

Meta-analysis of trial data may support a causal role of hyperglycaemia in cancer

X. L. Yang · R. C. W. Ma · J. C. N. Chan

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To the Editor: We read with interest the article by Johnson and Bowker published in *Diabetologia* [1]. However, this study had major methodological flaws that render the conclusion premature and invalid. First, the sample size was not sufficient to support the negative conclusion that intensive glycaemic control did not reduce cancer risk. We used the published data in the meta-analysis and performed the sample size and power analysis that would be required to make such a conclusion. In the control arm, 380 cancer events were recorded during 45,009 person-years of follow-up with an incidence of 8.44 (95% CI 7.60–9.29) per 1,000 person-years. Given an incidence of 7.44 (95% CI 6.67–8.12) per 1,000 person-years in the intensive glycaemic control arm (357 cancer events during a total follow-up time of 47,974 person-years), the current sample size had zero power at a type I error rate of 5% to make a conclusion of

equivalence. In other words, data from this meta-analysis were severely underpowered to justify the conclusion that ‘cancer risk’ was not reduced by improving glycaemic control.

Second, the incidence of cancer in the meta-analysis was likely to be underestimated. The meta-analysis used an endpoint of cancer events that would have occurred before the original study endpoint, death or the study end date. Thus, the follow-up time for cancer should have been recalculated as the period from the starting point to the cancer event, death or the study endpoint, whichever came first, but not the period to the original study endpoint, death or the original study endpoint. The analysis, as presented, would lead to a prolonged follow-up time for cancer, thereby giving rise to a deflation of the cancer incidence.

Third, the observed effect size of glucose control for cancer in fact supported the relationship between HbA_{1c} and cancer from cohort studies. In the intensive treatment arm, HbA_{1c} reduction ranged from 0.3% to 0.8% with 9% cancer risk reduction or a risk ratio of 0.91 (95% CI 0.79–1.05) [1]. In our previous study, we reported an adjusted hazard ratio of 1.18 (95% CI 1.04–1.33) for cancer for every 1% increase in HbA_{1c} [2], which can be translated to 1.09 (95% CI 1.02–1.17) per 0.55% increase in HbA_{1c} or 0.92 (95% CI 0.86–0.98) per 0.55% decrease in HbA_{1c}. Of note, the relationship between HbA_{1c} and cancer risk appeared to be linear [2, 3]. The low HbA_{1c} achieved through strict glycaemic control in a randomised clinical trial was not applicable to most settings. In the International Diabetes Management Practice Study (IDMPS), 30% of diabetic patients never had HbA_{1c} measured, and amongst those with HbA_{1c} values available, 70% had values >7% [4]. Thus, if the causal role of glycaemic control in cancer is proven, there are even more reasons to advocate the attainment of glycaemic control early to reduce these complications.

X. L. Yang (✉) · R. C. W. Ma · J. C. N. Chan (✉)
Department of Medicine and Therapeutics,
The Chinese University of Hong Kong,
The Prince of Wales Hospital, Shatin,
Hong Kong, SAR, People’s Republic of China
e-mail: yang.xilin@cuhk.edu.hk
e-mail: yxL@hotmail.com

J. C. N. Chan
e-mail: jchan@cuhk.edu.hk

X. L. Yang · R. C. W. Ma · J. C. N. Chan
Hong Kong Institute of Diabetes and Obesity,
The Chinese University of Hong Kong,
The Prince of Wales Hospital, Shatin,
Hong Kong, SAR, People’s Republic of China

Fourth, as agreed by the authors, a link between hyperglycaemia and cancer is biologically plausible. Low HDL-cholesterol and obesity, which are among the key components of the insulin resistance syndrome, may link with cancer via the serine/threonine kinase 11 (LKB1)—AMP-activated protein kinase (AMPK)—cellular tumour antigen p53 (P53) pathway [5, 6]. We have previously reported the associations of cancer risk with low triacylglycerol and co-occurrence of low LDL-cholesterol and albuminuria, which were attenuated in the presence of 3-hydroxy-3-methylgutaryl-coenzyme A (HMG-CoA) reductase treatment [7, 8]. To this end, both albuminuria and triacylglycerol are associated with hyperglycaemia or insulin deficiency/reduced insulin action. Here, hyperglycaemia may activate the renin–angiotensin system, which can interact with the cholesterol biosynthesis pathway to increase cancer risk through dysregulation of the IGF-1, sterol regulatory element binding proteins (SREBPs) and HMG-CoA reductase pathways [9]. In a uni-nephrectomised animal model, development of hyperglycaemia and renal impairment was associated with development of renal cancer that showed activation of these pathways [9]. In a tumour-prone animal model, both mean and total volumes of hepatocellular tumours in the insulin-deficient, hyperglycaemic animals were more than twofold greater than for tumours in the euglycaemic control animals, suggesting that hyperglycaemia may promote tumour formation, independent of insulin action [10].

In conclusion, instead of supporting a negative association between hyperglycaemia and cancer risk in diabetes, the results of the meta-analysis of these trial data in fact agreed with our epidemiological findings supporting the possible causal role of hyperglycaemia in cancer. These data call for further mechanistic studies and definitive intervention trials.

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