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META-ANALYSIS

Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials

J. A. Johnson · S. L. Bowker

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Abstract
Aims/hypothesis The purpose of this study was to explore the relationship between hyperglycaemia in type 2 diabetes and risk of cancer incidence or cancer mortality. We were interested to determine if data from major randomised controlled trials would support a hypothesis that improving glycaemic control may reduce the risk of cancer outcomes.
Methods We included major randomised controlled trials conducted with an overall aim of intensified glycaemic control in type 2 diabetes. We abstracted data from published papers and supplemental material and conducted separate meta-analyses of cancer mortality and cancer incidence.
Results Four trials reported cancer mortality for the intensive (222 events in 53,892 person-years) and standard control (155 events in 38,743 person-years) arms (UK Prospective Diabetes Study [UKPDS] 33, UKPDS 34, Action to Control Cardiovascular Risk in Diabetes [ACCORD] and Veterans Affairs Diabetes Trial [VADT]); the summary risk ratio for cancer mortality was 1.00 (95% CI 0.81–1.24; I^2=0%). Excluding the UKPDS metformin trial resulted in a pooled risk estimate of 1.03 (95% CI 0.83–1.29; I^2=0%). Three trials reported cancer incidence for the study arms (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], PROspective pioglitAzone Clinical Trial In macroVascular Events [PROactive], Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes [RECORD]) with 357 events in 47,974 person-years with improved glycaemic control and 380 events in 45,009 person-years in the control arms; the pooled risk ratio for cancer incidence was 0.91 (95% CI 0.79–1.05; I^2=0%).
Conclusions/interpretation Data from large randomised controlled trials of intensified glycaemic control suggest that cancer risk is not reduced by improving glycaemic control in type 2 diabetes. These data therefore do not support the hypothesis that hyperglycaemia is causally linked to increased cancer risk.

Keywords Cancer incidence · Cancer mortality · Intensive glycaemic control · Meta-analysis · Randomised trials

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AMPK	AMP-activated protein kinase
CONTROL	Collaboration on Trials of Lowering Glucose
PPAR	Peroxisome proliferator-activated receptor
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events
RCT	Randomised controlled trial
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

J. A. Johnson (✉) · S. L. Bowker
Department of Public Health Sciences, School of Public Health, 2-040 Health Research Innovation Facility, University of Alberta, Edmonton, AB, Canada T6G 2E1
e-mail: jeff.johnson@ualberta.ca

Introduction

Patients with type 2 diabetes have increased risks of various types of cancer and cancer mortality [1–5]. There is strong

evidence supporting the biologically plausible link between type 2 diabetes and cancer outcomes. It is suggested that insulin resistance, hyperinsulinaemia and elevated levels of IGF-1 in patients with type 2 diabetes promotes tumour cell growth [6, 7].

There is also growing evidence of a moderating role of glucose-lowering therapies in the relationship between type 2 diabetes and cancer outcomes. Several observational studies support the hypothesis that metformin [8–11] and glitazones [12–14] are associated with reduced risk of cancer. Given the biologically plausible link between diabetes and cancer, mediated through insulin resistance and hyperinsulinaemia, the observed association may be due to the ability of these drugs to reduce insulin resistance, although there may also be specific cellular mechanisms, mediated in part through AMP-activated protein kinase (AMPK) signalling pathways [6, 15–18].

On the other hand, sulfonylureas and exogenous insulin increase circulating insulin levels in the body, which, in the presence of insulin resistance and hyperinsulinemia, may accelerate tumour growth [12, 19]. Several observational studies have suggested increased risk of cancer or cancer mortality with insulin [8, 10, 11, 19, 20] and sulfonylureas [8, 21, 22]. More recently, a number of studies have evaluated cancer risks with different types of insulin [23–25], fuelling speculation of an increased risk of cancer associated with the insulin analogue insulin glargine (A21Gly,B31Arg,B32Arg human insulin), owing to its structural similarities to IGF-1. This controversial topic has been the subject of a number of editorials and commentaries [26–29], drawing increased attention to the relationship between diabetes and cancer, and a need to better understand the role played by different glucose-lowering therapies in this relationship.

To date, the majority of the evidence of the risk and benefits of glucose-lowering therapy and cancer outcomes is based on basic biomedical or epidemiologic studies. A number of limitations can be identified with much of the available epidemiologic studies, including a lack of attention to the time-varying nature of glucose-lowering drug therapy, and considerable residual confounding [6, 26–28]. A plausible alternative hypothesis is that the increased risk of cancer and cancer mortality in type 2 diabetes is due to elevated blood glucose levels. It has been suggested that cancer cells are obligate glucose users, and hyperglycaemia may drive the production of ATP through the glycolytic pathway in cancer cells, through a mechanism known as the Warburg effect [29]. This alternate explanation is also supported by epidemiologic evidence of an association between elevated blood glucose and increased cancer mortality [30, 31]. Of course, the same epidemiologic considerations must apply to these observational studies, whereby the relationship between glucose level and cancer mortality may be considered confounded by insulin resistance and hyperinsulinaemia.

To better understand whether the association between a risk factor and an outcome is causal, a higher order of evidence is often required, such as randomised controlled trials (RCT), with experimentally controlled exposure of the risk factor and rigorous assessment of the outcome of interest. Therefore, we sought to determine whether the data from the numerous recent large RCT aimed at questions of intensified glycaemic control would support the potential alternative hypothesis of hyperglycaemia being a modifiable factor for the increased risk of cancer or cancer mortality in type 2 diabetes.

Methods

Data sources The Collaborators on Trials of Lowering Glucose (CONTROL) recently conducted a systematic review and meta-analysis of large trials that studied the effect of intensive glycaemic control on macrovascular outcomes in type 2 diabetes [32]. We elected to not repeat that systematic review, but took the review as our starting point. We chose to also include in our list large trials of specific glucose-lowering agents conducted with an overall aim of intensive glycaemic control where a statistically significant and clinically important improvement was achieved in the active treatment arm. In this list we included the United Kingdom Prospective Diabetes Study (UKPDS) [33], UKPDS metformin [34], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [35], Veterans Affairs Diabetes Trial (VADT) [36], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) [37], PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) [38] and Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) [39] studies.

Data collection From the available publications and supplementary appendices for these studies, we abstracted information on the number of cancer deaths or incident cancers identified for all of the study arms. We also abstracted the magnitude of difference in A_{1c} achieved between study arms for each of the trials. The two authors extracted all data independently; we had 100% agreement on all abstracted elements.

Statistical analyses To summarise the effects of intensive glycaemic control on cancer outcomes of interest (i.e. mortality or incidence), we abstracted the raw event rates, sample sizes, follow-up time, published risk estimates and 95% CI from each study, where available.

Cancer mortality and incidence rates were estimated as events per person-years. Person-years were estimated as sample size × follow-up time. Follow-up time was abstracted as mean or median as reported in the original publications. We pooled data across studies using random effects models to calculate risk ratio and 95% CI. We planned, a priori, to exclude the UKPDS metformin study [34] in a secondary analysis. The inclusion and exclusion of this study was planned for two reasons, given the considerable available evidence for the role of metformin in the relationship between type 2 diabetes and cancer [8–11], but also due to the overlap in control individuals with the full UKPDS study [33, 34].

We assessed statistical heterogeneity for the pooled estimates using the I^2 statistic; defining a priori limits to reporting of pooled estimates if heterogeneity as $p \leq 0.10$ or $I^2 \geq 50\%$ [40]. All analyses were conducted using Cochrane Review Manager version 5.0 (the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, the Netherlands).

Results

Cancer mortality Four of the identified trials reported cancer deaths among the study participants (Table 1) [33–36]. The difference in A_{1c} achieved for the intensive treatment arm compared with standard treatment ranged from 0.6% to 1.4%; all were reported to be statistically significant ($p<0.0001$). Only the UKPDS overall and UKPDS metformin studies reported a risk estimate for cancer mortality for the intensive treatment compared with the standard treatment arms. From the four studies, in total 222 cancer deaths were experienced during 53,892 person-years of intensified glycaemic control compared with 155 cancer deaths during 38,743 person-years of standard control. The overall pooled risk ratio for cancer mortality was 1.00 (95% CI 0.81–1.24; $p=0.98$) [heterogeneity: $I^2=0\%$; $p=0.81$] (Fig. 1a). When we repeated the meta-analysis excluding data from the UKPDS metformin study [34], the pooled risk estimate for the remaining three trials was 1.03 (95% CI 0.83-1.29; $p=0.77$) [heterogeneity: $I^2=0\%$; $p=0.92$] (Fig. 1b).

Cancer incidence The remaining three trials reported cancer incidence (or cancer hospitalisation) among the study participants (Table 2) [37–39]. The difference in A_{1c} reduction for the intensive or active treatment arm compared with standard treatment ranged from 0.3% to 0.8%; the difference was reported to be statistically significant ($p<0.0001$) in PROactive [38] and RECORD [39], but statistical significance was not reported in ADVANCE [37]. From the three studies, a total of 357 incident cancers was experienced during 47,924 person-years randomised to active treatment where better glycaemic control was achieved, compared with 380 cancer events during 45,009 person-years of standard control. The overall pooled risk ratio for cancer incidence was 0.91 (95% CI 0.79–1.05; $p=0.20$) [heterogeneity: $I^2=0\%$; $p=0.66$] (Fig. 2).

Discussion

These meta-analyses suggest that improved glycaemic control does not confer an increased nor a decreased risk of cancer outcomes in patients with type 2 diabetes. This would suggest that while hyperglycaemia is associated with increased risk of cancer mortality in observational studies [30, 31], it is unlikely to be a modifiable, or causal, factor in the association linking diabetes and cancer. In this regard, this relationship resembles that between hyperglycaemia and cardiovascular events in type 2 diabetes, in that the association is strong and consistent, but is not reversed when glucose control is actually improved. Moreover, it is therefore unlikely that hyperglycaemia would be an important confounding factor in the pharmacoepidemiolgic studies of glucose-lowering drug exposure and cancer outcomes.

Although the tests of heterogeneity performed in our analyses were somewhat limited by the small number of trials, we nonetheless found the homogeneity of the included studies to be striking, as was the consistency of the crude risk estimates. The notable exception was the UKPDS metformin study [34], which compared metformin-based intensified therapy against dietary management for conventional glycaemic goals in overweight type 2 diabetes patients, and appears to support a hypothesis that metformin reduces cancer mortality. The UKPDS investigators originally reported the prospective risk ratio of 0.71 (95% CI 0.29–1.76), although this was not statistically significant given the small number of cancer deaths in the small number of trial participants [34]. Further, given the small sample size, its inclusion or exclusion in our meta-analysis had little effect on the overall pooled estimate. The inclusion of the UKPDS metformin study in the CONTROL meta-analyses [32] has been criticised because of the overlap in control individuals with the overall UKPDS. We felt it was important to include it in this review and meta-analysis, given the interest in this treatment for cancer outcomes. Taken together with the consistent risk estimates generated from four observational studies [8–11], there appears to be accumulating support for the hypothesis that metformin may have important benefits over and above the treatment of type 2 diabetes. Given the results of the meta-analysis, it would seem that this effect is likely to be independent of glucose lowering.

Table 1 Included studies and cancer events: cancer mortality

Cancer mortality	Date	Baseline			Follow-up[a]	Intensive					Standard				
		Age (years)	Diabetes duration	A_{1c}		Events	*n*	P-yr[b]	Rate[c]	Achieved A_{1c}[d] (%)	Events	*n*	P-yr[b]	Rate[c]	Achieved A_{1c}[d] (%)
ACCORD [35]	2008	62	10	8.3	3.5	65	5,128	17,948	3.6	6.4	63	5,123	17,931	3.5	7.5
UKPDS 33 [33]	1998	53	<1	7.1	10.0	120	2,729	27,290	4.4	7.0	50	1,138	11,380	4.4	7.9
UKPDS 34 [34]	1998	53	<1	7.2	10.7	13	342	3,659	3.6	7.9	21	411	4,398	4.8	8.5
VADT [36]	2009	60	11.5	9.4	5.6	24	892	4,995	4.8	6.9	21	899	5,034	4.2	8.4

[a] Follow-up time reported as mean or median years

[b] Person-years=n × follow-up time

[c] Rate=Events/1,000 person-years

[d] A_{1c} reported as achieved level or absolute reduction at end of study; $p<0.0001$ in all cases

There are several limitations of our methods, including those limitations inherent to all secondary analyses and meta-analyses. As such, the pooled data presented herein can only be seen as hypothesis-generating, rather than conclusive evidence. We recognise that cancer outcomes were reported as secondary or safety outcomes in these trials, and therefore were not formally adjudicated. As cancer outcomes were not the primary outcome measure in the trials included in our meta-analysis, it is important to acknowledge that appropriate comparisons of cancer incidence or mortality rates would require adjustment for age, and consideration of possible treatment-time interactions. To some extent this is controlled for, given the randomisation used in these major trials. Finally, we did not calculate a pooled estimate for the degree of improvement in A_{1c}, instead taking the individual study results to be representative of reductions considered to be statistically significant and clinically important. In the CONTROL meta-analysis, the pooled reduction in A_{1c} for the four included trials was 0.88% [32]; the difference in A_{1c} in the three additional trials we included was not as large, but still significantly different between active treatment and control arms [34, 38, 39].

We did not perform a formal systematic review of the literature, nor did we formally evaluate the quality of the included trials, given the fact that these major trials have been well publicised and are familiar to the clinical community. We recognise that only a small number of

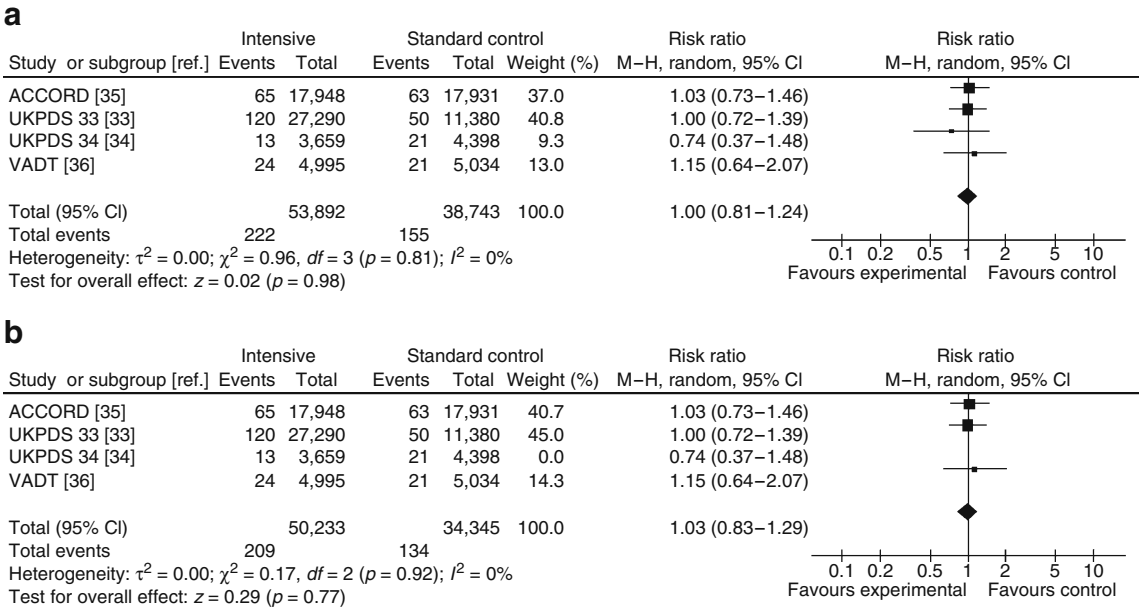

Fig. 1 Forest plot for intensive glycaemic control and cancer mortality: including UKPDS 34 – metformin in overweight type 2 diabetes [34] (**a**); excluding UKPDS 34 – metformin in overweight type 2 diabetes [34] (**b**)

Table 2 Included studies and cancer events: cancer incidence

Cancer incidence	Date	Baseline			Follow-up[a]	Intensive					Standard				
		Age (years)	Diabetes Duration	A_{1c}		Events	*n*	P-yr[b]	Rate[c]	Achieved A_{1c}[d] (%)	Events	*n*	P-yr[b]	Rate[c]	Achieved A_{1c}[d] (%)
ADVANCE [37]	2008	66	8	7.5	5.0	119	5,645	28,225	4.2	6.5	119	5,038	25,190	4.7	7.3
PROActive [38]	2005	62	8	7.9	2.9	112	2,605	7,489	15.0	–0.8	113	2,633	7,570	14.9	–0.3
RECORD [39]	2009	58	7	7.9	5.5	126	2,220	12,210	10.3	–0.36	148	2,227	12,249	12.1	–0.085

[a] Follow-up time reported as mean or median years

[b] Person-years=n×follow-up time

[c] Rate=Events/1,000 person-years

[d] A_{1c} reported as achieved level or absolute reduction at end of study; $p<0.0001$ in all cases

trials could be included in our meta-analysis, as the trials had to have long enough follow-up for comparisons of cancer incidence and cancer mortality to be meaningful. We included in our meta-analyses the PROactive [38] and RECORD [39] studies, which were not considered in the CONTROL meta-analysis [32], because they were not trials of intensified glycaemic control per se, but rather controlled trials of specific glucose-lowering regimens, with an overall aim of intensified glycaemic control. Nonetheless, the active treatment arms did achieve statistically significant and clinically important improvements in A_{1c} in both studies, which provides the physiologic effect we wished to assess, justifying their inclusion in our meta-analysis.

Moreover, we think it is important to recognise that the overarching aim of achieving a lower A_{1c} level all of these trials was pursued with protocol-driven treatment escalation, or 'rescue therapy', resulting in the post-randomisation addition of multiple oral agents or insulin. This design feature makes it difficult to discern an effect of individual drug therapy on cancer outcomes from these particular trials, as the risk associated with any one agent would be largely confounded by exposures to other glucose-lowering agents, many of which have been positively or negatively associated with cancer outcomes.

For example, in the PROactive study, the overall incidence of cancer was similar between groups, although the incidence of breast cancer was significantly higher in the placebo group, whereas the incidence of bladder cancer was non-significantly higher with pioglitazone [38]. Conflicting mechanistic studies might suggest increased or decreased risk of tumour growth with PPAR activation [17, 41, 42]. Regardless, the effect of pioglitazone alone on cancer outcomes cannot be easily discerned from the PROactive data because of the small number of events and, even though this was a placebo-controlled trial, the investigators also drew attention to achieving A_{1c} below the recommended target, which the investigators took to be <6.5% [38]. Therefore, there were post-randomisation changes to the non-study glucose-lowering medications (pioglitazone or placebo). By the end of the study, the pioglitazone group had achieved a 0.5% greater reduction in A_{1c}, although the placebo group was using more metformin and more insulin than the pioglitazone group; both groups had a similar decline in the use of sulfonylureas [38]. Secondary analyses of individual drug effects from these data, if conducted, should appropriately account for the individual and time-varying exposures of the different glucose-lowering agents; in essence, such secondary analyses should be viewed as observational prospective cohort studies, albeit with rigorously collected and therefore high-quality data. From the available RCT data, secondarily analysed as an RCT, we can only suggest that overall improvements in glycaemic control achieved through combination glucose-lowering therapies do not appear to increase nor decrease the risk of cancer.

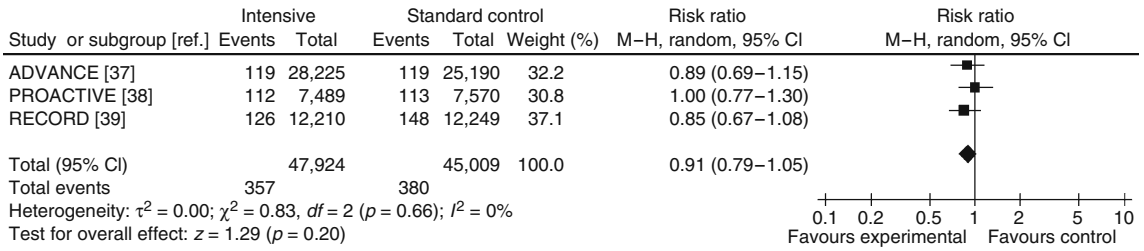

Fig. 2 Forest plot for intensive glycaemic control and cancer incidence

Ultimately, the potential benefits of individual glucose-lowering agents and cancer outcomes would best be tested through rigorously designed and conducted RCTs. Metformin is currently being explored as a potential adjuvant therapy for breast cancer in controlled trials [43, 44]. There are also numerous ongoing trials of rosiglitazone and pioglitazone for prevention or treatment of various cancer sites [44]. Results of those trials in cancer patients may or may not be generalisable to patients with diabetes, although, if positive RCT evidence were found, taken together with available epidemiologic evidence, such speculation may be warranted. However, it may be more difficult to further study the potential risks hypothesised by the epidemiologic evidence for glucose-lowering agents that increase circulating insulin in patients with type 2. Such hypotheses of potential harm do not easily lend themselves to RCT designs, which may not be practical for sample size considerations nor feasible from an ethical perspective. In such cases large, well-designed, observational studies may provide the best evidence of potential harms [45, 46].

In summary, we found no evidence to support a hypothesis that improved glycaemic control, through combination glucose-lowering medications, reduced the risk of cancer incidence or mortality. Our secondary analysis neither implicates nor absolves any specific individual glucose-lowering therapy in the relationship between diabetes and increased risk of cancer, although accumulating evidence does suggest metformin may be a special consideration. Clarification of the role of individual glucose-lowering agents in the relationship between type 2 diabetes and cancer will probably require an accumulation of evidence from a combination of observational and controlled clinical studies.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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