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ABOUT COVER

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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.

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.

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

REFERENCES

1   **Khan RMM**, Chua ZJY, Tan JC, Yang Y, Liao Z, Zhao Y. From Pre-Diabetes to Diabetes: Diagnosis, Treatments and Translational Research. *Medicina (Kaunas)* 2019; 55 [PMID: 31470636 DOI: 10.3390/medicina55090546]

2   **Shi Y**, Hu FB. The global implications of diabetes and cancer. *Lancet* 2014; 383: 1947-1948 [PMID: 24910221 DOI: 10.1016/S0140-6736(14)60886-2]

3   **Arneth B**, Arneth R, Shams M. Metabolomics of Type 1 and Type 2 Diabetes. *Int J Mol Sci* 2019; 20 [PMID: 31109071 DOI: 10.3390/ijms20102467]

4   **Yaribeygi H**, Bo S, Ruscica M, Sahebkar A. Ceramides and diabetes mellitus: an update on the potential molecular relationships. *Diabet Med* 2020; 37: 11-19 [PMID: 30803019 DOI: 10.1111/dme.13943]

5   **Vigneri P**, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. *Endocr Relat Cancer* 2009; 16: 1103-1123 [PMID: 19620249 DOI: 10.1677/ERC-09-0087]

6   **Giovannucci E**, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. *Diabetes Care* 2010; 33: 1674-1685 [PMID: 20587728 DOI: 10.2337/dc10-0666]

7   **Buysschaert M**, Sadikot S. Diabetes and cancer: a 2013 synopsis. *Diabetes Metab Syndr* 2013; 7: 247-250 [PMID: 24290094 DOI: 10.1016/j.dsx.2013.08.001]

8   **Phua WWT**, Wong MXY, Liao Z, Tan NS. An aPPARent Functional Consequence in Skeletal Muscle Physiology via Peroxisome Proliferator-Activated Receptors. *Int J Mol Sci* 2018; 19 [PMID: 29747466 DOI: 10.3390/ijms19051425]

9   **Chaudhry ZW**, Hall E, Kalyani RR, Cosgrove DP, Yeh HC. Diabetes and pancreatic cancer. *Curr Probl Cancer* 2013; 37: 287-292 [PMID: 24331184 DOI: 10.1016/j.currproblcancer.2013.10.006]

10   **Magruder JT**, Elahi D, Andersen DK. Diabetes and pancreatic cancer: chicken or egg? *Pancreas* 2011; 40: 339-351 [PMID: 21412116 DOI: 10.1097/MPA.0b013e318209e05d]

11   **Li Y**, Bian X, Wei S, He M, Yang Y. The relationship between pancreatic cancer and type 2 diabetes: cause and consequence. *Cancer Manag Res* 2019; 11: 8257-8268 [PMID: 31571983 DOI: 10.2147/CMAR.S211972]

12   **Antwi SO**, Oberg AL, Shivappa N, Bamlet WR, Chaffee KG, Steck SE, Hébert JR, Petersen GM. Pancreatic cancer: associations of inflammatory potential of diet, cigarette smoking and long-standing diabetes. *Carcinogenesis* 2016; 37: 481-490 [PMID: 26905587 DOI: 10.1093/carcin/bgw022]

13   **Munigala S**, Singh A, Gelrud A, Agarwal B. Predictors for Pancreatic Cancer Diagnosis Following New-Onset Diabetes Mellitus. *Clin Transl Gastroenterol* 2015; 6: e118 [PMID: 26492440 DOI: 10.1038/ctg.2015.44]

14   **Pang Y**, Kartsonaki C, Guo Y, Bragg F, Yang L, Bian Z, Chen Y, Iona A, Millwood IY, Lv J, Yu C, Chen J, Li L, Holmes MV, Chen Z. Diabetes, plasma glucose and incidence of pancreatic cancer: A prospective study of 0.5 million Chinese adults and a meta-analysis of 22 cohort studies. *Int J Cancer* 2017; 140: 1781-1788 [PMID: 28063165 DOI: 10.1002/ijc.30599]

15   **Setiawan VW**, Stram DO, Porcel J, Chari ST, Maskarinec G, Le Marchand L, Wilkens LR, Haiman CA, Pandol SJ, Monroe KR. Pancreatic Cancer Following Incident Diabetes in African Americans and Latinos: The Multiethnic Cohort. *J Natl Cancer Inst* 2019; 111: 27-33 [PMID: 29917105 DOI: 10.1093/jnci/djy090]

16   **Gupta S**, Vittinghoff E, Bertenthal D, Corley D, Shen H, Walter LC, McQuaid K. New-onset diabetes and pancreatic cancer. *Clin Gastroenterol Hepatol* 2006; 4: 1366-1372; quiz 1301 [PMID: 16945591 DOI: 10.1016/j.cgh.2006.06.024]

17   **Muniraj T**, Chari ST. Diabetes and pancreatic cancer. *Minerva Gastroenterol Dietol* 2012; 58: 331-345 [PMID: 23207610 DOI: 10.6092/1590-8577/2286]

18   **Bosetti C**, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. *Best Pract Res Clin Gastroenterol* 2014; 28: 753-770 [PMID: 25260306 DOI: 10.1016/j.bpg.2014.08.007]

19   **Wainwright P**, Scorletti E, Byrne CD. Type 2 Diabetes and Hepatocellular Carcinoma: Risk Factors and Pathogenesis. *Curr Diab Rep* 2017; 17: 20 [PMID: 28290049 DOI: 10.1007/s11892-017-0851-x]

20   **Lai MS**, Hsieh MS, Chiu YH, Chen TH. Type 2 diabetes and hepatocellular carcinoma: A cohort study in high prevalence area of hepatitis virus infection. *Hepatology* 2006; 43: 1295-1302 [PMID: 16729295 DOI: 10.1002/hep.21208]

21   **Mantovani A**, Targher G. Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease. *Ann Transl Med* 2017; 5: 270 [PMID: 28758096 DOI: 10.21037/atm.2017.04.41]

22   **Wang YG**, Wang P, Wang B, Fu ZJ, Zhao WJ, Yan SL. Diabetes mellitus and poorer prognosis in hepatocellular carcinoma: a systematic review and meta-analysis. *PLoS One* 2014; 9: e95485 [PMID: 24830459 DOI: 10.1371/journal.pone.0095485]

23   **El-Serag HB**, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; 4: 369-380 [PMID:

16527702 DOI: 10.1016/j.cgh.2005.12.007]

24   **Cunningham D**, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N. Colorectal cancer. *Lancet* 2010; **375**: 1030-1047 [PMID: 20304247 DOI: 10.1016/S0140-6736(10)60353-4]

25   **Amshoff Y**, Maskarinec G, Shvetsov YB, Raquinio PH, Grandinetti A, Setiawan VW, Haiman CA, Le Marchand L. Type 2 diabetes and colorectal cancer survival: The multiethnic cohort. *Int J Cancer* 2018; **143**: 263-268 [PMID: 29441528 DOI: 10.1002/ijc.31311]

26   **Erbach M**, Mehnert H, Schnell O. Diabetes and the risk for colorectal cancer. *J Diabetes Complications* 2012; **26**: 50-55 [PMID: 22321219 DOI: 10.1016/j.jdiacomp.2011.11.003]

27   **Campbell PT**, Deka A, Jacobs EJ, Newton CC, Hildebrand JS, McCullough ML, Limburg PJ, Gapstur SM. Prospective study reveals associations between colorectal cancer and type 2 diabetes mellitus or insulin use in men. *Gastroenterology* 2010; **139**: 1138-1146 [PMID: 20633560 DOI: 10.1053/j.gastro.2010.06.072]

28   **Larsson SC**, Giovannucci E, Wolk A. Diabetes and colorectal cancer incidence in the cohort of Swedish men. *Diabetes Care* 2005; **28**: 1805-1807 [PMID: 15983343 DOI: 10.2337/diacare.28.7.1805]

29   **Jacobs S**, Harmon BE, Ollberding NJ, Wilkens LR, Monroe KR, Kolonel LN, Le Marchand L, Boushey CJ, Maskarinec G. Among 4 Diet Quality Indexes, Only the Alternate Mediterranean Diet Score Is Associated with Better Colorectal Cancer Survival and Only in African American Women in the Multiethnic Cohort. *J Nutr* 2016; **146**: 1746-1755 [PMID: 27511927 DOI: 10.3945/jn.116.234237]

30   **Vona-Davis L**, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. *Obes Rev* 2007; **8**: 395-408 [PMID: 17716297 DOI: 10.1111/j.1467-789X.2007.00396.x]

31   **Boyle P**, Boniol M, Koechlin A, Robertson C, Valentini F, Coppens K, Fairley LL, Boniol M, Zheng T, Zhang Y, Pasterk M, Smans M, Curado MP, Mullie P, Gandini S, Bota M, Bolli GB, Rosenstock J, Autier P. Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer* 2012; **107**: 1608-1617 [PMID: 22996614 DOI: 10.1038/bjc.2012.414]

32   **Alokail MS**, Al-Daghri NM, Al-Attas OS, Hussain T. Combined effects of obesity and type 2 diabetes contribute to increased breast cancer risk in premenopausal women. *Cardiovasc Diabetol* 2009; **8**: 33 [PMID: 19545451 DOI: 10.1186/1475-2840-8-33]

33   **Wu AH**, Yu MC, Tseng CC, Stanczyk FZ, Pike MC. Diabetes and risk of breast cancer in Asian-American women. *Carcinogenesis* 2007; **28**: 1561-1566 [PMID: 17440036 DOI: 10.1093/carcin/bgm081]

34   **Lipscombe LL**, Fischer HD, Austin PC, Fu L, Jaakkimainen RL, Ginsburg O, Rochon PA, Narod S, Paszat L. The association between diabetes and breast cancer stage at diagnosis: a population-based study. *Breast Cancer Res Treat* 2015; **150**: 613-620 [PMID: 25779100 DOI: 10.1007/s10549-015-3323-5]

35   **Luo J**, Hendryx M, Virnig B, Wen S, Chlebowski R, Chen C, Rohan T, Tinker L, Wactawski-Wende J, Lessin L, Margolis KL. Pre-existing diabetes and breast cancer prognosis among elderly women. *Br J Cancer* 2015; **113**: 827-832 [PMID: 26158425 DOI: 10.1038/bjc.2015.249]

36   **Luo J**, Beresford S, Chen C, Chlebowski R, Garcia L, Kuller L, Regier M, Wactawski-Wende J, Margolis KL. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. *Br J Cancer* 2014; **111**: 1432-1439 [PMID: 25051408 DOI: 10.1038/bjc.2014.407]

37   **Lindemann K**, Cvancarova M, Eskild A. Body mass index, diabetes and survival after diagnosis of endometrial cancer: A report from the HUNT-Survey. *Gynecol Oncol* 2015; **139**: 476-480 [PMID: 26434365 DOI: 10.1016/j.ygyno.2015.09.088]

38   **Weiderpass E**, Gridley G, Persson I, Nyrén O, Ekbom A, Adami HO. Risk of endometrial and breast cancer in patients with diabetes mellitus. *Int J Cancer* 1997; **71**: 360-363 [PMID: 9139868 DOI: 10.1002/(sici)1097-0215(19970502)71:3<360::Aid-ijc9>3.0.Co;2-w]

39   **Saltzman BS**, Doherty JA, Hill DA, Beresford SA, Voigt LF, Chen C, Weiss NS. Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. *Am J Epidemiol* 2008; **167**: 607-614 [PMID: 18071194 DOI: 10.1093/aje/kwm333]

40   **Liao C**, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. *Gynecol Oncol* 2014; **135**: 163-171 [PMID: 25072931 DOI: 10.1016/j.ygyno.2014.07.095]

41   **Xu X**, Wu J, Mao Y, Zhu Y, Hu Z, Xu X, Lin Y, Chen H, Zheng X, Qin J, Xie L. Diabetes mellitus and risk of bladder cancer: a meta-analysis of cohort studies. *PLoS One* 2013; **8**: e58079 [PMID: 23472134 DOI: 10.1371/journal.pone.0058079]

42   **Zhu Z**, Wang X, Shen Z, Lu Y, Zhong S, Xu C. Risk of bladder cancer in patients with diabetes mellitus: an updated meta-analysis of 36 observational studies. *BMC Cancer* 2013; **13**: 310 [PMID: 23803148 DOI: 10.1186/1471-2407-13-310]

43   **Turati F**, Polesel J, Di Maso M, Montella M, Libra M, Grimaldi M, Tavani A, Serraino D, La Vecchia C, Bosetti C. Diabetes mellitus and the risk of bladder cancer: an Italian case–control study. *Br J Cancer* 2015; **113**: 127-130 [PMID: 25996204 DOI: 10.1038/bjc.2015.178]

44   **Prizment AE**, Anderson KE, Yuan JM, Folsom AR. Diabetes and risk of bladder cancer among postmenopausal women in the Iowa Women's Health Study. *Cancer Causes Control* 2013; **24**: 603-608 [PMID: 23296458 DOI: 10.1007/s10552-012-0143-3]

45   **Xu Y**, Huo R, Chen X, Yu X. Diabetes mellitus and the risk of bladder cancer: A PRISMA-compliant meta-analysis of cohort studies. *Medicine (Baltimore)* 2017; **96**: e8588 [PMID: 29145273 DOI: 10.1097/MD.0000000000008588]

46   **Goossens ME**, Zeegers MP, Bazelier MT, De Bruin ML, Buntinx F, de Vries F. Risk of bladder cancer in patients with diabetes: a retrospective cohort study. *BMJ Open* 2015; **5**: e007470 [PMID: 26033947 DOI: 10.1136/bmjopen-2014-007470]

47   **Fang H**, Yao B, Yan Y, Xu H, Liu Y, Tang H, Zhou J, Cao L, Wang W, Zhang J, Zhao L, Chen X, Zhang F, Zhao Y. Diabetes mellitus increases the risk of bladder cancer: an updated meta-analysis of observational studies. *Diabetes Technol Ther* 2013; **15**: 914-922 [PMID: 24180357 DOI: 10.1089/dia.2013.0131]

48   **Zhu Z**, Zhang X, Shen Z, Zhong S, Wang X, Lu Y, Xu C. Diabetes mellitus and risk of bladder cancer: a meta-analysis of cohort studies. *PLoS One* 2013; **8**: e56662 [PMID: 23437204 DOI: 10.1371/journal.pone.0056662]

49   **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]

50   **Onitilo AA**, Berg RL, Engel JM, Stankowski RV, Glurich I, Williams GM, Doi SA. Prostate cancer risk in pre-diabetic men: a matched cohort study. *Clin Med Res* 2013; **11**: 201-209 [PMID: 23656798 DOI: 10.3121/cmr.2013.1160]

51   **Bansal D**, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-

analysis of observational studies. *Prostate Cancer Prostatic Dis* 2013; **16**: 151-158, S1 [PMID: 23032360 DOI: 10.1038/pcan.2012.40]

52   **Dankner R**, Boffetta P, Keinan-Boker L, Balicer RD, Berlin A, Olmer L, Murad H, Silverman B, Hoshen M, Freedman LS. Diabetes, prostate cancer screening and risk of low- and high-grade prostate cancer: an 11 year historical population follow-up study of more than 1 million men. *Diabetologia* 2016; **59**: 1683-1691 [PMID: 27189066 DOI: 10.1007/s00125-016-3972-x]

53   **Sanderson M**, Fowke JH, Lipworth L, Han X, Ukoli F, Coker AL, Blot WJ, Hargreaves MK. Diabetes and prostate cancer screening in black and white men. *Cancer Causes Control* 2013; **24**: 1893-1899 [PMID: 23860952 DOI: 10.1007/s10552-013-0257-2]

54   **Lee J**, Giovannucci E, Jeon JY. Diabetes and mortality in patients with prostate cancer: a meta-analysis. *Springerplus* 2016; **5**: 1548 [PMID: 27652121 DOI: 10.1186/s40064-016-3233-y]

55   **Häggström C**, Van Hemelrijck M, Garmo H, Robinson D, Stattin P, Rowley M, Coolen ACC, Holmberg L. Heterogeneity in risk of prostate cancer: A Swedish population-based cohort study of competing risks and Type 2 diabetes mellitus. *Int J Cancer* 2018; **143**: 1868-1875 [PMID: 29744858 DOI: 10.1002/ijc.31587]

56   **Godsland IF**. Insulin resistance and hyperinsulinaemia in the development and progression of cancer. *Clin Sci (Lond)* 2009; **118**: 315-332 [PMID: 19922415 DOI: 10.1042/CS20090399]

57   **Liao Z**, Tan ZW, Zhu P, Tan NS. Cancer-associated fibroblasts in tumor microenvironment - Accomplices in tumor malignancy. *Cell Immunol* 2019; **343**: 103729 [PMID: 29397066 DOI: 10.1016/j.cellimm.2017.12.003]

58   **Liao Z**, Chua D, Tan NS. Reactive oxygen species: a volatile driver of field cancerization and metastasis. *Mol Cancer* 2019; **18**: 65 [PMID: 30927919 DOI: 10.1186/s12943-019-0961-y]

59   **Dong R**, Tan Y, Fan A, Liao Z, Liu H, Wei P. Molecular Dynamics of the Recruitment of Immunoreceptor Signaling Module DAP12 Homodimer to Lipid Raft Boundary Regulated by PIP2. *J Phys Chem B* 2020; **124**: 504-510 [PMID: 31888335 DOI: 10.1021/acs.jpcb.9b11095]

60   **Poloz Y**, Stambolic V. Obesity and cancer, a case for insulin signaling. *Cell Death Dis* 2015; **6**: e2037 [PMID: 26720346 DOI: 10.1038/cddis.2015.381]

61   **Price AJ**, Allen NE, Appleby PN, Crowe FL, Travis RC, Tipper SJ, Overvad K, Grønbæk H, Tjønneland A, Johnsen NF, Rinaldi S, Kaaks R, Lukanova A, Boeing H, Aleksandrova K, Trichopoulou A, Trichopoulos D, Andarakis G, Palli D, Krogh V, Tumino R, Sacerdote C, Bueno-de-Mesquita HB, Argüelles MV, Sánchez MJ, Chirlaque MD, Barricarte A, Larrañaga N, González CA, Stattin P, Johansson M, Khaw KT, Wareham N, Gunter M, Riboli E, Key T. Insulin-like growth factor-I concentration and risk of prostate cancer: results from the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* 2012; **21**: 1531-1541 [PMID: 22761305 DOI: 10.1158/1055-9965.EPI-12-0481-T]

62   **Collins KK**. The diabetes-cancer link. *Diabetes Spectr* 2014; **27**: 276-280 [PMID: 25647050 DOI: 10.2337/diaspect.27.4.276]

63   **Ferguson RD**, Gallagher EJ, Cohen D, Tobin-Hess A, Alikhani N, Novosyadlyy R, Haddad N, Yakar S, LeRoith D. Hyperinsulinemia promotes metastasis to the lung in a mouse model of Her2-mediated breast cancer. *Endocr Relat Cancer* 2013; **20**: 391-401 [PMID: 23572162 DOI: 10.1530/ERC-12-0333]

64   **Tsujimoto T**, Kajio H, Sugiyama T. Association between hyperinsulinemia and increased risk of cancer death in nonobese and obese people: A population-based observational study. *Int J Cancer* 2017; **141**: 102-111 [PMID: 28390156 DOI: 10.1002/ijc.30729]

65   **Vander Heiden MG**, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009; **324**: 1029-1033 [PMID: 19460998 DOI: 10.1126/science.1160809]

66   **Adekola K**, Rosen ST, Shanmugam M. Glucose transporters in cancer metabolism. *Curr Opin Oncol* 2012; **24**: 650-654 [PMID: 22913968 DOI: 10.1097/CCO.0b013e328356da72]

67   **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

68   **Li ZY**, Yang Y, Ming M, Liu B. Mitochondrial ROS generation for regulation of autophagic pathways in cancer. *Biochem Biophys Res Commun* 2011; **414**: 5-8 [PMID: 21951851 DOI: 10.1016/j.bbrc.2011.09.046]

69   **Rojas A**, González I, Morales E, Pérez-Castro R, Romero J, Figueroa H. Diabetes and cancer: Looking at the multiligand/RAGE axis. *World J Diabetes* 2011; **2**: 108-113 [PMID: 21860695 DOI: 10.4239/wjd.v2.i7.108]

70   **Zelenko Z**, Gallagher EJ. Diabetes and cancer. *Endocrinol Metab Clin North Am* 2014; **43**: 167-185 [PMID: 24582097 DOI: 10.1016/j.ecl.2013.09.008]

71   **Goldberg RB**. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulation in development of diabetes and its complications. *J Clin Endocrinol Metab* 2009; **94**: 3171-3182 [PMID: 19509100 DOI: 10.1210/jc.2008-2534]

72   **Esquivel-Velázquez M**, Ostoa-Saloma P, Palacios-Arreola MI, Nava-Castro KE, Castro JI, Morales-Montor J. The role of cytokines in breast cancer development and progression. *J Interferon Cytokine Res* 2015; **35**: 1-16 [PMID: 25068787 DOI: 10.1089/jir.2014.0026]

73   **Berraondo P**, Sanmamed MF, Ochoa MC, Etxeberria I, Aznar MA, Pérez-Gracia JL, Rodríguez-Ruiz ME, Ponz-Sarvise M, Castañón E, Melero I. Cytokines in clinical cancer immunotherapy. *Br J Cancer* 2019; **120**: 6-15 [PMID: 30413827 DOI: 10.1038/s41416-018-0328-y]

74   **Bertrand F**, Montfort A, Marcheteau E, Imbert C, Gilhodes J, Filleron T, Rochaix P, Andrieu-Abadie N, Levade T, Meyer N, Colacios C, Ségui B. TNFα blockade overcomes resistance to anti-PD-1 in experimental melanoma. *Nat Commun* 2017; **8**: 2256 [PMID: 29273790 DOI: 10.1038/s41467-017-02358-7]

75   **Komura T**, Sakai Y, Honda M, Takamura T, Matsushima K, Kaneko S. CD14+ monocytes are vulnerable and functionally impaired under endoplasmic reticulum stress in patients with type 2 diabetes. *Diabetes* 2010; **59**: 634-643 [PMID: 19959758 DOI: 10.2337/db09-0659]

76   **Lecube A**, Pachón G, Petriz J, Hernández C, Simó R. Phagocytic activity is impaired in type 2 diabetes mellitus and increases after metabolic improvement. *PLoS One* 2011; **6**: e23366 [PMID: 21876749 DOI: 10.1371/journal.pone.0023366]

77   **Gambineri A**, Pelusi C. Sex hormones, obesity and type 2 diabetes: is there a link? *Endocr Connect* 2019; **8**: R1-R9 [PMID: 30533003 DOI: 10.1530/EC-18-0450]

78   **Le TN**, Nestler JE, Strauss JF, Wickham EP. Sex hormone-binding globulin and type 2 diabetes mellitus. *Trends Endocrinol Metab* 2012; **23**: 32-40 [PMID: 22047952 DOI: 10.1016/j.tem.2011.09.005]

79   **Ding EL**, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, Buring JE, Gaziano JM, Liu S. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med* 2009; **361**: 1152-1163 [PMID: 19657112 DOI: 10.1056/NEJMoa0804381]

80   **Felix AS**, Yang HP, Bell DW, Sherman ME. Epidemiology of Endometrial Carcinoma: Etiologic Importance of Hormonal and Metabolic Influences. *Adv Exp Med Biol* 2017; **943**: 3-46 [PMID: 27910063 DOI: 10.1007/978-3-319-43139-0_1]

81   **Muka T**, Nano J, Jaspers L, Meun C, Bramer WM, Hofman A, Dehghan A, Kavousi M, Laven JS, Franco OH. Associations of Steroid Sex Hormones and Sex Hormone-Binding Globulin With the Risk of Type 2 Diabetes in Women: A Population-Based Cohort Study and Meta-analysis. *Diabetes* 2017; **66**: 577-586 [PMID: 28223343 DOI: 10.2337/db16-0473]

82   **Ding EL**, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2006; **295**: 1288-1299 [PMID: 16537739 DOI: 10.1001/jama.295.11.1288]

83   **Haffner SM**. Sex hormones, obesity, fat distribution, type 2 diabetes and insulin resistance: epidemiological and clinical correlation. *Int J Obes Relat Metab Disord* 2000; **24** Suppl 2: S56-S58 [PMID: 10997610 DOI: 10.1038/sj.ijo.0801279]

84   **Liu S**, Sun Q. Sex differences, endogenous sex-hormone hormones, sex-hormone binding globulin, and exogenous disruptors in diabetes and related metabolic outcomes. *J Diabetes* 2018; **10**: 428-441 [PMID: 27990781 DOI: 10.1111/1753-0407.12517]

85   **Kim TJ**, Lee H, Min YW, Min BH, Lee JH, Son HJ, Rhee PL, Baek SY, Jung SH, Kim JJ. Diabetic biomarkers and the risk of proximal or distal gastric cancer. *J Gastroenterol Hepatol* 2016; **31**: 1705-1710 [PMID: 26936514 DOI: 10.1111/jgh.13329]

86   **Gonzalez-Molina J**, Gramolelli S, Liao Z, Carlson JW, Ojala PM, Lehti K. MMP14 in Sarcoma: A Regulator of Tumor Microenvironment Communication in Connective Tissues. *Cells* 2019; 8 [PMID: 31466240 DOI: 10.3390/cells8090991]

87   **Seyfried TN**, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. *Carcinogenesis* 2014; **35**: 515-527 [PMID: 24343361 DOI: 10.1093/carcin/bgt480]

88   **Yang Y**, Yang T, Liu S, Cao Z, Zhao Y, Su X, Liao Z, Teng X, Hua J. Concentrated ambient $PM_{2.5}$ exposure affects mice sperm quality and testosterone biosynthesis. *PeerJ* 2019; **7**: e8109 [PMID: 31799077 DOI: 10.7717/peerj.8109]

89   **Chen Y**, Wu F, Saito E, Lin Y, Song M, Luu HN, Gupta PC, Sawada N, Tamakoshi A, Shu XO, Koh WP, Xiang YB, Tomata Y, Sugiyama K, Park SK, Matsuo K, Nagata C, Sugawara Y, Qiao YL, You SL, Wang R, Shin MH, Pan WH, Pednekar MS, Tsugane S, Cai H, Yuan JM, Gao YT, Tsuji I, Kanemura S, Ito H, Wada K, Ahn YO, Yoo KY, Ahsan H, Chia KS, Boffetta P, Zheng W, Inoue M, Kang D, Potter JD. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. *Diabetologia* 2017; **60**: 1022-1032 [PMID: 28265721 DOI: 10.1007/s00125-017-4229-z]

90   **Tan J**, You Y, Guo F, Xu J, Dai H, Bie P. Association of elevated risk of pancreatic cancer in diabetic patients: A systematic review and meta-analysis. *Oncol Lett* 2017; **13**: 1247-1255 [PMID: 28454242 DOI: 10.3892/ol.2017.5586]

91   **Dankner R**, Boffetta P, Balicer RD, Boker LK, Sadeh M, Berlin A, Olmer L, Goldfracht M, Freedman LS. Time-Dependent Risk of Cancer After a Diabetes Diagnosis in a Cohort of 2.3 Million Adults. *Am J Epidemiol* 2016; **183**: 1098-1106 [PMID: 27257115 DOI: 10.1093/aje/kwv290]

92   **Song S**, Wang B, Zhang X, Hao L, Hu X, Li Z, Sun S. Long-Term Diabetes Mellitus Is Associated with an Increased Risk of Pancreatic Cancer: A Meta-Analysis. *PLoS One* 2015; **10**: e0134321 [PMID: 26222906 DOI: 10.1371/journal.pone.0134321]

93   **Ogunleye AA**, Ogston SA, Morris AD, Evans JM. A cohort study of the risk of cancer associated with type 2 diabetes. *Br J Cancer* 2009; **101**: 1199-1201 [PMID: 19690547 DOI: 10.1038/sj.bjc.6605240]

94   **Li X**, Xu H, Gao Y, Pan M, Wang L, Gao P. Diabetes mellitus increases the risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis C patients in China. *Medicine (Baltimore)* 2017; **96**: e6508 [PMID: 28353605 DOI: 10.1097/MD.0000000000006508]

95   **Wang L**, Wang L, Zhang J, Wang B, Liu H. Association between diabetes mellitus and subsequent ovarian cancer in women: A systematic review and meta-analysis of cohort studies. *Medicine (Baltimore)* 2017; **96**: e6396 [PMID: 28422831 DOI: 10.1097/MD.0000000000006396]

96   **Chen J**, Han Y, Xu C, Xiao T, Wang B. Effect of type 2 diabetes mellitus on the risk for hepatocellular carcinoma in chronic liver diseases: a meta-analysis of cohort studies. *Eur J Cancer Prev* 2015; **24**: 89-99 [PMID: 24809655 DOI: 10.1097/CEJ.0000000000000038]

97   **Zhu B**, Wu X, Wu B, Pei D, Zhang L, Wei L. The relationship between diabetes and colorectal cancer prognosis: A meta-analysis based on the cohort studies. *PLoS One* 2017; **12**: e0176068 [PMID: 28423026 DOI: 10.1371/journal.pone.0176068]

98   **Guraya SY**. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. *World J Gastroenterol* 2015; **21**: 6026-6031 [PMID: 26019469 DOI: 10.3748/wjg.v21.i19.6026]

99   **Saed L**, Varse F, Baradaran HR, Moradi Y, Khateri S, Friberg E, Khazaei Z, Gharahjeh S, Tehrani S, Sioofy-Khojine AB, Najmi Z. The effect of diabetes on the risk of endometrial Cancer: an updated a systematic review and meta-analysis. *BMC Cancer* 2019; **19**: 527 [PMID: 31151429 DOI: 10.1186/s12885-019-5748-4]

100   **Khan S**, Cai J, Nielsen ME, Troester MA, Mohler JL, Fontham ET, Hendrix LH, Farnan L, Olshan AF, Bensen JT. The association of diabetes and obesity with prostate cancer aggressiveness among Black Americans and White Americans in a population-based study. *Cancer Causes Control* 2016; **27**: 1475-1485 [PMID: 27830399 DOI: 10.1007/s10552-016-0828-0]

101   **Fall K**, Garmo H, Gudbjörnsdottir S, Stattin P, Zethelius B. Diabetes mellitus and prostate cancer risk; a nationwide case-control study within PCBaSe Sweden. *Cancer Epidemiol Biomarkers Prev* 2013; **22**: 1102-1109 [PMID: 23580698 DOI: 10.1158/1055-9965.EPI-12-1046]