be appreciably biased by hyperglycemia.

LAUREL HABEL, PHD[1]
ASSIAMIRA FERRARA, MD, PHD[1]
WARREN B. BILKER, PHD[2,3]
CHARLES P. QUESENBERRY, JR, PHD[1]
JOE V. SELBY, MD, MPH[1]
STEPHEN K. VAN DEN EEDEN, PHD[1]
BRIAN L. STROM, MD, MPH[2,3,4,5]
JAMES D. LEWIS, MD, MSCE[2,3,4]

From the [1]Division of Research, Kaiser Permanente Northern California, Oakland, California; the [2]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania; the [3]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania; the [4]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and the [5]Department of Pharmacology, University of Pennsylvania, Philadelphia, Pennsylvania.

Corresponding authors: James D. Lewis, lewisjd@mail.med.upenn.edu, and Assiamira Ferrara, assiamira.ferrara@kp.org.

DOI: 10.2337/dc11-0763

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Acknowledgments—A.F. has received research funding from Takeda and Eli Lilly and Co. J.D.L. has received other research funding from Takeda and GlaxoSmithKline and has served as a consultant to Takeda and GlaxoSmithKline. B.L.S. has received research funding from Takeda and has served as a consultant to GlaxoSmithKline and Eli Lilly and Co. L.H. has received other research funding from Merck, Genentech (Roche), and sanofi-aventis. No other potential conflicts of interest relevant to this article were reported.

References

1. Yang X, Chan JCN. Comment: Analyses using time-dependent pioglitazone usage in Cox models may lead to wrong conclusions about its association with cancer. Diabetes Care 2011;34:e136. DOI: 10.2337/dc11-0627
2. 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
3. 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
4. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–560
5. 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
6. Johnson JA, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. Diabetologia 2011;54:25–31