Diabetes and cancer: Associations, mechanisms, and implications for medical practice

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Abstract
Both diabetes mellitus and cancer are prevalent diseases worldwide. It is evident that there is a substantial increase in cancer incidence in diabetic patients. Epidemiologic studies have indicated that diabetic patients are at significantly higher risk of common cancers including pancreatic, liver, breast, colorectal, urinary tract, gastric and female reproductive cancers. Mortality due to cancer is moderately increased among patients with diabetes compared with those without. There is increasing evidence that some cancers are associated with diabetes, but the underlying mechanisms of this potential association have not been fully elucidated. Insulin is a potent growth factor that promotes cell proliferation and carcinogenesis directly and/or through insulin-like growth factor 1 (IGF-1). Hyperinsulinemia leads to an increase in the bioactivity of IGF-1 by inhibiting IGF binding protein-1. Hyperglycemia serves as a subordinate plausible explanation of carcinogenesis. High glucose may exert direct and indirect effects upon cancer cells to promote proliferation. Also chronic inflammation is considered as a hallmark of carcinogenesis. The multiple drugs involved in the treatment of diabetes seem to modify the risk of cancer. Screening to detect cancer at an early stage and appropriate treatment of diabetic patients with cancer are important to improve their prognosis. This paper summarizes the associations between diabetes and common cancers, interprets possible mechanisms involved, and addresses implications for medical practice.

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Key words: Diabetes mellitus; Cancer; Association; Mechanism; Medical practice

Core tip: The diabetes-cancer link is summarized and discussed in detail and it may potentially be attributed to hormonal disorders, chronic inflammation and metabolic alterations. Besides, implications for medical practice are also addressed.
2 diabetes mellitus (T2DM) is 8.3%. The prevalence of T2DM varies by country and area. The highest rate is 10.5% in North America, 8.7% in South-East Asia, 6.7% in Europe and 4.3% in Africa. It is predicted that 552 million people worldwide will develop diabetes by 2030[1].

DM and cancer are frequently diagnosed in the same individual[2]. DM is reported to be associated with an increased risk of different types of cancer, including pancreatic, liver, breast, colorectal, urinary tract, gastric, and female reproductive cancers. The relative risk ranges from 2.0 to 2.5 for liver, pancreatic and endometrial cancers, and 1.2 to 1.5 for breast, colon and bladder cancers associated with DM[3]. It is worth noting that DM is a growing health problem worldwide. Even if the increased risk in cancer incidence and mortality due to DM is small, the consequence would be significant at the population level[4].

The mechanism of DM associated with cancer remains uncovered and needs to be examined in further studies. The mechanism for the diabetes-cancer link has been hypothesized to be mainly related to hormonal [insulin and insulin-like growth factor (IGF)-1], inflammatory or metabolic (hyperglycemia) characteristics of the DM and even to certain treatments[5]. Anti-diabetic medications may have effects on the risk for cancer. Increasing evidence shows that insulin sensitizers such as metformin and thiazolidinediones (TZDs) are associated with prostate cancer[6] and HER2-positive breast cancer[7] among diabetic patients. The diabetic patients who are treated with insulin or insulin secretagogues are more likely to develop cancer than those with metformin[8-11].

In this paper, we summarize the associations between diabetes and cancer in epidemiologic studies, possible mechanisms and implications for medical practice.

POSSIBLE BIOLOGIC LINKS BETWEEN DIABETES AND CANCER RISK

Insulin resistance

Insulin resistance is very common in T2DM, in which circulating insulin level is frequently increased. The insulin/IGF axis plays an important role in diabetes-associated increased risk and progression of cancer. The cancer cells overexpress insulin and IGF-1 receptors[2].

Hyperinsulinemia is a hallmark of insulin resistance. The mechanisms whereby hyperinsulinemia could link diabetes and cancer have been extensively investigated and discussed. Hyperinsulinemia may influence cancer development through ligand by binding with the insulin receptor (IR) and/or indirectly through increasing circulating IGF-1 levels[12,13]. Insulin signal transduction is mediated through two IR isoforms: IR-A and IR-B[14]. IR-A recognizes insulin and IGFs, with a higher affinity for IGF2 than IGF1, and IR-B is insulin specific and is mainly involved in glucose homeostasis. Insulin binds with IR-A and exerts a direct pro-growth mitogenic effect. When elevated, insulin can increase the hepatic expression of IGF-1 and then activate the IGF-1 receptor, further stimulating cell growth through this mechanism[14,15]. IR-A and IGF-1 receptor are expressed primarily in fetal tissues and cancer cells[16].

The independent role of the IR is confirmed by the observation that down-regulation of IRs in LCC6 cells reduces xenograft tumor growth in athymic mice and inhibits lung metastasis[17]. Besides, blockade of the IGF-1 receptor has been associated with decreased growth of breast cancer cells[18,19]. Hyperinsulinemia also results in decreased levels of IGF binding protein-1 and thus increased levels of bioactive IGF-1[20,21].

Multiple downstream signaling pathways are activated after IRs or IGF-1 receptors interact with their ligands. By phosphorylation of adaptor proteins, two major pathways are involved: (1) the phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt)/mammalian target of rapamycin (mTOR), PI3K/Akt/forerkhead box O, and Ras/ MAPK/extracellular signal-related kinase 1/2 pathway which plays important roles in cancer cell growth and carcinogenesis[22,23] is activated; and (2) the inhibitor of the oncogenic β-catenin signaling (glycogen synthase kinase 3β) is inactivated, through the PI3K/Akt signaling pathway, resulting in β-catenin signaling activation that has been related to cancer stem cells and chemo-resistance[24].

Hyperglycemia

Hyperglycemia has been classically considered as a subordi nate whereas hyperinsulinemia as a primary causal factor for cancer[25].

Several large cohort and case-control studies have found a positive relationship between hyperglycemia and the risk of cancer[26-29]. In a tumor-prone animal model, it was found that the number and size of liver tumors increased and apoptosis was reduced in insulin-deficient hyperglycemic mice compared with insulin-sufficient mice. This phenomenon was reversed by insulin therapy[30]. However, in vivo studies showed that T1DM, which is characterized by hyperglycemia, reduces the tumor growth. This finding does not support that hyperglycemia increases tumor growth, at least in the setting of insulin deficiency[31]. A recent research found that tumors continue to consume high amounts of glucose, regardless of plasma glucose levels[32]. A recent meta-analysis confirmed this finding that improved glycemic control does not reduce cancer risk in diabetic patients[33]. Hyperglycemia may be an independent risk factor for cancer. Further studies are needed to evaluate the relative roles of insulin and glucose.

The possible mechanisms of hyperglycemia increasing cancer risk include “indirect effect” and “direct effect”[34,35]. The “indirect effect” is the action that takes place at other organs and will later on influence tumor cells by inducing production of circulating growth factors (insu lin/IGF-1) and inflammatory cytokines. The “direct effect” is the effect that is exerted directly upon tumor cells by increasing proliferation, inducing mutations, augmenting invasion and migration and rewiring cancer-related signaling pathways. Recently, Wnt/β-catenin signaling has been suggested as a key cancer-associated pathway and
Table 1 Combined relative risk and 95%CI in meta-analyses of cohort studies of cancer risk in different organs of diabetic patients

| Cancer               | Ref.                  | No. of cohort studies | RR (95%CI) | RR (95%CI) male | RR (95%CI) female |
|----------------------|-----------------------|-----------------------|------------|----------------|-----------------|
| Pancreas             | Ben et al[36], 2011   | 35                    | 1.94 (1.66-2.27) | 1.70 (1.55-1.87)^1 | 1.60 (1.43-1.77)^1 |
| Liver                | Wang et al[37], 2012  | 18                    | 2.01 (1.61-2.51) | 1.96 (1.71-2.24)^1 | 1.66 (1.14-2.41)^1 |
| Breast               | De Brujin et al[38], 2013 | 20                  | 1.29 (1.12-1.44) | NA              | 1.23 (1.12-1.34) |
| Endometrium          | Zhang et al[39], 2013 | 15                    | 1.81 (1.38-2.37) | NA              | 1.81 (1.38-2.37) |
| Colon-rectum         | Jiang et al[40], 2011 | 30                    | 1.27 (1.21-1.34) | 1.25 (1.17-1.33)^1 | 1.23 (1.13-1.33)^1 |
| Kidney               | Bao et al[41], 2013   | 11                    | 1.39 (1.09-1.78) | 1.28 (1.10-1.48) | 1.47 (1.18-1.73) |
| Bladder              | Zhu et al[42], 2013   | 29                    | 1.29 (1.08-1.54) | 1.36 (1.05-1.77) | 1.28 (1.05-1.79) |
| Prostate             | Zhang et al[43], 2012 | 25                    | 0.92 (0.81-1.05) | 0.92 (0.81-1.05) | NA              |
| Gastric              | Yoon et al[44], 2013  | 11                    | 1.20 (1.08-1.34) | 1.10 (0.97-1.24) | 1.24 (1.03-1.52) |
| Non-Hodgkin’s lymphoma | Castillo et al[45], 2012 | 11                  | 1.21 (1.02-1.45) | 1.13 (0.96-1.34) | 1.24 (0.97-1.58) |

^1Based on the studies reported by gender. NA: Unavailable.

Chronic inflammation

The deregulated metabolism in poorly controlled diabetes causes a long-term pro-inflammatory condition characterized by increased levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C-reactive protein, and other markers of chronic inflammation. Emerging evidence suggests that persistent inflammation can promote genetic instability and chronic inflammation is associated with increased cancer risk[37-40]. This finding is also supported by the classical evidence that non-steroidal anti-inflammatory drugs can reduce the risk of certain cancers[41-44].

Tumor-promoting mechanism of inflammation in diabetic patients is not much clear. Chronic inflammation and chronic oxidative stress go hand-in-hand. Oxidants affect almost all stages of the inflammatory response process, including the release of inflammatory cytokines, the sensing by innate immune receptors from the families of Toll-like receptors and the nucleotide-binding oligomerization domain-like receptors, and the activation of signaling like receptors and the nucleotide-binding oligomerization domain-like receptors, and the activation of signaling pathways independent of obesity and inflammation[45]. Reactive oxygen species can cause damage to lipids, protein, and DNA, and then initiate carcinogenesis[46-48]. Meanwhile, chronic inflammation is associated with high levels of TNF-α, which would strongly activate nuclear factor-kappa B (NF-κB) and further induce downstream signaling transduction to promote the development and progression of many tumors. NF-κB is involved in the proliferation and survival of malignant cells, promotes angiogenesis and metastasis, subverts adaptive immunity, and mediates responses to hormones and/or chemotherapeutic agents[49-51]. Therefore, continued exposure to chronic inflammation and oxidative stress puts susceptible cells at risk of progression toward malignant transformation[52].

Impact of diabetes on cancer

Evidence from animal studies

DM is mainly characterized by insulin resistance, hyperinsulinemia, hyperglycemia, and dyslipidemia. The independent role of diabetes and obesity in cancer development has been difficult to distinguish since obesity is also related to inflammation and hyperinsulinemia. Studies in transgenic diabetic mice might shed light on the relative contributions of these factors. In a transgenic model of skin and mammary carcinogenesis, non-obese diabetic mice (A-ZIP/F-1) developed more tumors than wild-type controls[53]. In MKR mouse models of mammary carcinogenesis, female mice with T2DM showed accelerated mammary gland development and breast cancer progression independent of obesity and inflammation[54]. Hyperinsulinemia promoted the growth of primary mammary tumor and subsequent metastasis to the lung[55]. Tumor progression was abrogated with the decreased level of serum insulin after treatment with anti-insulin drugs[56]. Taken together, findings from animal studies support that diabetes plays interconnected roles in the development of cancer.

Epidemiologic findings

The findings from a meta-analysis of 12 cohort studies showed that diabetes increased the risk of all-cancer incidence for overall subjects, with a pooled adjusted RR of 1.14 (1.06-1.23) for men, and 1.18 (1.08-1.28) for women[57]. Diabetes is reported to be associated with several types of cancer, including pancreas, liver, breast, colorectal, urinary tract, gastric, and female reproductive cancers. Meta-analyses on the associations between diabetes and site specific cancer are summarized in Table 1.

Liver cancer: In various studies examining the link between DM and cancer, the highest risk has been seen for liver cancer. A meta-analysis demonstrated that individuals with diabetes had a 2.0-fold increased risk of developing hepatocellular carcinomas (HCC), compared with non-diabetics. And this link was observed in both men and women[58]. The liver is exposed to high concentrations of endogenously produced insulin transported via the portal vein. Hyperinsulinemia stimulates the production of IGF-1, which further promotes cellular proliferation and then inhibits apoptosis in the liver. The important role of hyperinsulinemia and IGF-1 in hepatic carcinogenesis has been demonstrated by in vitro, in vivo, and epidemiologic studies[59,60]. Liver steatosis, hepatitis,
and cirrhosis are more frequent among diabetic patients and are well-known risk factors for HCC. Insulin resistance stimulates the release of multiple pro-inflammatory cytokines and consequently promotes the development of hepatic steatosis and inflammation and subsequent cancer in the liver[89]. A causal relationship was also reported by Jee et al[89], who found that fasting glucose and liver cancer risk had a dose-responsive relationship. Besides, T2DM-induced hyperglycemia induces the release of TNF-α and IL-6 in patients with hepatic steatosis and enhances the pathogenesis of cancer[91].

Colorectal cancer: A meta-analysis comprising 30 cohort studies showed that diabetes was associated with an increase in the risk of colorectal cancer, with a combined RR of 1.27 (1.21-1.34). This association was consistent for both men and women[92]. Our previous retrospective cohort study showed that a significant association of diabetes was found with colon cancer and not with rectal cancer[93]. This finding indicated that there was a subsite-specific association of T2DM with colorectal cancer. General factors like hyperinsulinemia and IGF-1 have contributed to intramucosal adenocarcinomas. Diabetic patients have slower bowel peristalsis and more common constipation and thus increased exposure to bowel toxins (i.e., elevated concentrations of fecal bile acids) and potential carcinogens[94]. Animal models have demonstrated that increased concentrations of fecal bile acids could induce colorectal carcinogenesis[95-97].

Breast and other female cancers: A meta-analysis including 20 cohort studies found an association between diabetes and breast cancer with a summary RR of 1.23 (1.12-1.34)[66]. A meta-analysis including 15 cohort studies reported an increased risk [RR = 1.81 (1.38-2.37)] of endometrial cancer in diabetic women[67]. Hyperinsulinemia could increase the levels of bioactive estrogens by reducing the concentration of circulating sex hormone binding protein in diabetic women. It is well known that bioactive estrogens are the risk factors for malignancies of female reproductive organs[68,69]. Increased bioactive estrogen will stimulate the proliferation of breast and endometrial cells and the inhibition of apoptosis to increase cancer risk.

Kidney and bladder cancers: A meta-analysis including eleven cohort studies showed that diabetes was significantly associated with an increased risk of kidney cancer [RR = 1.39 (1.09-1.78)]. The association was slightly stronger in women [RR = 1.47 (1.18-1.83)] than in men [RR = 1.28 (1.10-1.48)][70]. Hypertension and late stage renal disease, two common comorbidities of DM, contribute to the increased incidence of kidney cancer[71,72]. Impaired renal function results in higher circulating levels of carcinogens and toxins and immune inhibition and thereby renders the kidney susceptible to carcinogens and tumor growth. Findings from a meta-analysis of 29 cohort studies suggest that individuals with DM display an increase in the risk of bladder cancer [RR = 1.29 (1.08-1.54)]. The positive association is only observed in men [RR = 1.36 (1.05-1.77)][73]. In addition to general factors, the frequent infections of the urinary tract in diabetic patients might also be involved[74].

Pancreatic cancer: In a 3-year follow-up study[75], subjects with new-onset DM had a higher risk of pancreatic cancer with a RR of 7.94 than the subjects without DM. A meta-analysis of 35 cohort studies showed that DM was associated with an increased risk of pancreatic cancer in both men and women[76]. However, the question arises about whether diabetes is a risk factor or the consequence of the pancreatic cancer (so-called “reverse causality”). Pancreatic cancer might induce a diabetic status because of impaired pancreatic beta cells. In vitro studies show that blockage of insulin receptors and impaired insulin action and glucose transport in a model of pancreatic cancer led to insulin resistance[77]. However, the new onset of pancreatic cancer induced DM depends on the peripheral insulin resistance rather than on the impaired pancreatic beta cells. On the other hand, in patients with T2DM exocrine pancreatic cells are exposed to very high insulin levels because of their proximity to insulin secreting islets. Insulin stimulates the growth of cancer cells. Thus, hyperinsulinemia might account for the risk of developing pancreatic cancer in T2DM.

Prostate cancer: Prostate cancer risk appears to decrease in patients with diabetes. An inverse association was observed between diabetes and risk of prostate cancer in the studies from the United States but not in the studies from other countries, as shown by an updated meta-analysis[78]. The protective effect of DM was also observed in different grades or stages of prostate cancer in another meta-analysis[79]. One possible explanation is that low testosterone levels have been shown in diabetic men. The conversion of testosterone to dihydrotestosterone promotes prostate cell growth[80].

Other cancers in diabetes: A 20% increased gastric cancer risk in diabetic patients was found in a meta-analysis. A positive association was observed in female diabetic patients, whereas it was not the case in diabetic men[81]. The IGF/IGF-IR axis interacts with the vascular endothelial growth factor/vascular endothelial growth factor receptor system in gastrointestinal malignancies[82,83]. It is also possible that reactive oxygen-dependent DNA damage further enhances the effect of Helicobacter pylori on epithelial cell proliferation[84]. A meta-analysis of large prospective cohort studies has shown a moderate increase of non-Hodgkin's lymphoma in diabetic patients, whereas stratified analysis by gender shows no significance based on the studies with reported cancer incidence by gender[85]. The immune dysfunction related to impaired neutrophil activity and abnormalities in cellular and humoral immunity in diabetes may contribute to cancer development[86].

Mortality

A meta-analysis suggests that preexisting diabetes is as-
sociated with a higher risk of all-cause long term cancer mortality compared with non-diabetic individuals HR = 1.41 (1.28-1.55)[67]. Mortality among diabetes was significantly increased for liver, breast, and bladder cancers, with pooled RRs of 1.56 (1.30-1.87)[66], 1.38 (1.20-1.58)[66], and 1.33 (1.14-1.55)[5], respectively. Similar but mild results are also seen in gastric cancer[66] and colorectal cancer[5], with 29% and 20% increased all-cause mortalities, respectively (Table 2). Non-significance is found for the cancers of the pancreas[66], prostate[66], kidney[5], endometrium[67], and non-Hodgkin’s lymphoma[66] (Table 2).

Several possible explanations might elucidate the increased risk of cancer death in DM. Impaired immune function and pro-inflammatory condition in diabetes may make the cancer more aggressive, favor cancer growth by making host organism less resistant to cancer progression, and strengthen the metastatic potential of cancer. Hyperglycemia may be an important risk factor. There is evidence that poor glycemic controls can lead to poorer outcomes. Survival rates in cancer are decreasing linearly with declining glycemic controls[90]. Diabetic patients may have a worse response to chemotherapy with a higher occurrence of adverse effects compared with non-diabetic individuals.

Diabetes patients are more often poor candidates for surgery. Preexisting diabetes was associated with increased odds of postoperative mortality across all cancer types [OR = 1.51 (1.13-2.02)]91.

**IMPLICATIONS FOR MEDICAL PRACTICE**

**Cancer screening is required for patients with preexisting diabetes**

As shown by the above studies, patients with DM have a higher risk of developing certain types of cancer. A healthy diet, physical activity, and weight management could decrease the risk and improve outcomes of DM and some types of cancer. This was supported by a consensus report of the American Diabetes Association and the American Cancer Society[91]. In order to improve the prognosis, early screening of DM-related cancers is important for T2DM patients. Cancer screening tests of proven benefit for malignancies (breast, colon, endometrial cancer, etc.) in at-risk individuals/populations should begin relatively earlier than the general population. Future cancer screenings should be based on current existing recommendations. However, specific DM-related cancer screening recommendations remain to be made.

**The impact of anti-diabetic treatments on cancer risk**

The major classes of DM drugs function to replace circulating insulin and reduce hyperglycemia by different mechanisms or to reduce the associated obesity[89]. Insulin sensitizers, including metformin and TZDs, are oral anti-diabetic drugs that decrease insulin resistance by altering signaling through the AKT/mTOR pathway[97,98]. Metformin has been used with confidence in the treatment of T2DM[99]. Emerging evidence from research on humans and from the preclinical setting suggests that metformin has an anti-cancer effect. A meta-analysis of 17 randomized controlled trials showed a clinically significant 39% decreased risk of cancer with metformin use in patients with or at risk for diabetes, compared to no use of metformin[90]. Metformin can decrease cell proliferation and induce apoptosis in certain cancer cell lines[97,99]. In a recent retrospective cohort study, metformin use is not associated with improved survival in subjects with advanced pancreatic cancer[97]. Whereas metformin use was also reported to be associated with a lower risk of colon, liver, pancreas, or breast cancers, it was not associated with the risk of prostate cancer[100,101]. Metformin therapy decreases and insulin and insulin secretagogues slightly increase the risk of certain cancers in T2DM. Nonetheless, it is premature to prescribe metformin and TZDs solely for those as yet unproven indications for cancers.

**Managing diabetic patients with cancer**

Managing diabetes can be a daunting task for patients with cancer. Diabetes may negatively impact both cancer risk and outcomes of cancer treatment. It is clear that comorbidities may play a role in clinical outcomes in patients with cancer. Clinicians who treat cancer patients with T2DM should pay more attention to comorbidities...
ties. Thus, rigorous and multifactorial approaches should be adopted to control diabetes for patients undergoing treatment for malignancies. Poor glycemic control increases morbidity and mortality in patients with cancer. Therefore, hyperglycemia management in patients with cancer is important. Monitoring symptoms of both hyperglycemia and hypoglycemia is necessary. DM patients with cancer and their family members should monitor these symptoms and render suitable medical treatment once these symptoms occur. For hospitalized patients with acute concurrent complications, aggressive glycemic management should be taken to improve the prognosis.

CONCLUSION

Previous evidence provides strong support for an increase of both cancer risk and mortality in diabetic patients and more evidence for certain site-specific cancers. The molecular mechanisms for the association between diabetes and cancer development are still uncovered. As underlined in this review, mechanisms on hormonal (insulin and IGF-1), inflammatory and metabolic (hyperglycemia) characteristics have been proposed to elucidate this association. Guidelines specific for diabetic patients should include both treatment in medical practices and mass screening for specific cancers according to the risk factor profile of each patient.

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