

Diabetes and cancer: Epidemiological and biological links

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Abstract

The incidence of diabetes and cancer has increased significantly in recent years. Furthermore, there are many common risk factors for both diabetes and cancer, such as obesity, sedentary lifestyle, smoking, and ageing. A large body of epidemiological evidence has indicated that diabetes is considered as an independent risk factor for increased rates of heterogeneous types of cancer occurrence and death. The incidence and mortality of various types of cancer, such as pancreas, liver, colorectal, breast, endometrial, and bladder cancers, have a modest growth in diabetics. However, diabetes may work as a protective factor for prostate cancer. Although the underlying biological mechanisms have not been totally understood, studies have validated that insulin/insulin-like growth factor (IGF) axis (including insulin resistance, hyperinsulinemia, and IGF), hyperglycemia, inflammatory cytokines, and sex hormones provide good circumstances for cancer cell proliferation and metastasis. Insulin/IGF axis activates several metabolic and mitogenic signaling pathways; hyperglycemia provides energy for cancer cell growth; inflammatory cytokines influence cancer cell apoptosis. Thus, these three factors affect all types of cancer, while sex hormones only play important roles in breast cancer, endometrial cancer, and prostate cancer. This minireview consolidates and discusses the epidemiological and biological links between diabetes and various types of cancer.

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Core tip: The incidence of diabetes and cancer has increased significantly in recent years. The incidence and mortality of various types of cancer, such as pancreas, liver, colorectal, breast, endometrial, and bladder cancers, have a modest growth in diabetics. However, diabetes may work as a protective factor for prostate cancer. This minireview consolidates and discusses the epidemiological and biological links between diabetes and various types of cancer.

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INTRODUCTION

Both diabetes and cancer are serious and prevalent diseases which are increasing rapidly worldwide. Diabetes is a kind of metabolic disease whereby the patients have high levels of blood sugar. Worldwide, the number of people with diabetes was 422 million in 2014 and a new study has projected that the number of cases will increase to at least 592 million in 2035^[1]. Meanwhile, cancer has been considered as a metabolic disease by most medical researchers, and the World Health Organization estimated that the number of global cancer patients would increase from 14 million in 2012 to 22 million in 2032^[2].

The most common types of diabetes are type 1 and type 2. On the one hand, the autoimmune impairment of insulin-producing beta cells, causing absolute insulin deficiency, leads to type 1 diabetes mellitus (T1DM) and it accounts for about 5% to 10% of all diabetes cases. On the other hand, T2DM is associated with metabolic disorders, by which cells become insensitive to insulin and hence manifest relative insulin deficiency^[3,4]. Several studies have found that although T1DM and T2DM are associated with increased risks for cancer, T2DM has a stronger link with cancer both epidemiologically and biologically^[5]. The potential explanation is that cancer and T2DM share risk factors, such as obesity, smoking, and ageing. Therefore, diabetes (primarily type 2) has been closely linked to many forms of cancer, including cancers of the pancreas, liver, colorectal, breast, endometrium, bladder, and prostate^[6]. The underlying mechanisms for the association of diabetes and the incidence of cancer are still unclear. However, several lines of evidence have indicated that insulin/insulin-like growth factor (IGF) axis, hyperglycemia, inflammatory cytokines, and sex hormones could be the possible reasons^[7,8]. Therefore, this minireview aims to illustrate the correlations between diabetes and cancer and the underlying mechanisms.

ASSOCIATION BETWEEN DIABETES AND PANCREATIC CANCER

Pancreatic cancer (PC) is one of the deadliest malignant diseases, with a 5-year survival rate less than 10%. Currently, PC is the tenth most common cancer and the fourth lethal cause in the United States^[9]. The positive relationship of diabetes with PC has been noted for nearly 200 years^[10], and recently, there are two hypotheses about the correlation of these two diseases. On the one hand, epidemiological studies have demonstrated that the incidence of PC in diabetics is significantly higher than that in non-diabetics, thus, diabetes is a risk factor for PC. On the other hand, many studies have also proved that new-onset diabetes is a sign of PC, which is caused by PC^[10-13]. A prospective study was conducted in China to find out the association between diabetes and PC. The study recruited 512000 people aged 30-79 years from ten different regions of China between 2004 and 2008. After an 8-year follow-up, 595 cases of PC were recorded. It has been shown that diabetes was associated with a 1.87-fold

increase in the risk of PC [adjusted hazard ratio (HR) = 1.87, 95% confidence interval (CI): 1.48-2.37], proving that diabetes is a risk factor for PC^[14]. A multiethnic cohort study was carried out in African Americans and Latinos to reveal the correlation between new-onset diabetes and PC. It is illustrated that new-onset diabetes was associated with a 2.3-fold higher increase in the risk of PC than long-term diabetes, supporting that new-onset diabetes is a sign of PC^[15]. More studies have indicated that the association between diabetes and PC is bidirectional, and there is an inverse duration-dependent risk of diabetes and PC. In the first 2 years after diagnosis of diabetes, there is a remarkable rate of PC occurrence, and the rate will have a modest decrease as time goes by. For those who suffer diabetes for more than 5 years, the risk of PC decreases significantly^[16,17]. Therefore, we can conclude that, long-term diabetes is a risk factor for PC, and new-onset diabetes is a sign of PC.

ASSOCIATION BETWEEN DIABETES AND LIVER CANCER

Primary liver cancer, also known as hepatocellular carcinoma (HCC), has emerged globally as the fifth most common malignancy in men as well as the seventh one in women, and its incidence is especially high in oriental Asia and Africa^[18]. This neoplasm is also regarded as a highly fatal disease. Recent studies have suggested that diabetes is strongly associated with HCC, pointing out an independent risk factor for HCC. Before elucidating the relationship between diabetes and HCC, we need to take note that persistent infections by hepatitis B virus and hepatitis C virus (HCV), aflatoxin exposure, and non-alcoholic fatty liver disease (NAFLD) are three important risk factors for the development of HCC. Hence, diabetes and HCC are closely linked because of their correlation with hepatitis viruses and NAFLD^[18,19]. A perspective cohort study investigated the association of diabetes and HCC in Taiwan with a high prevalence of hepatitis virus infections. Fifty-four thousand nine hundred seventy-nine subjects were screened, and 5732 subjects were diabetics who were followed until they were diagnosed with HCC. That study found that the effect of diabetes in increasing the risk of HCC is more significant in patients who were HCV negative than in those who were HCV positive^[20]. NAFLD includes various progressive hepatic diseases, ranging from pure steatosis to steatohepatitis. Furthermore, more than 70% of diabetics have NAFLD due to insulin resistance^[20,21], which means that people with diabetes are more susceptible to severe hepatic diseases, such as HCC. Several systematic reviews and meta-analyses also have indicated that NAFLD is a spotlight of the correlation of diabetes and HCC^[22,23]. As a result, diabetes is a modifiable risk factor and its association with an increased rate of HCC cannot be ignored.

ASSOCIATION BETWEEN DIABETES AND COLORECTAL CANCER

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of death in the United States. Moreover, CRC-specific mortality rate is about 33% in the developed countries^[24]. The correlation of diabetes and an elevated risk of CRC has been verified in many studies that have displayed that there are many common risk factors between diabetes and CRC, such as age, obesity, sedentary lifestyle, and smoking. Meanwhile, diabetes serves as an independent risk factor for CRC. Furthermore, a higher mortality has been found in CRC patients with diabetes^[25]. Interestingly, sex differences have been strongly reported in many studies, which have demonstrated only a small increased risk in women with diabetes, while a significantly growing risk of diabetics among men^[26]. In a cohort study, 73312 men and 81663 women were successfully followed, and 1567 men (227 with diabetes) and 1242 women (108 with diabetes) were diagnosed with CRC. There was a 1.24-fold increased risk of incident CRC in men with diabetes [RR (relative risk) = 1.24; 95% CI: 1.08-1.44]. However, among women, there was no association with the risk of incident CRC (RR = 1.22, 95% CI: 1.04-1.45)^[27]. And in another Swedish study, the authors showed that men with diabetes had a 49% increased risk of CRC with all subsites in the colorectum^[28]. Last but not least, diet is also an important factor in the incidence of diabetes and CRC, but research has revealed that only women but not men have the ability to lower the risk of CRC, even if both woman and men have a similarly healthy diet^[29].

ASSOCIATION BETWEEN DIABETES AND BREAST CANCER

Breast cancer is the foremost carcinoma in women in developed countries and with the popularity of Western lifestyle, its incidence is rapidly growing in developing countries as well. Diabetes, as a metabolic disorder, is robustly associated with an increased risk of breast cancer^[30]. Large amounts of epidemiological evidence have indicated that diabetes contributes to higher incidence and mortality rates of breast cancer. Additionally, a meta-analysis has suggested that the correlation between diabetes and breast cancer seems to be confined to post-menopausal women^[31]. However, this result is inconsistent with another study showing that the increased risk of breast cancer in pre-menopausal women is attributed to diabetes^[32]. Moreover, in a study investigating the relation of diabetes and breast cancer among Asian-American women, the authors found that after adjusting body mass index and waist to hip ratio, the incidence of breast cancer still increased. This indicated that the history of diabetes has an intense relation with breast cancer^[33]. Besides, there are two studies that had similar conclusions, introducing that diabetes may interfere with focus to other health problems and cause a low rate of diagnosis of breast cancer. Moreover, diabetes may promote the growth of tumors. A retrospective cohort study assessed the impact of diabetes on stages of breast cancer, and among 38407 women with breast cancer, 6115 (15.9%) were diabetics, who had more advanced breast cancer stages than their nondiabetics counterparts - Stage II [adjusted odds ratio (aOR) = 1.14, 95%CI: 1.07-1.22], Stage III (aOR = 1.21, 95%CI: 1.11-1.33), and Stage IV (aOR = 1.16, 95% CI: 1.01-1.33) *vs* Stage I breast cancer^[34]. In another study, the impact of pre-existing diabetes on breast cancer prognosis was examined. Compared to nondiabetic women, the overall mortality had a remarkable increase among women who suffered diabetes (HR = 1.57, 95%CI: 1.23-2.01). Radiation therapy was difficult to carry out on diabetic women^[35]. Therefore, diabetes accounts for a delayed diagnosis and limited treatment choices, thus leading to a more aggressive breast cancer and a higher mortality.

ASSOCIATION BETWEEN DIABETES AND ENDOMETRIAL CANCER

Endometrial cancer (EC) is the fourth most common cancer in women in the United States and the most common type of gynecological cancer. Compared to other types of cancer, EC often has an earlier diagnosis and a better prognosis. However, the death rate of EC rose significantly during the past 20 years. This phenomenon could be explained by longer life expectancy and lifestyle changes as ageing and physical activities are linked to diabetes^[36,37]. Therefore, diabetes is associated with EC, which has been consistently supported by cohort study, case-control study, and meta-analysis. These studies have demonstrated that diabetes leads to a higher mortality of EC as an independent risk factor. A cohort study, conducted in Sweden, assessed the incidence of EC among 80005 women with diabetes, with the standardized incidence ratios as 1.8 and CI as 1.6-2.0, and the results indicated that diabetes elevates the incidence of EC^[38]. Besides, a case-control study in Washington illustrated that irrespective of other present risk factors, diabetes is strongly related to EC (OR = 1.7, 95%CI: 1.2-2.3), and new-onset diabetics (< 5 years) have a 2-fold increased odds of EC compared with those with a more distant diagnosis (≥ 5 years)^[39]. Furthermore, a systematic review and meta-analysis of cohort studies summarized 29 cohort studies and revealed the morbidity of EC in women with *vs* without diabetes. The summary RR was 1.89 (95%CI: 1.46-2.45; $P < 0.001$) and the summary incidence rate was 1.61 (95%CI: 1.51-1.71; $P < 0.001$), once again confirming that diabetes is an independent risk factor for the increased EC incidence. However, the correlation of diabetes and EC-specific mortality remains to be validated by more studies^[40].

ASSOCIATION BETWEEN DIABETES AND BLADDER CANCER

Bladder cancer (BC) is one of the most prevalent malignancies in the world, and its morbidity and mortality are expected to be associated with age, smoking, and occupational exposure^[41]. Recently, researchers have paid attention to deducing the effect of diabetes on BC. A meta-analysis of 36 observational studies has demonstrated that most studies were carried out in Western countries, and only one study was performed in Korea^[42]. Therefore, the current results cannot fully represent

global correlation of diabetes and BC. Moreover, this meta-analysis also pointed out that there is a negative relation of BC and diabetic duration, and people with diabetes less than 5 years have a higher risk of BC^[42]. But a case-control study has a totally different result, which has suggested that the risk of BC increases with diabetic duration (OR = 1.92 for 1-5 years, 1.63 for 5-10 years, 2.39 for 10-15 years, and 2.58 for ≥ 15 years)^[43]. Furthermore, a cohort study has confirmed a positive association between diabetes and BC in women^[44]. However, a meta-analysis indicated that the relation of diabetes and increased risk of BC or cancer mortality in women requires further explorations^[45]. Findings from epidemiological studies are controversial, nevertheless, most meta-analyses support that diabetes is a risk factor for BC, and both incidence and death rates of BC increase in diabetics^[41,46-48].

ASSOCIATION BETWEEN DIABETES AND PROSTATE CANCER

The latest study performed by the American Cancer Society has reported that the number of new prostate cancer cases is the highest in the United States, and prostate cancer is also the second leading cause of cancer death in American males^[49]. Although diabetes appears to be a risk factor for many types of cancer, studies have, however, elucidated an inverse association between diabetes and prostate cancer^[50]. A meta-analysis, including 45 studies (29 cohort and 16 case-control studies) with 8.1 million participants and 132331 prostate cancer cases, has provided strong evidence to verify the association of diabetes with a reduced risk of prostate cancer^[51]. Besides, two cohort studies have expressed the underlying reason for the inverse relationship: The likelihood of receiving a prostate screening test increases with diabetes comorbidity, thus, the incidence of early stage prostate cancer is reduced^[52,53]. However, the incidence of advanced stage is irrelevant with diagnosis of diabetes, which has been mentioned in several studies^[52]. Furthermore, a meta-analysis has illustrated that the inverse association between diabetes and prostate cancer is limited to incidence but not mortality, and prostate cancer patients with diabetes have a worse prognosis^[54]. In spite of the negative consequences reported in many studies, a different conclusion has been declared in a Swedish cohort study showing that after eliminating the confused risk factors, there is no association between diabetes and prostate cancer^[55]. Therefore, further investigations need to be carried out to draw a consistent conclusion.

In short, the links between diabetes and various types of cancers are apparent. **Table 1** provides a non-exhaustive list of association studies between diabetes and cancers in the past 5 years.

BIOLOGICAL LINKS BETWEEN DIABETES AND CANCER

Insulin/IGF axis

Insulin is a peptide hormone which can regulate carbohydrate and fat metabolism by improving glucose absorption. However, insulin loses the function to enhance cellular glucose uptake and utilization in diabetics, which is defined clinically as insulin resistance. Therefore, beta cells secrete more insulin to compensate, resulting in hyperinsulinemia^[56]. Also, the high level of insulin is a hallmark of hyperinsulinemia, which stimulates the liver cells to produce IGF-1 when insulin binds to the insulin receptor on the surface of target cells. IGF-1 binds to IGF 1 receptor (IGF-1R), a receptor tyrosine kinase, to activate several metabolic and mitogenic signaling pathways to regulate cancer cell proliferation, differentiation, and apoptosis^[6,57]. After numerous downstream targets, phosphoinositide-3-kinase-protein kinase B and rat sarcoma-mitogen-activated protein kinase/extracellular signal regulated kinase signaling pathways are activated^[58,59]. Phosphoinositide-3-kinase-protein kinase B signaling pathway leads to cancer cell survival and migration, whereas rat sarcoma-mitogen-activated protein kinase/extracellular signal regulated kinase signaling pathway governs cancer cell metabolism and proliferation^[60]. Therefore, patients with diabetes are associated with higher levels of IGF-1, which makes it more susceptible to an increased risk of developing many types of cancer such as colorectal, breast, and prostate cancers. Besides, many studies have revealed that IGF-1 is more frequently expressed in breast cancer cells than other cancer types^[61,62], and the reason is related to the location where IGF-1 is expressed: The stromal cells beside normal epithelial cells of the breast. An experiment used a mouse model of HER2-mediated breast cancer in a condition of hyperinsulinemia to investigate the effect of increased levels of insulin on HER2 mediated primary tumor growth and lung metastasis. It has

Table 1 Non-exhaustive summary of representative association studies between diabetes and various types of cancers in the past 5 years (2015-2019)

Cancer	Ref.	Design	Findings	
Pancreatic Cancer	Setiawan <i>et al</i> ^[15] , 2019	Cohort study	Positive association between diabetes and pancreatic cancer	
	Chen <i>et al</i> ^[89] , 2017	Cohort study		
	Pang <i>et al</i> ^[14] , 2017	Meta-analysis of 22 cohort studies		
	Tan <i>et al</i> ^[90] , 2017	Systematic review and meta-analysis		
	Dankner <i>et al</i> ^[91] , 2016	Cohort study		
	Song <i>et al</i> ^[92] , 2015	Meta-analysis		
	Ogunleye <i>et al</i> ^[93] , 2009	Cohort study		
	Gupta <i>et al</i> ^[16] , 2006	Cohort study		
Liver cancer	Li <i>et al</i> ^[94] , 2017	Case-control study	Increased risk of liver cancer in diabetes	
	Wang <i>et al</i> ^[95] , 2017	Metaanalysis		
	Chen <i>et al</i> ^[96] , 2015	Meta-analysis of 21 cohort studies	Diabetes is independently associated with a poorer survival in HCC patients	
	El-Serag <i>et al</i> ^[23] , 2006	Systematic review		
	Wang <i>et al</i> ^[22] , 2014	Systematic review and meta-analysis		
	Lai <i>et al</i> ^[20] , 2006	Cohort study		Diabetes increases risk of HCC in HCV negative individuals
Colorectal cancer	Zhu <i>et al</i> ^[97] , 2017	Meta-analysis	Positive correlation of diabetes with colorectal cancer	
	Guraya <i>et al</i> ^[98] , 2015	Meta-analysis of 8 cohort studies		
	Larsson <i>et al</i> ^[28] , 2005	Cohort study	Pre-existing T2DM has no influence on disease-specific and all-cause survival among CRC patients	
	Amshoff <i>et al</i> ^[25] , 2018	Cohort study		
	Jacobs <i>et al</i> ^[29] , 2016	Cohort study		The aMED score is related to lower mortality only in African-American women
	Campbell <i>et al</i> ^[27] , 2010	Cohort study		Modest association between T2DM and CRC among men, but not among women
Breast cancer	Luo <i>et al</i> ^[35] , 2015	Cohort study	Pre-existing diabetes increases the risk of total mortality among women with breast cancer	
	Lipscombe <i>et al</i> ^[34] , 2015	Cross-sectional study		
	Alokail <i>et al</i> ^[32] , 2009	Cohort study	Diabetes may predispose to more aggressive breast cancer	
	Boyle <i>et al</i> ^[31] , 2012	Meta-analysis		Risk of breast cancer is increased by 27% in diabetic women
Endometrial cancer	Saed <i>et al</i> ^[99] , 2019	Systematic review and meta-analysis	Diabetes increases the risk of endometrial cancer in women	
	Saltzman <i>et al</i> ^[39] , 2008	Systematic review of case-control study		
	Lindemann <i>et al</i> ^[37] , 2015	Cohort study	Diabetes, but not BMI, is associated with an increased risk of all-cause death and death from EC	
Bladder cancer	Xu <i>et al</i> ^[45] , 2017	Meta-analysis of 21 cohort studies and case-control studies	Diabetes increases the risk of bladder cancer	
	Turati <i>et al</i> ^[43] , 2015	Case-control study		
	Zhu <i>et al</i> ^[42] , 2013	Meta-analysis of 36 observational studies	Positive association between diabetes and bladder cancer risk among White post-menopausal women	
	Prizment <i>et al</i> ^[44] , 2013	Cohort study		
Prostate cancer	Häggström <i>et al</i> ^[55] , 2018	Cohort study	An inverse association between diabetes and prostate cancer	
	Lee <i>et al</i> ^[54] , 2016	Metaanalysis		
	Dankner <i>et al</i> ^[52] , 2016	Cohort study		
	Khan <i>et al</i> ^[100] , 2016	Cross-sectional, case-only study		
	Fall <i>et al</i> ^[101] , 2013	Case-control study		

BMI: Body mass index; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; T2DM: Type 2 diabetes mellitus; CRC: Colorectal cancer; EC: Endometrial cancer.

revealed that tumor mass grew and IR and IGF-1R had higher phosphorylation levels, demonstrating that hyperinsulinemia contributes to the elevated growth of mammary tumors through the insulin/IGF axis^[63]. Another epidemiological study assessed the correlation between hyperinsulinemia and increased cancer mortality in both obese and non-obese people. The study successfully followed 3060 obese participants (2303 with hyperinsulinemia) and 6718 non-obese participants (2057 with hyperinsulinemia). The overall cancer mortality was remarkably higher in those with hyperinsulinemia than in their counterparts (adjusted HR = 2.04, 95%CI: 1.24-3.34, $P = 0.005$)^[64]. Therefore, the insulin/IGF-1 axis (hyperinsulinemia, IR, and IR signaling pathway) promotes cancer cell growth and metastasis.

Hyperglycemia

It is necessary to provide energy for cell growth and proliferation. Generally, cells obtain energy through tricarboxylic acid cycle, whereas cancer cells shift to glycolysis, leading to an easier glucose uptake which is known as the Warburg Effect^[65]. Thus, hyperglycemia of diabetics provides cancer cells great condition to survive and proliferate. Meanwhile, the synthesis of tumor protein and DNA is associated with glucose metabolism. Therefore, a high level of blood glucose affects tumor growth and metastasis^[66]. Studies have also indicated that hyperglycemia accelerates mitochondrial dysfunction and the generation of free radicals and other reactive molecules, such as reactive oxygen species (ROS), triggering the formation of advanced glycation end products (AGEs) and activating protein kinase C isomers^[67]. ROS can not only directly damage DNA, inducing genetic mutation, but regulate mitogen activated protein kinases and p21 activated kinase, promoting tumor metastasis. Moreover, ROS are able to oxygenate protein kinase C and protein tyrosine phosphatase, which are the key molecules that are involved in the invasion of cancer cells and help cancer cells to adapt the adverse environment^[68]. AGEs receptor exists in many types of cancer cells, such as immune cells, neurons, osteoblasts, activated endothelial cells, and vascular smooth muscle cells. Furthermore, it can be triggered by AGEs, leading to chronic inflammation which links to many cancer-related signaling pathways^[69], eventually increasing cell genetic mutation and evolution and resulting in advanced stages of cancer^[5,58,70]. However, since hyperglycemia and hyperinsulinemia simultaneously exist in most diabetic patients and it is difficult to distinguish the independent role of each abnormality, there is no congruent opinion on whether hyperglycemia is an independent factor to promote tumor growth and metastasis.

Inflammatory cytokines

Diabetes has a strong connection with obesity and both hyperinsulinemia and visceral adiposity can augment the production of inflammatory cytokines. With the increase in the production of inflammatory cytokines, chemicals of acute phase such as C-reactive protein and plasminogen activator inhibitor-1 increase as well, promoting the formation of inflammatory network at the early stage of diabetes. With the development of diabetes, inflammatory network spreads^[71]. Although a plenty of inflammatory cytokines are associated with the development of cancer, interleukin-6 (IL-6) and tumor necrosis factor α (TNF α) secreted by adipose tissue have been verified as the major inflammatory cytokines related to diabetes and cancer at the same time^[70]. In breast cancer, IL-6 can activate nuclear factor- κ B and increase cyclin D1, and therefore, neoplastic transformation develops. Besides, IL-6 can cause cells to isolate from each other but remain alive by activating the process of epithelial-to-mesenchymal transition, which leads to cancer metastasis^[72]. Normally, TNF- α is an important mediator of anti-tumor immune responses, but chronic exposure to TNF- α can activate a series of signaling pathways, such as nuclear factor- κ B, mitogen activated protein kinase, and Jun kinase, thus preventing cancer cell apoptosis and accelerating cancer cell growth and metastasis^[73]. An animal experiment has demonstrated that the blockade of TNF- α prevents the expression of programmed cell death ligand 1 in cancer cells, thereby preventing tumor proliferation^[74]. Moreover, researchers have found that despite higher basic levels of inflammatory cytokines in diabetics, the production of cytokines is impaired during immune defense. Also, complement dependent phagocytic activities and chemotactic phagocytosis of macrophages are inhibited, resulting in immune dysfunction, which causes easier infection and provide tumor a better place to survive^[75,76]. **Table 2** summarizes the three main biological links between diabetes and cancer as mentioned above.

Sex hormones

Basically, sex hormone binding globulin (SHBG) and albumin are capable of binding to circulating sex hormones such as androgens and estrogens to regulate the levels of free sex hormones and their bioavailability. However, SHBG has a higher affinity to

Table 2 Biological links between diabetes and cancer

Characteristic of diabetes	Consequences which promote cancer
High blood sugar level	DNA damage ROS production Chronic inflammation Promote cancer cell proliferation Promote cancer cell growth Promote cancer cell metastasis Provide alternative energy source for cancer cell survival
High blood insulin level (as in T2DM)	Increase level of IGF-1 Promote cancer cell proliferation Promote cancer cell differentiation Promote cancer cell survival Promote cancer cell migration Promote cancer cell growth Promote cancer cell metastasis
Inflammation	Promote cancer cell proliferation Accelerate cancer cell growth Accelerate cancer cell metastasis Promote EMT Promote cancer cell survival Inhibit certain immune responses

ROS: Reactive oxygen species; T2DM: Type 2 diabetes mellitus; IGF-1: Insulin-like growth factor-1; EMT: Epithelial-to-mesenchymal transition.

sex hormones than albumin, and the affinity to testosterone is twice that of estradiol and distinct between gender^[77]. Recently, more and more studies have indicated that high blood glucose and insulin are associated with low levels of circulating SHBG, which affects the maintenance of glucose homeostasis^[78,79]. A nested case-control study investigated the correlation between SHBG and the risk of diabetes on 718 postmenopausal women (359 with newly diagnosed type 2 diabetes and 359 controls) and suggested that low circulating levels of SHBG are strongly associated with the risk of diabetes. Moreover, the same result was found in an independent cohort study of 340 men (170 with newly diagnosed type 2 diabetes and 170 controls)^[79]. Therefore, the synthesis of SHBG decreases indirectly with increased levels of blood glucose and serum insulin, which promotes free estrogen and testosterone synthesis. High levels of free estrogen and testosterone are associated with higher risks of many types of cancer, such as breast, endometrial, and prostate cancers^[6,80]. Studies have found that both biologically available estrogen and testosterone are elevated in diabetic women^[81], while total testosterone concentrations are lower in diabetic men than in nondiabetic men^[82,83]. Although the mechanism remains unclear, it is probably attributed to the different affinities to SHBG^[77,84]. This is the main reason why diabetes may play an important role in protecting patients from prostate cancer.

BIOMARKERS

There are many diabetes-related biomarkers, such as fasting glucose, glycated hemoglobin, glycated albumin, adiponectin, serum insulin, and C-peptide, among which the increased levels of serum insulin and C-peptide are regarded as associated biomarkers of several types of cancer. However, further studies are still needed to figure out the mutual biomarkers of diabetes and cancer^[62,85].

CONCLUSION

Cancer can be a metabolic disease resulting from both internal factors and external factors^[86-88]. The association between diabetes and increased cancer incidence and

mortality has been well demonstrated in many studies. Also, the incidence of both diabetes and cancer has a rapid growth worldwide because of lifestyle changes and longer life expectancy. Therefore, precautionary measures such as physical exercise and regular cancer screening are necessary to improve both diabetes and cancer outcomes. Moreover, diabetes and cancer are global problems, and international health experts or organizations should develop guidelines on the prevention, diagnosis, and treatment of diabetes and cancer to reduce the social burden. As the intrinsic heterogeneity of both diabetes and cancer makes studies difficult to conduct, there are still many unanswered questions: Do T1DM and T2DM affect cancer in a same way? How should we define the general and specific cancer risks in each individual? Also, how can we fully understand the underlying biological mechanisms? More studies should be carried out to answer these questions in order to provide more preventive and therapeutic choices for diabetes and cancer patients.

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