Latest insights into the risk of cancer in diabetes

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ABSTRACT
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. Meta-analyses have shown that diabetes increases the risks of total cancer, and of site-specific cancers of the breast, endometrium, bladder, liver, colorectum and pancreas, and that it decreases the risk of prostate cancer. Insulin resistance and secondary hyperinsulinemia is the most frequently proposed hypothesis, and hyperglycemia itself might promote carcinogenesis. In addition to several facets of lifestyle including obesity, smoking and lack of exercise, treatment for diabetes might affect the risk of cancer. For instance, metformin, an insulin sensitizer, reportedly has a potential anticancer effect. In light of the exploding global epidemic of diabetes, even a modest increase in the cancer risk will translate into a substantial socioeconomic burden. The current insights underscore the need for clinical attention and better-designed studies of the complex interactions between diabetes and cancer. (J Diabetes Invest, doi: 10.1111/jdi.12068, 2013)

KEY WORDS: Cancer, Diabetes, Risk factors

INTRODUCTION
Emerging 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 yet to be investigated, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis, as insulin might have a possible mitogenic effect through binding the insulin-like growth factor-1 receptor1. In addition, hyperglycemia itself might promote carcinogenesis by increasing oxidative stress2–5.

In light of the fact that cancer is the second leading cause of death worldwide, diabetes is the 12th6, the current worldwide diabetes epidemic and the higher mortality in cancer patients with diabetes7,8, elucidating the association between these diseases in general populations is crucial for making timely, rational, and informed decisions, not only in the areas of public health and socioeconomic, but also for the prevention and targeted management of diabetes in daily clinical practice. The American Diabetes Association and the American Cancer Society recently published a consensus statement that reviewed evidence regarding the association between diabetes and cancer incidence or prognosis, risk factors common to both diabetes and cancer, possible biological links between diabetes and cancer risk, and whether diabetes treatments influence risk of cancer or cancer prognosis9.

EPIDEMOLOGY
Several meta-analyses have shown that diabetes is associated with increased risks of site-specific cancers of the liver, endometrium, pancreas, colorectum, bladder, breast and total cancer (Table 1). The evidence for non-Hodgkin’s lymphoma remains inconclusive18. Exceptionally, the risk of prostate cancer in diabetics is significantly decreased17.

Evidence has been accumulating to suggest that diabetic patients have a higher risk of cancer death than non-diabetic peo-

| Site | Risk ratio (95% CI) |
|------|-------------------|
| Cancer incidence | Overall10 |
| Men | 1.14 (1.06-1.23) |
| Women | 1.18 (1.08-1.28) |
| Combined | 1.10 (1.04-1.17) |
| Liver11 | 2.50 (1.93-3.24) |
| Endometrium12 | 2.10 (1.75-2.53) |
| Pancreas13 | 1.82 (1.66-1.89) |
| Colorectum14 | 1.30 (1.20-1.40) |
| Bladder15 | 1.24 (1.08-1.42) |
| Breast16 | 1.20 (1.12-1.28) |
| Prostate17 | 0.84 (0.76-0.93) |
| Cancer mortality | Overall10 |
| Men | 1.10 (0.98-1.23) |
| Women | 1.24 (1.11-1.40) |
| Combined | 1.16 (1.03-1.30) |

CI, confidence interval.
ple (Table 1)10,19. Furthermore, cancer patients with pre-existing diabetes have higher short-term8 and long-term7 mortalities.

The same as in Western countries, the prevalence of diabetes is markedly increasing in Asia. This trend is presumably attributable to the rapid Westernization of lifestyle, a trend that is likely shared by the majority of Asian populations20. Although cardiovascular disease is the main cause of mortality in Western countries, and patients with diabetes have a high risk of such disease, cancer is emerging as a major cause of death in Asian countries21–23. Our meta-analysis24 showed that the pooled adjusted risk ratio (RR) of all-cancer mortality in diabetics was significantly higher than in non-diabetic people (RR 1.32, 95% confidence interval [CI] 1.20–1.45 for Asians; RR 1.16, 95% CI 1.01–1.34 for non-Asians). Diabetes was also associated with an increased RR of incidence across all cancer types (RR 1.23, 95% CI 1.09–1.39 for Asians; RR 1.15, 95% CI 0.94–1.43 for non-Asians). The RR of incident cancer for Asian men was significantly higher than for non-Asian men (P = 0.021).

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 contribute to their hyperinsulinemia. Multiple and complex mechanisms are postulated. First, insulin might bind and activate its structurally related insulin-like growth factor-1 (IGF-1) receptor, which is the most frequently proposed mechanism to explain the clearly increased risk of cancer in diabetic patients (Figure 1)1,25. Second, hyperinsulinemia might increase cancer risk by unregulated insulin receptor signaling, leading to proliferative and anti-apoptotic effects26. Finally, the mitogenic activity of insulin might be enhanced at the cellular level by postreceptor molecular mechanisms including insulin residence time on the receptor and the intracellular upregulation of the insulin mitogenic pathway27. It has been reported that this mitogenic pathway, unlike the metabolic pathway, might not be blunted in the condition of insulin resistance28.

Several findings were consistent with this insulin supply hypothesis. Pancreatic cancer has been reportedly induced more effectively with a carcinogen or by implantation of cancer cells when experimental insulin-deficient animals were given supplemental insulin29. In humans, patients with type 1 diabetes, who are insulin deficient, have a lower risk of cancer than patients with type 2 diabetes30, although the evidence of the risk as compared with that in the general population remains inconclusive31. However, these speculations need to be interpreted with caution, as they are derived from retrospective observational studies and might not necessarily show causality because of possible biases and confounders, such as coexisting obesity.

Figure 1 | The insulin/insulin-like growth factor-1 (IGF-1) receptor. Both the insulin receptor and the IGF receptor are encoded by single genes, which are processed into an α-chain and β-chain that remain linked by disulfide bonds. These α/β complexes can either homodimerize to form insulin receptors or IGF receptors, or heterodimerize to form hybrid receptors. Insulin binds preferentially to the insulin receptor, whereas IGF-1 binds preferentially to the IGF-1 and hybrid receptors. Although there is a great deal of overlap in their function, the insulin receptor is more closely linked with metabolic effects, whereas the hybrid receptor and IGF receptor are more closely linked with proliferation. Adapted from Biddinger et al.25 with permission.
and age. In fact, more recent studies have shown no or minimal increments in cancer risk, and the data from insulin-treated patients are controversial.

Of interest, diabetes has been reported to 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. The degree of the decrease in cancer risk as a result of testosterone deficiency is likely to be higher than the magnitude of the increase in cancer risk as a result of insulin resistance, and thus this effect of diabetes on prostate cancer might 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 men have been either significantly elevated in Taiwan or non-significant in Japan and Korea, which points to the possibility that the effect of diabetes on prostate cancer might not be universal, probably secondary to genetic/cultural/socioeconomic factors.

**Hyperglycemia**

Hyperglycemia has also been reported to promote carcinogenesis and cancer metastasis in type 2 diabetes. Indeed, this forms the basis for 18F-fluorodeoxyglucose positron emission tomography of cancers, which detects tissues with high rates of glucose uptake. In addition, hyperglycemia itself might promote carcinogenesis by generating oxidative stress, which is frequently observed to be increased in a variety of cells in diabetes. The increase in oxidative stress would damage DNA, the initial step in carcinogenesis. Community-based prospective surveys have documented associations between plasma glucose levels and the risk of cancer. 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 patients with diabetes, who have been deemed to be insulinopenic. However, a meta-analysis of large randomized-controlled trials (RCTs) of intensified glycemic control did not support the hypothesis that hyperglycemia is causally linked to increased cancer risk.

These observations point to the crucial need for understanding the role of glucose metabolism and insulin resistance in carcinogenesis.

**Confounding Factors**

Potential common risk factors of cancer and diabetes need to be addressed, because it remains to be clarified whether the association between diabetes and the risk of cancer is a result of shared risk factors or whether diabetes itself causes some types of cancer.

First, several comorbidity confounders exist. Diabetes and cancer share multiple lifestyle-related risk factors (Table 2). For example, coexisting obesity and a sedentary lifestyle, which induce hyperinsulinemia, might be the true causes, and diabetes might merely be an innocent bystander. A meta-analysis showed that obesity is associated with increased risk for pancreatic cancer, thyroid cancer, non-Hodgkin’s lymphoma, leukemia and myeloma, whereas bariatric surgery resulted in 60% reduction in cancer mortality over the course of 7 years. Exercise is suggestively associated with overall cancer, colon cancer, hepatocellular cancer, pancreas cancer and gastric cancer. The other possible confounding factors include age, sex, diet, alcoholic intake, smoking, cirrhosis, hepatitis C viral infection and the indication of insulin therapy. These factors are generally interrelated, and thus it is difficult to assess the contribution of each factor. Second, an alternative explanation is that diabetic patients might receive medical care more frequently and have more opportunities for cancer detection than non-diabetic subjects. Third, diabetes might develop as a consequence of cancer, as cancers generally cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis factor-α. Fourth, the previous studies might have left room for confounding by treatment indication; differences between the treatment of cancer according to whether or not they had diabetes might have contributed to the increased mortality of the subjects. Diabetic patients often have other diabetes-related comorbidities that might influence the treatment decisions and prognosis. For example, diabetes might be accompanied by a higher risk of infection, and the diagnosis of cancer might result in inappropriate glucose management.

### Table 2 | Shared risk factors of diabetes and cancer

| Risk Factor         |
|---------------------|
| Age                 |
| Sex                 |
| Genetic factors     |
| Obesity             |
| Diets               |
| Lack of exercise    |
| Smoking             |
| Alcohol intake      |

**MEDICAL TREATMENT OF DIABETES AND CANCER**

**Insulin, Sulfonylureas and Glinides**

As discussed earlier, insulin injection might increase the risk of cancer because of its structural similarity to IGF-1. 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 show 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. In contrast, the oncogenic effect of hyperinsulinemia might be offset by the cancer-protective effect through amelioration of hyperglycemia. RCTs and more recent cohort studies have not shown significant associations of insulin with cancer risk.
Sulfonylureas and glinides induce hyperinsulinemia, and thus there is a concern of increased cancer risks\(^5\)\(^4\)--\(^6\)\(^3\)\(^6\)\(^6\). However, the estimates in other reports are inconsistent\(^6\)\(^7\). Further investigations are required to verify its oncogenic safety.

**Metformin**

Metformin is an insulin sensitizer that is the drug of first choice in the management of type 2 diabetes\(^6\)\(^8\), given its safety profile and lower cost. Our recent meta-analysis including observational studies and RCTs showed that metformin usage is associated with a lower risk of cancer incidence and mortality in diabetes\(^6\)\(^9\) (Table 3), and similar effects have been seen across different regions in the world\(^3\)\(^8\),\(^6\),\(^7\),\(^0\)--\(^7\)\(^3\).

As shown in Figure 2, metformin activates activating adenosine 5’-mono-phosphate-activated protein kinase (AMPK) through LKB-1, a tumor suppressor protein kinase. AMPK, the mammalian target of rapamycin (mTOR) and the 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. In human breast cancer cells, it reduces HER-2 protein expression by inhibiting mTOR. Metformin also induces cell cycle arrest and apoptosis, and reduces growth factor signaling. To support the hypothesis of these direct effects, metformin reportedly potentiated the effect of neoadjuvant chemotherapy in early-stage breast cancer\(^7\)\(^4\), decreased the risk of colorectal cancer in a small RCT involving non-diabetic subjects\(^7\)\(^5\), and was associated with a decreased cancer risk while another insulin-sensitizer, thiazolidinedione, was not\(^7\)\(^6\)--\(^7\)\(^9\).

Our research\(^6\)\(^9\) showed that metformin use is associated with reduced mortality and incidence of cancer at any site, supporting the generalizability of the proposed anticancer mechanisms. In contrast, the magnitude of the risk reduction

### Table 3 | Metformin and cancer risk in diabetes: meta-analysis\(^6\)\(^9\)

| Site            | Risk ratio (95% CI) |
|-----------------|---------------------|
| Cancer incidence* |                     |
| Overall         | 0.67 (0.53–0.85)    |
| Liver           | 0.20 (0.07–0.88)    |
| Lung            | 0.67 (0.45–0.99)    |
| Colorectum      | 0.68 (0.53–0.88)    |
| Cancer mortality |                     |
| Overall         | 0.66 (0.49–0.88)    |

*Risk ratios for the cancer of pancreas, breast, stomach and bladder were not statistically significant. CI, confidence interval.

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![Figure 2](image-url) | Mechanisms of anti-oncogenic effect of metformin. AMPK, adenosine 5’-mono-phosphate-activated protein kinase; HER2, epithelial growth factor receptor 2; IGF, insulin-like growth factor; IGF-1R, insulin-like growth factor 1; IR, insulin receptor; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; TSC2, tuberous sclerosis complex 2; VEGF, vascular endothelial growth factor. Adapted from Jalving et al.\(^8\)\(^7\) with permission.
tumors of the colon
in elevated levels of insulin and glucose might exert an important
differences in carcinogenesis at certain sites. For instance,
study, whereas it was not con
Adapted from Lewis et al.
varies among site-specific cancers. This variance might result
elevated levels of insulin and glucose might exert an important
influence in the development or growth of epithelial malignant
tumors of the colon, pancreas and breast, and metformin
metformin reportedly prevents incident colon cancer in non-diabetic
results, the mechanism is
metformin simply augmented the ef
cancers. This variance might result
in animal study that metformin prevented
smoking-related lung cancer in mice, probably by inducing
some hormone from the liver. The fact that one preliminary
study suggested a promising effect of metformin on pathological
complete responses to neoadjuvant chemotherapy in diabetic
patients with breast cancer might point to the possibility
that metformin simply augmented the efficacy of chemotherapy
for breast cancer. Several prospective clinical trials to evaluate
its safety and efficacy are currently ongoing.

Pioglitazone

Pioglitazone is another insulin sensitizer that activates peroxi-
some proliferator-activated receptor-γ. Recent reports including
meta-analyses have suggested that it might significantly increase
the risk of bladder cancer in a exposure/dose-response pattern (Table 4), whereas its effect on total cancer or
cancers at other sites might be neutral. The carcinogenic effect
was also seen in an animal study, although the mechanism is
not clarified yet. The risk is not conclusive at present, and several surveys are in progress. It is currently not on the market in France and Germany because of this potential harm.

α-Glucosidase Inhibitors

Data on the cancer risk associated with α-glucosidase inhibitors are sparse. An increased risk of bladder cancer was reported in one study, whereas it was not confirmed in another.

Glucagon-Like Peptide-1 Analogs and Dipeptidyl Peptidase-4 Inhibitors

The risk of pancreas cancer and thyroid cancer was reportedly elevated among exenatide, a glucagon-like peptide-1 analog, users. An increased risk of thyroid C-cell cancer was seen in rodent studies. The risk of pancreas cancer might be increased with sitagliptin, a DPP-4 inhibitor. Although a meta-analysis suggested oncogenic safety of dipeptidyl peptidase-4 (DPP-4) inhibitors, the included studies were of short follow-up periods and the long-term effect remains elusive.

FUTURE DIRECTIONS

In light of the exploding global epidemic of diabetes, a modest increase in the risk of cancer will translate into a substantial socioeconomic burden. The present review underscores the need for diabetes prevention, particularly by weight management, and for investigation of effective cancer prevention, screening policies and implementation of diabetes treatment with potentially protective effects against cancer. Attention should be directed to elucidating the association between these diseases in populations with increased risks to make timely, rational and informed decisions, not only in the public health area and socioeconomic area, but also for the prevention and targeted management of diabetes in routine clinical practice. For the time being, healthful diets, physical activity and weight management should be promoted for all. Patients with diabetes should be strongly encouraged by their healthcare professionals to undergo appropriate cancer screenings as recommended for all people of their age and sex, and cancer risk should not be a major factor in choosing between available diabetes therapies for the average patient.

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The authors have declared that no competing interests exist.

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