Emerging Link between Diabetes and Cancer

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It has been suggested that diabetes mellitus is associated with an increased risk of cancer. Epidemiological data in Japan demonstrate that diabetes is associated with increased risk for total cancers and site-specific cancers at colorectum, liver, and pancreas. Insulin resistance with subsequent hyperinsulinemia is the most frequently proposed hypothesis to explain this link. In addition, several facets of lifestyle including obesity, smoking, and lack of exercise, and treatment for diabetes may also affect the risk of cancer. In light of the exploding global epidemic of diabetes, even a modest increase in the cancer risk will translate into a substantial socioeconomic burden, which led to a joint committee being formed, enlisting experts from the Japan Diabetes Society and the Japanese Cancer Association to address this issue. The current insights underscore the need for clinical attention and better-designed studies of the complex interactions between diabetes and cancer.

Keywords: diabetes, cancer, risk factors, metformin, insulin, pioglitazone

Backgrounds
A growing body of evidence from observational studies and meta-analyses of the data suggest that diabetes mellitus is associated with an increased risk of cancer. The mechanisms are not fully elucidated, but insulin resistance with secondary hyperinsulinemia is the favored hypothesis, as insulin might have a possible mitogenic effect via binding the insulin-like growth factor-1 receptor.1 In addition, it has been reported that hyperglycemia itself may be pro-carcinogenic by increasing oxidative stress.2 In light of the exploding global epidemic of diabetes, even a modest increase in the cancer risk will translate into a substantial social burden. The joint committee consisting of experts from...
the Japan Diabetes Society (JDS) and the Japanese Cancer Association (JCA) recently published a report\(^3\) to address this issue, which reviewed evidence concerning the association between diabetes and cancer incidence or prognosis, risk factors in common to diabetes and cancer, their postulated biologic links, and the influence of diabetes treatments on the risk of cancer.

**Epidemiology**

Several meta-analyses have demonstrated that diabetes is associated with increased risks of cancer mortality and cancer incidence including site-specific cancers of the liver, endometrium, pancreas, kidney, colorectum, bladder, and breast (Table 1). Exceptionally, the risk of prostate cancer in diabetes is significantly decreased. It is also suggested that diabetic patients have a higher risk of cancer death than non-diabetic people (Tables 1 and 2).\(^3,5\) Furthermore, cancer patients with pre-existing diabetes reportedly have higher short-term\(^14\) and long-term\(^15\) mortalities.

The same as in Western countries, the prevalence of diabetes is markedly increasing in Asia. This trend is presumably attributable to the Westernization of people’s lifestyle. Our meta-analysis\(^16\) demonstrated that the risk ratio (RR) of all-cancer mortality was significantly higher than non-diabetic people (RR, 1.32 [CI, 1.20 to 1.45] for Asians; RR, 1.16 [CI, 1.01 to 1.34] for non-Asians). Diabetes was also associated with an increased RR of incidence across all cancer types (RR, 1.23 [CI, 1.09 to 1.39] for Asians; RR, 1.15 [CI, 0.94 to 1.43] for non-Asians). The RR of incident cancer for Asian men was significantly higher than for non-Asian men (\(p = 0.021\)). Epidemiological data in Japan provides evidence to demonstrate that diabetes is associated with increased risk for colorectal, liver and pancreatic cancers.\(^3\)

**Mechanisms**

**Hyperinsulinemia**

Type 2 diabetes is characterized by insulin resistance and compensatory hyperinsulinemia, and people with type 2 diabetes are typically obese and lead sedentary lives, both of which also promote their hyperinsulinemia. Multiple and complex mechanisms involving these factors are proposed to explain the clearly increased risk of cancer in diabetes. First, insulin may bind and activate its structurally related insulin-like growth factor-1 (IGF-1) receptor.\(^17\) Secondly, hyperinsulinemia may increase cancer risk by unregulated insulin receptor signaling, leading to proliferative and anti-apoptotic effects.\(^18\) Finally, the mitogenic activity of insulin might be enhanced at the cellular level by post-receptor molecular mechanisms including insulin residence time on the receptor and the intracellular up-regulation of the insulin mitogenic pathway.\(^19\)

In humans, patients with type 1 diabetes, who are insulin deficient, have a lower risk of cancer than subjects with type 2 diabetes,\(^20\) although the evidence of the risk as compared with that in the general population remains inconclusive. However, these speculations need to be interpreted with caution since

### Table 1. Cancer risk in diabetes: meta-analysis

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Incidence</td>
<td></td>
</tr>
<tr>
<td>Overall(^5)</td>
<td>1.14 (1.06–1.23)</td>
</tr>
<tr>
<td>Men</td>
<td>1.18 (1.08–1.28)</td>
</tr>
<tr>
<td>Women</td>
<td>1.10 (1.04–1.17)</td>
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<tr>
<td>Liver(^6)</td>
<td>2.50 (1.93–3.24)</td>
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<tr>
<td>Endometrium(^7)</td>
<td>2.10 (1.75–2.53)</td>
</tr>
<tr>
<td>Pancreas(^8)</td>
<td>1.82 (1.66–1.89)</td>
</tr>
<tr>
<td>Kidney(^9)</td>
<td>1.42 (1.06–1.91)</td>
</tr>
<tr>
<td>Colorectum(^10)</td>
<td>1.30 (1.20–1.40)</td>
</tr>
<tr>
<td>Bladder(^11)</td>
<td>1.24 (1.08–1.42)</td>
</tr>
<tr>
<td>Breast(^12)</td>
<td>1.20 (1.12–1.28)</td>
</tr>
<tr>
<td>Prostate(^13)</td>
<td>0.84 (0.76–0.93)</td>
</tr>
<tr>
<td>Cancer Mortality</td>
<td></td>
</tr>
<tr>
<td>Overall(^5)</td>
<td>1.10 (0.98–1.23)</td>
</tr>
<tr>
<td>Men</td>
<td>1.24 (1.11–1.40)</td>
</tr>
<tr>
<td>Women</td>
<td>1.16 (1.03–1.30)</td>
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</table>

### Table 2. Cancer risk in diabetes: pooled analysis in Japan\(^3\)

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1.97 (1.65–2.36)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.85 (1.46–2.34)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>1.40 (1.19–1.64)</td>
</tr>
</tbody>
</table>
they are derived from retrospective observational studies and may not necessarily demonstrate causality because of possible biases and confounders, such as co-existing obesity and age. Of note, diabetes reportedly protect against the development of prostate cancer which is testosterone-dependent. Testosterone deficiency is common in men with diabetes, because they have low levels of sex-hormone-binding globulin, and testosterone levels have been shown to be partly influenced by insulin resistance. Thus, this effect of diabetes on prostate cancer may have contributed to the attenuation of the increase in cancer risk in men. However, those meta-analyses were mainly based on data for Caucasian men and the reported risks for Asian have been inconsistent.

**Hyperglycemia**
Hyperglycemia has been demonstrated to promote cancer development and cancer metastasis in type 2 diabetes. In addition, hyperglycemia itself may promote carcinogenesis by generating oxidative stress. The increase in oxidative stress would damage DNA, the initial step in carcinogenesis. The results of our study support this hypothesis, because the results showed that the risk of both cancer incidence and mortality is also generally higher among Japanese and Korean subjects with diabetes, who have been deemed to be insulinopenic.

**Confounding bias**
Observational analyses should be interpreted with caution. Potential risk factors to cancer and diabetes in common need to be addressed as potential confounders because it remains to be clarified whether the association between diabetes and the risk of cancer is mainly due to shared risk factors (Table 3) or whether diabetes itself increases cancer risk. Although data are mathematically adjusted, these confounding factors are generally interrelated and thus it is difficult to assess the exact contribution of each factor. An alternative explanation is also plausible: diabetic subjects might receive medical care more frequently and have more opportunities for cancer detection than non-diabetic subjects. Diabetes might develop as a consequence of cancer, since cancers generally cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis-α. A recent review suggested only a minority of associations between type 2 diabetes and risk of developing cancer or death from cancer have robust supporting evidence without hints of bias.

**Influence of Medical Treatment of Diabetes**
Current evidence regarding the cancer risk of any particular anti-diabetic agents is limited to determine the casual relation between anti-diabetic drugs and cancer not only due to their inadequate adjustment for confounding factors and therapeutic indications, but because of not accounting for dosage and duration of medications and their short duration of follow-up.

**Insulin, sulfonylureas and glinides**
As discussed earlier, injected insulin potentially increase the risk of cancer. In fact, several reports based on observational studies suggested that insulin glargine usage might be associated with an elevated risk of cancer. However, these observational studies were subject to considerable biases: retrospective studies only demonstrate an association and not necessarily causality; it is very difficult to adjust all possible confounders in observational studies; the effects of treatment by indication and informative censoring cannot be excluded. On the other hand, the oncogenic effect of hyperinsulinemia might be offset by the cancer-protective effect through amelioration of hyperglycemia. Randomized-controlled trials (RCTs) and more recent cohort studies have not indicated significant associations of insulin with cancer risk and the causality is now practically negated.
Sulfonylureas and glinides induce hyperinsulinemia and there is a concern of increased cancer risks. However, the estimate in a meta-analysis of the cancer risk of sulfonylureas is neutral. Data for glinides are limited and further investigations are needed to evaluate their oncogenic safety.

**Metformin**

Our recent meta-analysis including observational studies and RCTs suggested that metformin users have a lower risk of cancer incidence and mortality\(^\text{35}\) (Table 4) although bias could not be entirely eliminated. Metformin activates activating adenosine 5'-mono-phosphate-activated protein kinase (AMPK) through LKB-1, a tumor suppressor protein kinase. AMPK, mammalian target of rapamycin (mTOR) and insulin-signaling pathway represent three interrelated components of a complex mechanism controlling cell responses to nutrient availability. AMPK inhibits protein synthesis and gluconeogenesis during cellular stress and inhibits mTOR, a downstream effector of growth factor signaling, which is frequently activated in malignant cells. To support the hypothesis of these direct effects, metformin potentiated the effect of neoadjuvant chemotherapy in early-stage breast cancer,\(^\text{36}\) decreased the risk of colorectal cancer in a small RCT involving non-diabetic subjects,\(^\text{37}\) and was associated with a decreased cancer risk while another insulin-sensitizer, thiazolidinediones, was not.\(^\text{38}\) An animal study suggested that metformin prevented smoking-related lung cancer in mice, probably by inducing some hormone from the liver.\(^\text{39}\) There are more recent meta-analyses supporting this potential benefit of metformin\(^\text{40–43}\) and several prospective clinical trials to evaluate its safety and efficacy are currently ongoing.

**Pioglitazone**

Recent reports including meta-analyses have suggested that it might be associated with an increased risk of bladder cancer in a exposure/dose-response pattern.\(^\text{44,45}\) The carcinogenic effect was also seen in an animal study\(^\text{46}\) although the mechanism is not clarified yet. The causality is not conclusive at present\(^\text{47}\) and several surveys are in progress. It is currently out of market in some countries because of this potential harm and it is prudent to follow its latest warning label.

**α-Glucosidase inhibitors**

Data on the cancer risk associated with α-glucosidase inhibitors are sparse and highly biased. Cancer risk associated with α-glucosidase inhibitors remains inconclusive.\(^\text{48–51}\)

**Glucagon-like peptide (GLP)-1 analogues and dipeptidyl peptidase (DPP-4) inhibitors**

It was initially reported that the risk of pancreas cancer and thyroid cancer was elevated among GLP-1 analogue users.\(^\text{52}\) The risk of pancreas cancer was possibly increased with a DPP-4 inhibitor.\(^\text{52}\) Although a meta-analysis suggested an oncogenic safety of DPP-4 inhibitors,\(^\text{53}\) the included studies were of short follow-up periods and the long-term effect remains elusive. More recent RCTs have not demonstrated a significant risk of cancer.\(^\text{54,55}\)

**Sodium glucose co-transporter (SGLT) 2 inhibitors**

Long-term data on the oncogenic risk/safety in relation to these novel medications are lacking at present.

**Conclusion**

The present review underscores the need of more attention directed to elucidating the association between diabetes and cancer, which is pivotal for making timely, rational and informed decisions, not only in the areas of public health and economy, but also for the prevention and targeted management of these diseases in clinical practice.

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**Table 4. Metformin and cancer risk in diabetes: meta-analysis\(^\text{35}\)**

<table>
<thead>
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<th>Risk Ratio (95%CI)</th>
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<tbody>
<tr>
<td>Cancer Incidence</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.67 (0.53–0.85)</td>
</tr>
<tr>
<td>Liver</td>
<td>0.20 (0.07–0.88)</td>
</tr>
<tr>
<td>Lung</td>
<td>0.67 (0.45–0.99)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>0.68 (0.53–0.88)</td>
</tr>
<tr>
<td>Cancer Mortality</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.66 (0.49–0.88)</td>
</tr>
</tbody>
</table>
Acknowledgments
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