Report of the Japan diabetes society/Japanese cancer association joint committee on diabetes and cancer, Second report

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Background

The Japan Diabetes Society (JDS)/Japanese Cancer Association (JCA) Joint Committee on diabetes and cancer (hereafter, JDS/JCA Joint Committee) published its first report in July 2013 on the epidemiological assessment of the associations of diabetes with cancer risk/prognosis, the common risk factors for diabetes and cancer, and cancer risk associated with diabetes treatment. The Joint Committee continued its work to assess the role of glycemic control in the development of cancer in patients with diabetes. This review shows that high-quality evidence examining the association between glycemic control and cancer risk is lacking.

In 2014, the Japan Diabetes Society (JDS) and the Japanese Cancer Association (JCA) restarted the JDS/JCA Joint Committee on Diabetes and Cancer, which published the second committee report in Japanese [1]. This is the English version of that report. This article has been jointly published in Diabetology International (doi:10.1007/s13340-016-0257-z) and Cancer Science by the Japan Diabetes Society and the Japanese Cancer Association.

Members of the JDS/JCA Joint Committee on Diabetes and Cancer: JDS: Mitsuhiro Noda, Kohjiro Ueki, Masato Kasuga, Naoko Tajima, and Ken Ohashi; Editorial collaborators: Atsushi Goto and Hiroshi Noto; JCA: Ryuichi Sakai, Shoichiro Tsugane, Nobuyuki Hamajima, Kazuo Tajima, Kohzoh Imai, and Hitoshi Nakagama.

Thus, the current report of the JDS/JCA Joint Committee intends to provide a summary of the evidence available for an association between glycemic control and cancer risk in patients with diabetes.

Evidence from Randomized Controlled Trials

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study investigators evaluated the effect of intensive glycemic control on cancer risk in patients with diabetes by using data obtained from that study. (6) The ADVANCE study was a large-scale randomized controlled trial carried out in 80 countries worldwide and included, in total, 11 140 patients with type 2 diabetes and a history of a major cardiovascular disease or microangiopathy or at least one risk factor for cardiovascular disease. (7) In that study, the subjects were randomly assigned to receive intensive glycemic control with...
glycemic control target was defined as a glycated hemoglobin (HbA1c) level of 6.5% or less (intensive therapy group), or to receive conventional glycemic control with standard therapy in each region or country (conventional therapy group). The mean HbA1c value in the ADVANCE study decreased from 7.5% at baseline in both the groups to 6.5% in the intensive therapy group versus 7.5% in the conventional therapy group after a 5-year follow-up. In addition, intensive glycemic control was prospectively evaluated for its influence on cancer risk, defined as cancer morbidity or mortality according to the reported adverse events and documented deaths; death from cancer was assessed by an independent assessment committee blinded to the subject allocation. During the median follow-up of 5 years, cancer events occurred in 363 patients (1.39 cases/100 person-years) in the intensive therapy group versus 337 patients (1.28 cases/100 person-years) in the conventional therapy group, and this difference between the groups was not significant (hazard ratio, 1.08; 95% confidence interval [CI], 0.93–1.26). The cancer events included 41 and 35 deaths from cancer in the intensive and conventional therapy groups, respectively. The allocation sequence was appropriately generated and concealed and the patient dropout rate was low in both the intensive and conventional therapy groups (seven vs. 10 patients, respectively); however, the study had limitations, in that the assessors were not blinded to the subject allocation information. Cancer events were not evaluated as the primary outcome measures, and the follow-up was not sufficiently long to draw any conclusions on the cancer risk associated with glycemic control.

To date, a meta-analysis of seven randomized controlled trials, including the ADVANCE study, has been carried out to evaluate the cancer risk associated with intensive glycemic control (Table 1).\(^{(8)}\) The UK Prospective Diabetes Study (UKPDS) 33,\(^{(9)}\) UKPDS 34,\(^{(10)}\) Action to Control Cardiovascular Risk in Diabetes study,\(^{(11)}\) and Veterans Affairs Diabetes Trial\(^{(12)}\) were included for the analysis of cancer mortality as an outcome measure. The results of the analysis showed that during the follow-up of 3.5–10.7 years, cancer deaths occurred in 222/5892 person-years receiving intensive glycemic control versus 155/38 743 person-years receiving conventional glycemic control, and the overall risk ratio as estimated by a random-effects model was 1.00 (95% CI, 0.81–1.24; \(I^2 = 0\%\)). The ADVANCE study,\(^{(7)}\) Prospective Pioglitazone Clinical Trial in Macrovascular Events study,\(^{(13)}\) and Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes study\(^{(14)}\) were included for the analysis of the incidence of cancer as an outcome measure. The results of the analysis showed that during the follow-up of 2.9–5.5 years, cancer occurred in 357/47 924 person-years receiving intensive glycemic control versus 380/45 009 person-years receiving conventional glycemic control, and the overall risk ratio as estimated by a random-effects model was 0.91 (95% CI, 0.79–1.05; \(I^2 = 0\%\)). However, this meta-analysis has some limitations, in that it included very few studies and might have been associated with a publication bias. Furthermore, cancer mortality or incidence was not a primary outcome measure in the original studies, the analysis included non-blinded studies, and the follow-up period in the included studies was very short.

Thus, to date, no high-quality randomized controlled trial has been undertaken to estimate cancer risk associated with glycemic control.

Table 1. Incidence of cancer and cancer deaths in major randomized controlled trials

|                      | ACCORD | ADVANCE | RECORD | PROACTIVE | UKPDS 33 | UKPDS 34 | VADT |
|----------------------|--------|---------|--------|-----------|----------|----------|------|
| No. of patients on intensive/conventional therapy | 5128/5123 | 5645/5038 | 2220/2227 | 2605/2633 | 2729/1138 | 342/411 | 892/899 |
| Mean age, years      | 62     | 66      | 58     | 62        | 53       | 53       | 60   |
| Duration of diabetes, years | 10.0   | 8.0     | 7.0    | 8.0       | <1.0     | <1.0     | 11.5 |
| HbA1c at the initiation of therapy, % | 8.3    | 7.5     | 7.9    | 7.9       | 7.1      | 7.2      | 9.4  |
| Cancer incidence in intensive/conventional therapy group, n | 119/119 | 126/148 | 112/113 | nd        | nd       | nd       | nd   |
| Cancer mortality in intensive/conventional therapy group, n | 65/63  | nd      | nd     | 120/50    | 13/21    | 24/21   |

Adapted from Johnson et al.,\(^{(8)}\) ACCORD, Action to Control Cardiovascular Risk in Diabetes study; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation; nd, no data; PROACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events study; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.
associated analyses were carried out in a cohort study in which 9486 American patients with type 2 diabetes were followed. In that study, the incidence of cancer was defined according to the electronic medical records or cancer registry data, which showed that HbA1c values were not associated with the risk of breast cancer or colorectal cancer. Furthermore, patients with lower HbA1c values (<6.5%) had a higher risk for prostate cancer than those with higher HbA1c values (≥7%; hazard ratio, 1.57; 95% CI, 1.09–2.26). This inverse association between HbA1c values and prostate cancer risk is consistent with the observation that diabetes is associated with a decreased risk for prostate cancer.

In summary, although some observational studies suggest an association between glycemic control and cancer risk, the results are not consistent among the studies, and in general, published reports on high-quality epidemiological studies are scarce.

In this review, we provide an overview of the evidence currently available for the association between glycemic control and cancer risk. Given the paucity of high-quality evidence at present, well-designed randomized controlled trials and observational studies are required to explore this issue further.

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