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Review

Anti-diabetic medications and cancer: links beyond glycemic and body weight control

Meng Cao,[‡] Chu Lin,[‡] Xiaoling Cai,[*] Fang Lv, Wenjia Yang, Linong Ji[*]

Department of Endocrinology and Metabolism, Peking University People's Hospital, Peking University Diabetes Center, Beijing 100044, China

*Corresponding authors: Xiaoling Cai, dr_junel@sina.com; Linong Ji, jiln@bjmu.edu.cn

[‡]Meng Cao and Chu Lin contributed equally to this work.

Abstract

Cancer is becoming one of the leading causes of death among patients with diabetes. Hyperglycemia and obesity, two key characteristics of type 2 diabetes, modify the risks of cancer in patients with type 2 diabetes. However, recent studies suggested that glycemic control and weight loss mediated by anti-diabetic medications might not be sufficient to lower the risks of cancer in patients with type 2 diabetes. Thus, there is a need to explore the association between anti-diabetic medications and cancer beyond glycemic and body weight control. This review has summarized the preclinical and clinical evidence between various anti-diabetic drugs and cancer. More importantly, this review focused on the underlying links between anti-diabetic medications and cancer beyond glycemic and body weight control, including modified cell proliferation, altered levels of some hormones, inflammation and oxidative stimuli, autophagy and apoptosis, intestinal flora shift, and angiogenesis and epithelial–mesenchymal transition. This review may provide insights for future clinical and mechanistic studies to further elucidate the association between anti-diabetic medications and cancer.

Keywords: type 2 diabetes; cancer; anti-diabetic medications

Introduction

Diabetes is linked to a higher risk of cancer, with 8%–18% of patients with cancer suffering from diabetes [1]. A 5.7% higher risk of cancer has been reported to be associated with diabetes and obesity [2]. A 41% increase in all-cause mortality in patients with cancer was linked to type 2 diabetes mellitus (T2DM) [3]. Studies indicated associations between T2DM and increased risk for hepatocellular carcinoma (HCC) [4], pancreatic cancer [5], colorectal cancer [6], breast cancer [7], kidney cancer [8], and bladder cancer [9]. Mendelian randomization (MR) studies revealed higher risks of breast cancer, pancreatic cancer, lung cancer, kidney cancer, and uterine cancer in T2DM, with fasting insulin being the casual factor [2, 10]. However, in the case of prostate cancer, a lower risk was observed in patients with T2DM [11]. Patients with T2DM were also found to have a reduced risk of developing esophageal cancer and melanoma in a MR study [10] (Fig. 1).

T2DM and cancer

Hyperglycemia and obesity modify the risks of cancer in T2DM

Hyperglycemia and obesity are two key characteristics of T2DM. Research has shown that both hyperglycemia and obesity could increase the risks of cancer and fuel cancer growth by amplifying inflammation [12], inducing epigenetic modifications [13], and promoting the formation of tumor microenvironment (TME) [14]. Furthermore, hyperglycemia could promote glycolysis [15], induce DNA damage [16], and enhance cell proliferation [17] to promote carcinogenesis. Obesity could alter lipid metabolism [18], aggravate insulin resistance [19], and alter gut microbiome to influence the risks of cancer [20] (Fig. 2).

Glycemic control and weight loss mediated by anti-diabetic medications could not lower the risks of cancer

It was reported that hypoglycemic drugs and strategies did not lower the risks of cancer through their hypoglycemic effects [21]. However, improved glycemic control was associated with reduced mortality and slowed cancer progression in various types of cancers including prostate cancer [22], colorectal cancer [23, 24], pancreatic cancer [25, 26], lung cancer [27], and bladder cancer [28]. But some studies showed that the anti-cancer effects of glycemic control were limited in certain cancer types including pancreatic cancer [29] and advanced colorectal cancer [30]. The impact of strict glycemic control on breast cancer remain debated [31].

Meanwhile, a study indicated that weight change induced by hypoglycemic agents or strategies in short and medium periods could not lower the incidence of most cancers in patients with T2DM [32]. However, other studies showed that weight loss might reduce the risk of some obesity-related cancers in adults. Studies revealed that the time of being overweight could influence the risks of postmenopausal breast cancer, colorectal cancer, pancreatic cancer, kidney cancer, gallbladder cancer, endometrium cancer, ovarian cancer, liver cancer, lower esophagus cancer, and cardia stomach cancer [33].

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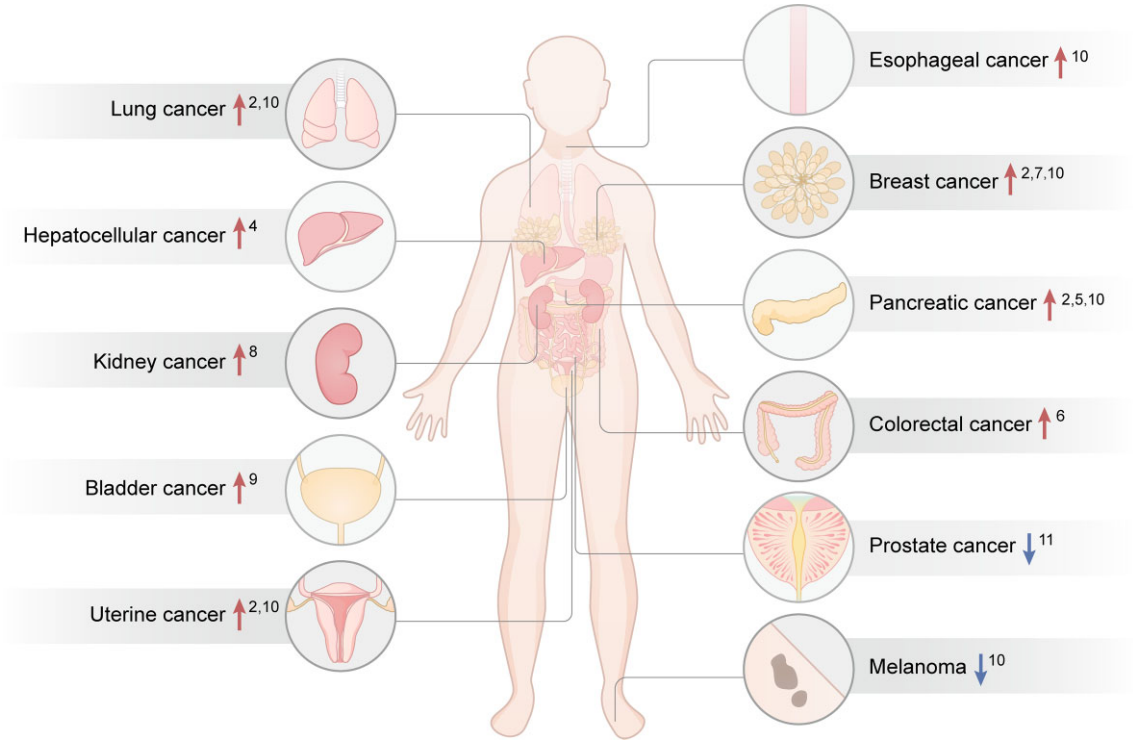

Figure 1. Type 2 diabetes and the risks of cancer. The picture illustrates the association between diabetes and the risk of developing specific types of cancer, indicated by the presence of an upward arrow (↑) or a downward arrow (↓), suggesting an increased or decreased risk of cancer.

Association between anti-diabetic medications and cancer beyond glycemic and body weight control

Metformin and cancer

Mechanistic insight

Metformin might reduce the risks of cancer via multiple ways, ranging from improving anti-cancer immunity to impeding the formation of TME (Table 1). Metformin could improve the functions of immune cells by improving hypoxia status in cancer and affecting the metabolism of immune cells [34]. The adenosine monophosphate-activated protein kinase (AMPK) pathway activated by metformin could inhibit programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) signaling, which inhibited cancer immune escape [35]. Metformin also inhibited the expression of immunosuppressive interleukin-10 (IL-10) and pro-inflammatory cytokines, which improved anti-cancer immunity and prevented pro-carcinogenesis inflammation. These alterations in cytokine production could also be achieved by metformin through AMPK-independent pathways [36]. Experiments showed that metformin could slow down the recruitment of cancer-supportive cells like myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) [37]. Meanwhile the functions and numbers of natural killer T (NKT) cells, cancer-resolving dendric cells, and $CD8^+$ T cells were enhanced by metformin [38]. As for M2 macrophages equipped with anti-inflammatory ability [39], studies suggested a hypothesis called the M2 cell paradox. Metformin could exert anti-cancer effects by increasing M2 cell number in normal adipose tissues via the AMPK-mammalian target of rapamycin (mTOR) pathway; and in TME the same pathway led to a decrease in M2 cell numbers, indicating a cancer-specific toxic effect [39].

Metformin could inhibit cancer proliferation and metastasis and induce apoptosis to repress cancer progression. First of all, the activation of AMPK could affect important cancer-related pathways such as the phosphoinositide 3-kinase (PI3K)/AKT (Ak transforming) pathway, which promoted the expression of nuclear factor κlight-chain-enhancer of activated B cells (NF-κB) and inhibited FOXO3 transcription factor to influence cellular autophagy and cancerous differentiation [40]. The activation of AMPK could also reduce forkhead-box A1 transcription factor, an important factor in cancer cell growth [41]. Moreover, mTOR activity could be suppressed through AMPK activation or other alternative AMPK-independent mechanisms [42]. It was discovered that mTOR was a central regulator of protein synthesis and cell proliferation [43]. Its downregulation led to increased p27 phosphorylation in Thr198, promoted p53 expression, and decreased cyclin D1 expression [42, 44–46], all of which resulted in cell cycle arrest. Furthermore, mTOR was linked to the inhibition of pyruvate kinase M2-signal transducer and the pyruvate kinase M2/signal transducer and activator of transcription 3 (STAT3)/Twist family BHLH transcription factor 1 pathway, which hindered epithelial–mesenchymal transition (EMT) [42]. The inhibition of mTOR suppressed protein synthesis largely by preventing the phosphorylation and activation of ribosomal protein S6 kinase 1 and 4E-binding protein [47]. The inhibition of mTOR increased cellular apoptosis and autophagy via the AKT and NF-κB pathways [36, 48]. Metformin could also trigger the oxidative stress pathway and increase the lactate dehydrogenase factor to induce apoptosis [49]. Notably, despite this pro-oxidant effect in the tumor context, metformin was associated with the systemic attenuation of inflammation. This anti-inflammatory effect was achieved by inhibiting the production of excessive reactive oxygen species (ROS) and pro-inflammatory cytokines in stimulated macrophages [50]. In addition, downregulated Aurora-A observed

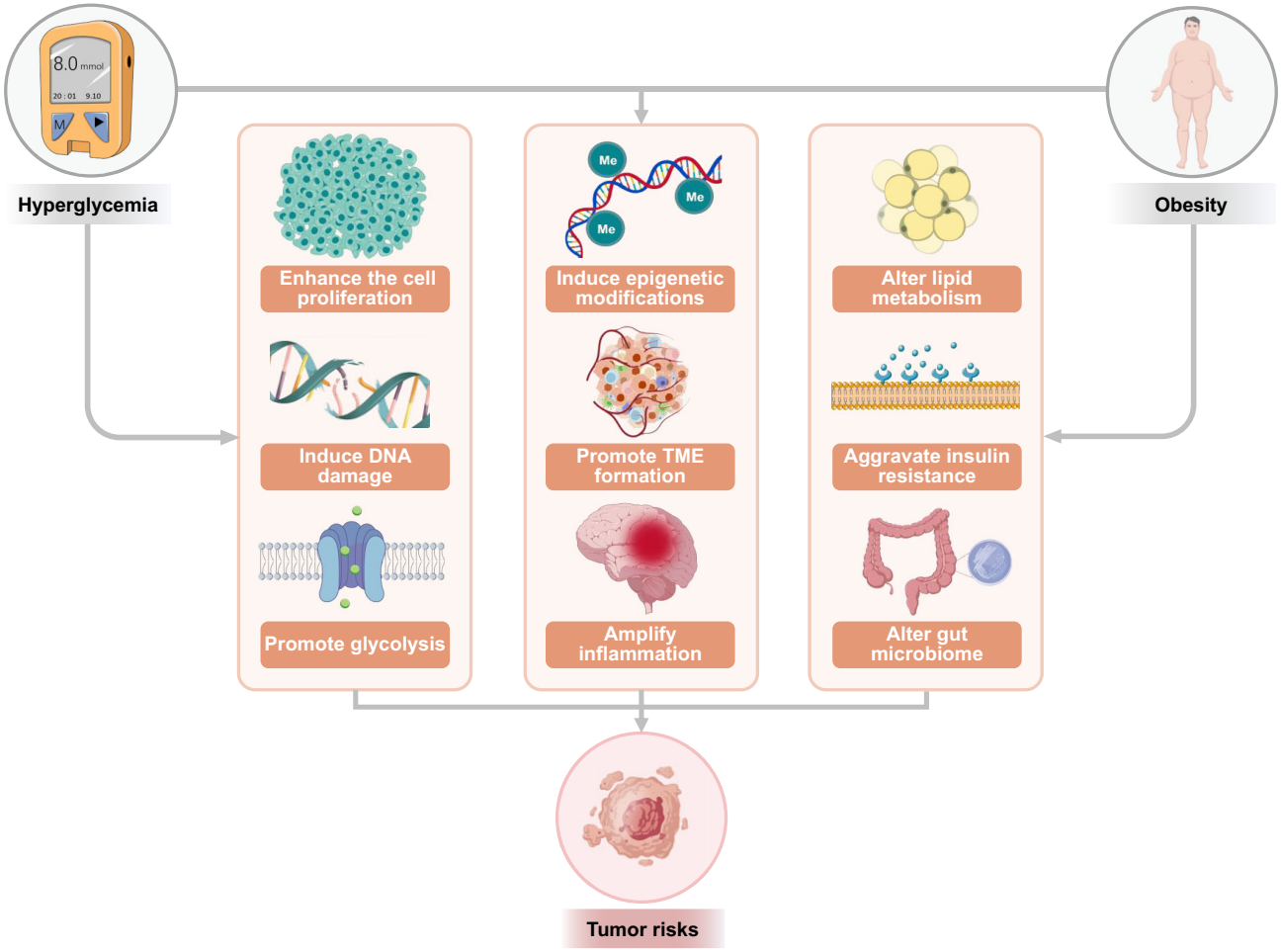

Figure 2. Mechanisms underlying the links between hyperglycemia, obesity, and cancer. Hyperglycemia and obesity are two significant factors affecting the link between diabetes and cancer. Hyperglycemia increases the risks of cancer through inducing epigenetic changes, enhancing cell proliferation, inducing DNA damage, and promoting glycolysis. Obesity increases risks of cancer through altering lipid metabolism, altering the microbiome, promoting insulin resistance, and releasing obesity-related factors. Both hyperglycemia and obesity could promote the formation of TME and amplify inflammation to increase risks of cancer.

in metformin treatment led to cell cycle arrest in G2/M transition [42].

Metformin could inhibit the formation of TME. Recent investigations revealed that metformin was able to alter cancer cell induced alteration in fibroblast phenotype and secretion [51]. Metabolic coupling, an important factor in TME shaping, was inhibited by metformin via restoring the expression of fibroblast caveolin-1 and cancer cell monocarboxylate transporter [52]. Cancer cells establish cellular interactions with cancer-associated fibroblasts by expressing CCN family member 1 and hypoxia-inducible factor-α (HIF-α). This cellular interaction could be inhibited by metformin as well [53]. Angiogenesis was important for cancer nutrition supply. Vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor-1 were vital for angiogenesis, but this could be blocked by metformin via activating AMPK [54].

Intestinal flora was another way for metformin to exert its anticancer effects. It was proved that metformin-treated microbiota was more sensitive to glucose [55]. This microbiota was also anti-inflammatory [56] and produced more short-chain fatty acids to inhibit carcinogenesis [57].

Given that insulinemia is a risk factor for cancer, metformin could inhibit cancer via reducing insulin. It was indicated that by activating AMPK, metformin could inhibit the production and release of insulin and insulin-like growth factor 1 [a key ligand of the insulin-like growth factor (IGF) family]. Additionally, metformin reduced PI3K activation by affecting insulin receptor (IR) and IGF-1 receptor. These all contributed to inhibited cell proliferation [58].

Epigenetics alteration was another important factor affecting cancer occurrence and progression. Metformin was proved to impact DNA methylation [42], histone acetylation [59], noncoding RNA transcription [39, 42], and mRNA alternative splicing [60].

EMT, a signal for onset of cancer, was decreased with metformin treatment, via pathways both dependent and independent of Wnt/β-catenin inhibition [36, 61]. Cancer stem cells could also be reduced by metformin. This might be the result of inhibited sonic hedgehog pathway and transforming growth factor β (TGFβ) pathway [62].

Preclinical evidence

An *in vitro* experiment using human pancreatic cancer cell lines showed that metformin could inhibit cell proliferation, migration, and invasion and improve therapeutic resistance of tumor cells [63]. Another experiment showed that metformin concentration was inversely associated with bladder cancer cell viability [64]. In cervical cancer-derived cell lines, metformin decreased cell growth and promoted the expression of a group of antitumoral genes [47]. Oral squamous cell carcinoma cell lines

Table 1. Mechanismsunderlying the links between anti-diabetic medications and cancer[a].

Mechanism	Metformin	AGI	SGLT2i	DPP4i	GLP-1RA	Thiazolidinedione	Insulin
Proliferation	Decreasing insulin levels to inhibit cellular proliferation [58]	Inhibiting proliferation [75, 76]	Inducing cell cycle arrest [84–86]	Inhibiting proliferation [102, 103]	Inhibiting proliferation of breast cancer cells [123] but promoting proliferation of pancreatic β cells and C cells [124–126]	Inhibiting proliferation [139, 140, 144]	Affecting insulin sensitivity to promote proliferation [151, 153]
Apoptosis	Promoting apoptosis [42,49]	Promoting apoptosis [73]	Promoting apoptosis [87]		Promoting apoptosis [118]	Promoting apoptosis [141, 144, 145]	Promoting apoptosis [155]
Angiogenesis			Inhibiting angiogenesis [88]		Promoting the expression of VEGF [118]	Reducing the expression of VEGF [139]	
Metabolism regulation	Inhibiting protein synthesis [47]	Improving systemic metabolic homeostasis and inducing metabolic stress within cancer cells [73, 75, 76]					
Metastasis	Inhibiting EMT [36, 61, 62]			Inhibiting invasion [106, 107] & Inducing invasion [102, 104]			Inhibiting cancer migration [139, 142]
Inflammation	Attenuating inflammation [50]		Attenuating inflammation [86, 89, 90]	Attenuating inflammation [110, 111]	Attenuating inflammation [119]	Attenuating inflammation [139, 143]	
Immune function	Improving immune function [34–36, 38, 39]	Potentially impairing the production of cytokines and CD8$^+$T cell functions [74]		Improving immune function [108, 109]	Improving the function of innate immune cells [120]	Restoring immune tonus [143]	
Epigenetics alteration	Triggering beneficial epigenetic alterations [39, 42, 59, 60]						
Tumor microenvironment	Inhibiting the formation of TME [52–54]			Inhibiting the formation of TME [104]			
Intestinal flora	Enhancing glucose sensitivity and the production of gut microbiota-derived short-chain fatty acid [55–57]	Enriching gut Bifidobacterium longum to attenuate intestinal inflammation [77]					
DNA mutation						Promoting mutation via generating ROS [145]	Promoting mutagenic DNA repair [152]

[a]AGI, α-Glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; EMT, epithelial–mesenchymal transition; GLP-1RA, glucagon-like peptide-1 receptor agonist; ROS, reactive oxygen species; SGLT2i, sodium–glucose co-transporter 2 inhibitor; VEGF, vascular endothelial growth factor.

(OSCC) treated with metformin showed inhibited viability and colony formation [59]. Metformin treatment inhibited the proliferation of cell lines derived from myelodysplastic syndromes and acute myeloid leukemia (AML) [45]. Mouse models of melanoma supported the anti-metastasis ability of metformin in melanoma [46]. Additionally, a scoping review focused on the association between head and neck cancer and metformin, and analyzed studies that used cell culture and animal models in preclinical laboratory settings, and most research showed anti-tumor effects of metformin [42]. However, conflicting evidence exists in breast

cancer. According to a MR study, among the three targets of metformin (PRKAB1, ETFDH, GPD1L), the main target (PRKAB1) related to the anti-diabetic effects of metformin could not protect patients against breast cancer. Conversely, metformin could elevate the risks of ER^+ breast cancer and $HER2^-$ breast cancer by inhibiting the other two targets [65] (Table 2).

Clinical evidence

A retrospective cohort study of 480 984 participants and a randomized controlled trial (RCT) of 19 114 patients with diabetes both demonstrated that metformin was associated with a reduction in the overall incidence of cancer [66, 67]. However, the RCT showed no reductions in cancer-specific mortality [66].

The cohort study unveiled associations between metformin and lowered risks of colorectal cancer and HCC [67]. Moreover, long-term use of metformin in an Asian population with T2DM was associated with lower risks of esophageal cancer, whereas in Western patients with T2DM or a population without T2DM the clinical studies did not generate consistent results [68].

The use of metformin was associated with reduced overall mortality in diabetic patients with esophageal cancer [69] and hypopharyngeal cancer [44]. Furthermore, a RCT found that metformin induced specific changes in breast tissue gene expression, suggesting a potential benefit for inhibiting recurrence [70]. Hower, metformin failed to improve cancer-specific survival in patients with endometrial cancer [71] or overall survival in patients with glioblastoma [36] (Table 3).

α-Glucosidase inhibitor and cancer

Mechanistic insight

α-Glucosidase inhibitor (AGI) might be able to inhibit the progression of cancer. AGI could improve insulin resistance, which was a risk factor for HCC [72]. Furthermore, AGI could downregulate glucose levels, which forced cancer cells to adopt more oxidative phosphorylation for energy generation. Hence more ROS were produced within cancer cells, leading to apoptosis [73]. The cancer cells that underwent apoptosis released cancer-associated antigens to recruit $CD8^+$ T to prevent the immune escape [74]. Voglibose could downregulate serum levels of IGF-1 to inhibit cell proliferation [75]. Acarbose could decrease colorectal cancer by promoting the production of butyrate, which is a short-chain free fatty acid indirectly affecting cancer cell survival and proliferation [76].

AGI also contributed to the intestinal flora shift. Unabsorbed acarbose increased gut *Bifidobacterium longum* in patients with T2DM to reduce intestinal inflammation [77]. AGI inhibited colorectal adenomas via restoring intestinal flora diversity and modulating the relative abundance of specific bacterial genera [78]. Intestinal proteolytic bacteria and saccharolytic bacteria number would increase to reduce blood ammonia levels, which would influence the cancer cell metabolism and the immune escape, thus exerting anti-cancer effects [79] (Table 1).

Preclinical evidence

AGIs showed anti-cancer potential across different cancer types. Voglibose prevented colorectal pre-neoplastic lesions in diabetic mice [75], while a novel sp2-iminosugar AGI derivative inhibited pro-metastatic protein glycation in breast cancer cells via inhibiting glucosidase [80]. Collectively, these findings suggest the anti-glycation activity of AGIs as a potential mechanism for their protective effects (Table 2).

Clinical evidence

A meta-analysis involving 1 285 433 patients with diabetes showed that AGI could lower the risk of developing cancer, especially gastrointestinal cancer [76]. Additionally, retrospective studies indicated associations between AGI and reduced risks of HCC [81] and colorectal adenoma [78]. (Table 3).

Sodium-glucose co-transporter 2 inhibitor and cancer

Mechanistic insight

The mechanisms lying behind the association between sodium–glucose co-transporter 2 inhibitor (SGLT2i) and lowered risks of cancer might include inhibiting cell proliferation, suppressing angiogenesis, reducing the levels of inflammation, and inducing autophagy and apoptosis (Table 1).

Firstly, SGLT2i could induce cell cycle arrest. This was mediated by disrupting glutamine metabolism [82], inducing mitochondrial dysfunction [83], inhibiting the β-catenin signaling pathway [84], inhibiting the activation of mTOR [85], and decreasing the levels of cyclin D, Cdk4 proteins, and certain growth factors [86]. By inducing endoplasmic reticulum stress (ERS), SGLT2i could restore autophagy and apoptosis in cancer tissues [87]. Furthermore, SGLT2i downregulated the expression of VEGF, a direct transcriptional target of HIF-α, by promoting the degradation of HIF-α protein [88].

Secondly, SGLT2i could alleviate the levels of inflammation. The mechanisms underlying the reduction of inflammation might involve the inhibition of the sodium hydrogen exchanger1–Ca^{2+}–tumor necrosis factor α (TNFα) pathway [89] and the downregulation of α-fetoprotein mRNA [86]. A recent study revealed that empagliflozin mitigated liver lesion and fibrosis by promoting the acetyl-CoA carboxylase 1–acyl-CoA oxidase 1 (ACC1) pathway and inhibiting the inositol-requiring enzyme 1α (IRE1α)–X-box binding protein 1 (XBP1)–pleckstrin homology-like domain family A member 3 (PHLDA3) pathway [90].

Preclinical evidence

Experiments revealed the anti-cancer potential of SGLT2i in liver cancer, osteosarcoma, and prostate cancer. According to an experiment conducted on genetically obese mice with nonalcoholic steatohepatitis fed on chemical carcinogens, tofogliflozin could inhibit the progression of liver tumors [91]. Meanwhile, SGLT2i significantly inhibited osteosarcoma tumor growth and induced immune cell infiltration in human osteosarcoma cell lines and mice with subcutaneous implantation of murine osteosarcoma cells [92]. MR analysis also showed that genetically proxied inhibition of SGLT2 was significantly associated with a reduced risk of prostate cancer [93] (Table 2).

Clinical evidence

The effect of SGLT2 inhibitors on the risk of overall cancer remains inconclusive in existing clinical research. A retrospective study revealed no significant association between SGLT2i and risks of overall cancer in 107 972 patients with T2DM [94]. Similarly, a meta-analysis found no links between SGLT2i and overall neoplasm [95]. But another retrospective study found that SGLT2i might confer reduced incidences of cancer in patients with T2DM [96].

Retrospective clinical studies showed that SGLT2i could decrease incidences of certain types of cancer, including gastric cancer [97], breast cancer [96], renal cell carcinoma (RCC) [98], and pulmonary neoplasm [95]. Conversely, SGLT2i was associated with increased incidences of reproductive and hematologic/lymphatic cancers [99]. The association with prostate neoplasms remains

Table 2. Preclinical evidence for associations between the anti-diabetic medications and cancer[a].

Drug type	System	Cancer type	Influence[b]	Study design	Reference
Metformin	Digestive system	Pancreatic cancer	↓ Tumor proliferation, migration, invasion, and therapeutic resistance	*In vitro*	[63]
	Urinary system	Bladder cancer	↓ Tumor viability	*In vitro*	[64]
	Reproductive system	Breast cancer (ER^+ or $HER[2]^-$)	↑Tumor incidence	MR study	[65]
		Cervical cancer	↓ Tumor growth ↑ Anti-tumor gene expression	*In vitro*	[47]
	Head and neck system	OSCC	↓ Viability and colony formation	*In vitro*	[59]
	Hematologic system and lymphatic system	AML	↓ Tumor proliferation	*In vitro*	[45]
	Integumentary system	Melanoma	↓ Tumor metastasis	*In vivo*	[46]
AGI	Digestive system	Colorectal pre-neoplastic lesions	↓ Tumor progression	*In vitro*	[75]
	Reproductive system	Breast cancer	↓ Tumor metastasis	*In vitro*	[80]
SGLT2i	Digestive system	Liver cancer	↓ Tumor progression	*In vivo*	[91]
	Reproductive system	Prostate cancer	↓ Tumor incidence	MR study	[93]
	Musculoskeletal system	Osteosarcoma	↓ Tumor growth ↑ Immune infiltration	*In vitro and in vivo*	[92]
DPP4i	Reproductive system	Breast cancer	↑ Tumor metastasis	*In vivo*	[116]
		Cervical cancer	↓ Tumor migration and adhesion	*In vitro*	[114]
		Endometrial cancer	↓ Tumor proliferation	*In vitro*	[113]
		Ovarian cancer	↓ Tumor migration and invasiveness	*In vitro*	[115]
GLP-1RA	Reproductive system	Breast cancer	↓ Tumor proliferation	*In vitro*	[123]
Thiazolidinedione	Digestive System	HCC	↓ Tumor proliferation ↑Anti-tumor gene expression	*In vivo*	[140]
	Urinary System	Basal/squamous bladder cancer	↓ Tumor invasion	*In vitro*	[141]
	Respiratory system	Premalignant lung cancer	↓ Tumor progression	*In vivo*	[148]
	Reproductive system	Breast cancer	↓ Tumor incidence	*In vivo*	[146]
		Ovarian cancer	↑ Cell apoptosis	*In vitro*	[139]
	Endocrine system	Follicular thyroid cancer	↓ Tumor progression and metastasis	*In vivo*	[147]
	Central nervous system	Glioblastoma	↓ Tumor survival, migration, and invasion	*In vitro*	[142]
Insulin	Digestive system	Colon cancer	↓ Tumor proliferation and metastasis	*In vitro*	[156]
	Integumentary system	Melanoma	↓ Tumor growth	*In vivo*	[155]

[a]Effects are indicated by arrows (↑for enhanced effects and↓for reduced effects).
[b]AGI, α-Glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma.

Table 3. Clinical evidence for associations between the antidiabetic medications and cancer[a].

Drug type	System	Cancer type	Influence[b]	Number of patients	Study duration	HR/RR/OR (95% CI)	Diabetic status	Study design	Reference
Metformin	Digestive system	Esophageal cancer	Improved outcome	852	1.7 years	HR: 0.86 (0.75–1.00)	DM	Retrospective cohort study	[69]
		HCC	Reduced risk	480 984	3.49–3.80 years	HR: 0.06 (0.02–0.16)	Without DM	Prospective cohort Study	[67]
		Colorectal cancer	Reduced risk	480 984	3.49–3.80 years	HR: 0.36 (0.13–0.98)	Without DM	Prospective cohort Study	[67]
	Reproductive system	Breast cancer	Improved outcome	36	1 year	NA	Without DM	RCT	[70]
		Endometrial cancer	Unimproved outcome	664	9.08 years	HR: 0.87 (0.70–1.07)	DM	Retrospective cohort study	[71]
	Head and neck system	Hypopharyngeal cancer	Improved outcome	92	4 years	HR: 0.63 (0.46–0.86)	T2DM	Retrospective cohort study	[44]
AGI	Digestive cancer	Gastrointestinal cancer	Reduced risk	1 285 433	–	OR: 0.83 (0.71–0.97)	DM	Meta-analysis of RCTs	[76]
		HCC	Reduced risk	48 351	19 years	HR: 0.55 (0.46–0.67)	T2DM	Retrospective Cohort Study	[81]
		Colorectal cancer	Reduced risk	311	4 years	HR: 0.399 (0.22–0.723)	T2DM	Retrospective Cohort Study	[78]
SGLT2i	Digestive system	HCC	No significant association	107 972	3.04 years	HR: 0.87 (0.61–1.24)	T2DM	Retrospective cohort study	[94]
			Reduced risk	2 798	3.13 years	HR: 0.45 (0.22–0.92)	T2DM	Retrospective cohort study	[94]
	Respiratory system	NSCLC	Improved outcome	24 915	1.77 years	HR: 0.68 (0.60–0.77)	T2DM	Retrospective cohort study	[101]
		Pulmonary neoplasm	Reduced risk	108 061	–	RR:0.83 (0.69–0.99)	T2DM	Meta-analysis of RCTs	[95]
	Urinary system	RCC	Reduced risk	725 316	4 years	HR: 0.68 (0.58–0.81)	T2DM	Retrospective cohort study	[98]
	Reproductive system	Breast cancer	Reduced risk	60 112	6 years	HR: 0.51 (0.32–0.80)	T2DM	Retrospective cohort study	[96]
		Prostate cancer	Reduced risk	48 310	1.33 years	HR: 0.77 (0.61–0.99)	T2DM	Retrospective cohort study	[93]
			Increased risk	112 351	–	RR:1.21 (1.00–1.48)	T2DM	Meta-analysis of RCTs	[95]
		Reproductive cancer	Increased risk	54 666	–	RR: 1.24 (0.99–1.56)	T2DM	Meta-analysis of RCTs	[99]
	Hematologic system and lymphatic system	Hematologic/lymphatic cancer	Increased risk	54 666	–	RR: 1.44 (0.99–2.10)	T2DM	Meta-analysis of RCTs	[99]
	Digestive system	Pancreatic cancer	Unimproved outcome	5 359	8 years	HR: 1.07 (0.93–1.24)	T2DM	Retrospective cohort study	[105]
		Rectal neoplasm	Reduced risk	6,4089	–	OR: 0.58 (0.37–0.93)	T2DM	Meta-analysis of RCTs	[117]
		Rectal malignant neoplasm	Reduced risk	6,4089	–	OR:0.59 (0.36–0.94)	T2DM	Meta-analysis of RCTs	[117]

Table 3. (*Continued*)

Drug type	System	Cancer type	Influence[b]	Number of patients	Study duration	HR/RR/OR (95% CI)	Diabetic status	Study design	Reference
	Reproductive system	Breast cancer	Unimproved outcome	16 085	8 years	HR: 1.07 (0.93–1.25)	T2DM	Retrospective cohort study	[105]
		Prostate cancer	Improved outcome	15 330	8 years	HR: 0.77 (0.64–0.93)	T2DM	Retrospective cohort study	[105]
	Integumentary system	Skin neoplasm	Reduced risk	74 806	–	OR:0.85 (0.72–0.99)	T2DM	Meta-analysis of RCTs	[117]
GLP-1RA	Digestive system	HCC	Reduced risk	1 195 744	9 years	HR: 0.20 (0.14–0.31) (compared with insulin treatment)	T2DM	Retrospective cohort study	[119]
				186 708	9 years	HR: 0.39 (0.21–0.69) (compared with sulfonylureas treatment)			
		Pancreatic cancer	No significant association	46 719	–	OR: 0.25 (0.03–2.24)	T2DM/Without T2DM (The enrolled patients in RCTs comprised both individuals with and without T2DM)	Meta-analysis of RCTs	[133]
				56 004	5.4 years	OR: 1.12 (0.77–1.63)	T2DM	Meta-analysis of RCTs	[132]
		Colorectal cancer	Reduced risk	1 221 218	15 years	0.56 (0.44–0.72) (compared with insulin treatment) 0.75 (0.58–0.97) (compared with metformin treatment) 0.77 (0.62–0.97)) (compared with SGLT2i treatment 0.82 (0.68–0.98)	T2DM	Retrospective cohort study	[129]

Table 3. (*Continued*)

Drug type	System	Cancer type	Influence[b]	Number of patients	Study duration	HR/RR/OR (95% CI)	Diabetic status	Study design	Reference
						(compared with sulfonylureas treatment) 0.82 (0.69–0.97) (compared with thiazolidine-dione)			
		Cholangiocarcinoma	Reduced risk	3 816 071	7 years	HR: 0.72 (0.63–0.83)	DM	Retrospective cohort study	[130]
	Endocrine system	Thyroid cancer	No significant association	145 410	3.9 years	HR: 0.93 (0.66–1.31)	27.7% with DM	Retrospective cohort study	[134,135]
				16 839	–	OR: 2.04 (0.33–12.61)	T2DM/Without T2DM (The enrolled patients in RCTs comprised both individuals with and without T2DM)	Meta-analysis of RCTs	[133]
			Increased risk	47 746	13 years	HR: 1.58 (1.27–1.95)	T2DM	Retrospective cohort study	[136]
		MTC	Increased risk	47 746	13 years	HR: 1.78 (1.04–3.05)	T2DM	Retrospective cohort study	[136]
			No significant association	14 752	3.2 years	HR: 0.87 (0.32–2.40)	T2DM	Retrospective cohort study	[108]
	Reproductive system	Prostate cancer	Reduced risk	9340	3.8 years	HR: 0.54 (0.34–0.88)	T2DM	RCT	[131]
Thiazolidinedione	Urinary system	Bladder cancer	No significant association	193 099	2.8 years	HR:1.06 (0.89–1.26)	DM	Retrospective cohort study	[150]
	Reproductive system	Prostate cancer	No significant association	16 711	–	RR: 0.97 (0.78–1.20)	T2DM	Meta-analysis of RCTs [12]	[149]
Insulin	Digestive system	Liver caner	Increased risk	171 million	–	RR: 1.74 (1.08–2.80)	DM	Meta-analysis of RCTs, cohort studies and case–control studies	[161]

Table 3. (*Continued*)

Drug type	System	Cancer type	Influence[b]	Number of patients	Study duration	HR/RR/OR (95% CI)	Diabetic status	Study design	Reference
		Gastric cancer	No significant association	10 646	7.51 years	HR: 1.07 (0.43–2.71)	T2DM	Retrospective cohort study	[151]
		Pancreatic cancer	Unimproved outcome	538	1.5 years	HR: 1.13 (0.81–1.57)	34% with DM	RCT	[162]
			Increased risk	171 million	–	RR: 2.41 (1.08–5.36)	DM	Meta-analysis of RCTs, cohort studies and case–control studies	[161]
		Colorectal cancer	Increased risk	374 950	–	RR: 1.37 (1.01–1.73)	T2DM	Meta-analysis of RCTs	[160]
	Reproductive system	Breast cancer	Reduced risk	171 million	–	RR: 0.90 (0.82–0.98)	DM	Meta-analysis of RCTs, cohort studies and case–control studies	[161]
			No significant association	10 646	7.51 years	HR: 1.09 (0.54–2.20)	T2DM	Retrospective cohort study	[151]
		Prostate cancer	Reduced risk	171 million		RR: 0.74 (0.56–0.98)	DM	Meta-analysis of RCTs, cohort studies and case–control studies	[161]
		Cervical cancer	No significant association	10 646	7.51 years	HR: 0.07 (0.24–4.77)	T2DM	Retrospective cohort study	[151]
		Ovarian cancer	No significant association	10 646	7.51 years	HR: 1.60 (0.55–4.69)	T2DM	Retrospective cohort study	[151]
	Integumentary system	Non-melanoma skin cancer	No significant association	10 646	7.51 years	HR: 1.22 (0.66–2.23)	T2DM	Retrospective cohort study	[151]
	Central nervous system	Central nervous system cancer	No significant association	10 646	7.51 years	HR: 1.84 (0.52–6.48)	T2DM	Retrospective cohort study	[151]
	Head and neck system	Mouth and pharynx cancer	No significant association	10 646	7.51 years	HR: 2.23 (0.60–8.26)	T2DM	Retrospective cohort study	[151]
	Urinary system	Bladder cancer	No significant association	193 099	2.8 years	HR:1.06 (0.89–1.26)	DM	Retrospective cohort study	[150]
	Reproductive system	Prostate cancer	No significant association	16 711	–	RR: 0.97 (0.78–1.20)	T2DM	Meta-analysis of RCTs	[161]

HR, hazard ratio; RR, risk ratio; OR, odds ratio. [a]AGI, alpha-glucosidase inhibitors; DM, diabetes mellitus; DPPP4i, DPP4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma; MTC, medullary thyroid cancer; NA, not available; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SGLT2i, SGLT2 inhibitor. [b]For the studies that evaluated the association between anti-diabetic medications and the risk of cancer, the effects were summarized as "Increased risk", "Reduced risk", and "No significant association". For the studies that evaluated the effects of anti-diabetic medications on the clinical outcome of patients with cancer, the effects were summarized as "Improved outcome" or "Unimproved outcome".

complex. While a retrospective study suggested a reduced risk of prostate cancer with SGLT2i [93], a subsequent meta-analysis indicated an association with an increased incidence of prostate neoplasms [95]. As for HCC, although no significant association between HCC and SGLT2i was reported in a patient cohort with non-alcoholic fatty liver disease and T2DM, the data from another cohort with fatty liver disease, chronic viral hepatitis, and T2DM revealed a significant association between SGLT2i and decreased risk of HCC [94]. Thus, more research and clinical trials are needed to investigate the exact impact on cancer of SGLT2i.

Additionally, SGLT2i was associated with improved outcomes in colon cancer and non-small cell lung cancer (NSCLC). A case report recorded that a patient with colon cancer and T2DM showed improved tumor markers associated with the use of SGLT2i [100]. An American retrospective clinical study containing 24 915 patients with NSCLC showed improved overall survival in SGLT2i users [101] (Table 3).

Dipeptidyl peptidase-4 inhibitor and cancer

Mechanistic insight

The mechanisms underlying the impacts of dipeptidyl peptidase-4 inhibitor (DPP4i) on cancer might involve cell proliferation, ECM formation, cancer metastasis, immune regulation, and inflammation (Table 1).

DPP4i could inhibit cellular proliferation. This might be due to the inhibition of the promotion of IGF receptor and E2F1 expression induced by DPP4 [102]. Additionally, DPP4i could improve insulin resistance to lower the risks of cancer [103].

However, DPP4i promoted the reprogramming of TME via the ROS–NF-κB-NOD-like receptor family pyrin domain containing 3 axis in breast cancer, which enhanced the expression of matrix metalloproteinase-2 (MMP-2), MMP-9, IL-6, VEGF, intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [104].

The link between DPP4i and cancer metastasis was complex. On the one hand, DPP4 served as an adhesion receptor for fibronectin on some cancer cell membranes, so DPP4i might inhibit invasion by blocking DPP4 [105]. A recent study found that sitagliptin could repress metastasis by lowering fasting blood glucose and inhibiting the TGFβ/Sma and Mad-related protein 2/3 signaling pathway [106]. Furthermore, it was also revealed that sitagliptin could reduce cell adhesion even without acting on DPP4 [107]. The chemokines such as C-X-C motif chemokine ligand 12 (CXCL12) and C-X-C motif chemokine receptor 4 (CXCR4) that increase in DPP4i treatment were likely to induce breast cancer metastasis and EMT [102]. In breast cancer, DPP4i could promote cancer metastasis via promoting the production of ROS, which then activated the nuclear factor erythroid 2-related factor 2–heme oxygenase-1 axis to facilitate cancer metastasis [104].

DPP4i could regulate the immune system. Higher levels of DPP-4/CD26-positive white blood cells (WBCs) were associated with an increased risk of cancer. The DPP4 pathway was known to elevate the levels of cytotoxic granzymes, such as TNFα, interferon γ, and first apoptosis signal ligand [108]. Therefore, inhibiting DPP4 might potentially reduce the risk of cancer. Additionally, CXCL10, a chemokine that promoted the infiltration of T cells and natural killer (NK) cells into cancer tissues, remained in its active form when treated with DPP4i [109].

The impact of DPP4i on inflammation was complex. DPP4i could block DPP4 to reduce the production of TNFα, thereby attenuating inflammation [110]. Furthermore, DPP4i could ease inflammation by inhibiting the NF-κB pathway [111]. However, by activating mitogen-activated protein kinase (MAPK), DPP4i could promote inflammatory responses [112].

Preclinical evidence

In an *in vitro* study of endometrial cancer cell lines, cancer progression could be fueled by DPP4 and DPP4i treatment suppressed cell proliferation [113]. Moreover, DPP4i could also suppress the migration of ovarian and cervical cancer cells [114, 115]. However, DPP4i could facilitate murine breast cancer metastasis in cell line experiments [116] (Table 2).

Clinical evidence

A meta-analysis indicated that the use of DPP4i was associated with the risks of overall neoplasm, rectal neoplasm, and skin neoplasm [117]. Furthermore, DPP4i was associated with improved survival in patients with prostate cancer but not in those with pancreatic or breast cancer [105] (Table 3).

Glucagon-like peptide-1 receptor agonist and cancer

Mechanistic insight

Glucagon-like peptide-1 receptor agonist (GLP-1RA), as a potent anti-diabetic agent, has gained increasing attention in cancer treatment. During GLP-1RA treatment, cellular proliferation and tissue inflammation were inhibited, while apoptosis and the anticancer immune system was promoted (Table 1). The downstream signaling pathways of GLP-1R activation diverged depending on the cellular context. For example, ERK-MAPK was inhibited by GLP-1R-induced cAMP increase in most cells, leading to a decrease in the expression of cyclin A2 and cyclin D1. It also inhibited DNA replication [118]. Furthermore, GLP-1RA could inhibit the PI3K/AKT/mTOR pathway via activating GLP-1R to induce cell cycle arrest. Inhibited cell proliferation would promote cell apoptosis. Meanwhile, GLP-1RA could also induce cellular apoptosis by inhibiting glycogen synthase kinase 3 production and increasing the Bax/Bcl-2 ratio [118].The activation of GLP-1R resulted in the inhibition of the NF-kB signaling pathway, thus reducing the levels of several pro-inflammation factors and impeding chronic inflammation [118, 119].

Recent studies showed that GLP-1RA could improve the function of innate immune cells, especially macrophages. Recent studies indicate that GLP-1RA enhanced innate immunity by promoting macrophage M2 polarization. This effect was mediated through the suppression of the c-Jun N-terminal kinase (JNK) and protein kinase A (PKA) signaling pathways and the activation of STAT3, leading to a shift from M1 to M2 phenotypes [120]. Additionally, GLP-1R expression in human neutrophils and eosinophils downregulated eosinophil-surface activation markers and inflammatory cytokines including IL-4, IL-8, and IL-13 [121], whereas the production of IL-6 could be elevated by GLP-1 via the MAPK pathway [122].

GLP-1RAs exhibited context-dependent effects on cellular proliferation. Activation of GLP-1R by GLP-1RAs suppresses breast cancer cell proliferation, partially through inhibition of the NF-κB signaling pathway [123]. But in rodent thyroid, GLP-1RA could promote C cells proliferation by enhancing hormone synthesis via GLP-1 activation. But it should be noted that long-term high dose liraglutide had no influence on the C cells of nonhuman primates [124, 125]. In an *in vitro* study, 50% of pancreatic neuroendocrine neoplasm cell lines tested expressed GLP-1R, and semaglutide treatment promoted their growth [126]. Notably, in pancreatic neuroendocrine neoplasm cells with low expression of

GLP-1R and high expression of glucagon receptor, semaglutide had no significant effect on proliferation [127]. These complicated outcomes all suggested that the growth-promoting effect of GLP-1RA was specific to GLP-1R-expressing tumors and highlighted the heterogeneity within different cancer subtypes.

Preclinical evidence

Studies showed that GLP-1Rs were present in endocrine cancers, but carcinoma and lymphoma cells did not express GLP-1Rs [128], which indicated that the influence of GLP-1RA on carcinomas, lymphomas, and endocrine cancers could be different. An *in vitro* study found a dose-dependent association between inhibited breast cancer cell proliferation and GLP-1RA [123]. However, the impact of GLP-1RA on medullary thyroid cancer (MTC) remained debated. Semaglutide induced thyroid C-cell proliferation in rats but not in humans or nonhuman primates, as GLP-1Rs were present on rodent C-cells but were largely absent or expressed at low levels on human C-cells [124, 125] (Table 2).

Clinical evidence

Three retrospective clinical studies associated GLP-1RA treatment with lower risks of colorectal cancer [129], HCC [119], and cholangiocarcinoma [130] in patients with T2DM. Additionally, a RCT conducted among patients with T2DM showed lowered incidences of prostate cancer in patients treated with liraglutide [131]. However, no significant association between the risk of pancreatic cancer and GLP-1RA treatment was found [132, 133].

The association between GLP-1RA and thyroid cancer remains inconclusive. Multiple studies consistently reported that GLP-1RA would not increase the risk of thyroid cancer [133–135], while a nested case-control analysis observed an increased risk of all thyroid cancer in patients treated with GLP-1RA [136]. Furthermore, evidence was particularly conflicting for the association between GLP-1RA and the incidence of MTC. A disproportionality analysis suggested a potential risk signal for GLP-1RA [137], whereas a large retrospective cohort study found no such association [108]. Thus, more large-scale, long-term investigations should focus on the impact of GLP-1RA on thyroid cancer, especially MTC (Table 3).

Thiazolidinedione and cancer

Mechanistic insight

Thiazolidinedione, an anti-diabetic medication that activated peroxisome proliferator-activated receptor γ (PPARγ) to improve insulin sensitivity [138], has been explored for its impact on cancer. This medication exerted anti-cancer effects through PPARγ-dependent or independent pathways (Table 1).

PPARγ is a transcription factor and nuclear receptor that promoted adipose differentiation [139]. Activated PPAR-signaling in PPAR-γ agonist treatment led to luminal differentiation in a type of bladder cancer [140]. Activated PPAR-γ led to upregulated phosphatase and tensin homolog, resulting in the promotion of cell apoptosis [141] but the inhibition of inflammation, VEGF expression, and cancer migration [139]. Additionally, activated PPAR-γ increased transcription factor regulatory factor X1 expression to downregulate MMP2 activity, thus leading to the suppression of migration [142]. PPAR-γ activation could change cellular energy state and activate AMPK, which then led to inhibition of the NF-kB pathway, thus resulting in reduction of TGFβ expression, improved inflammation state, and restored immune tonus [143]. AMPK activation also led to the downregulation of mTOR, which induced apoptosis and inhibited cellular proliferation [144]. Thiazolidinedione could inhibit mitochondrial complex I (NADH: ubiquinone oxidoreductase), complex III (ubiquinol: cytochrome c oxidoreductase), and cComplex IV (cytochrome c oxidase) [145] without acting on PPARγ, leading to a higher level of ROS, which promoted apoptosis by inducing ERS.

Preclinical evidence

Pioglitazone exerted dose-dependent preventive effects on *N*-methyl-*N*-nitrosourea-induced breast cancer *in vivo* [146] and showed efficacy against follicular thyroid carcinoma featuring a PAX8–PPARγ fusion oncoprotein [147]. Meanwhile, rosiglitazone could inhibit the progression of premalignant lung cancer [148] and suppress the invasion of basal/squamous bladder cancer cells [140]. It also induced apoptosis, inhibited proliferation and promoted expression of anti-oncogene in HCC cells [141]. Furthermore, the coadministration of rosiglitazone and paclitaxel not only promoted the sensitivity of ovarian cancer cells to paclitaxel, but also induced apoptosis and downregulated cancer stemness [139]. Pioglitazone, rosiglitazone, and WY-14643 all inhibited the survival, migration, and invasion of glioblastoma cells [142] (Table 2).

Clinical evidence

Despite the anti-cancer potential revealed in experiments, clinical studies did not find significant associations between thiazolidinedione and specific cancer types. A meta-analysis reported that thiazolidinedione use was not associated with an increased risk of prostate cancer, compared to thiazolidinedione non-use or use of metformin, insulin secretagogues, insulin, and sulfonylurea [149]. Similarly, a retrospective cohort study including 193 099 patients with diabetes reported that pioglitazone did not increase the risk of bladder cancer [150] (Table 3).

Insulin and cancer

Mechanistic insight

Insulin directly bound to IR or increased serum levels of insulin and IGF-1 to trigger the PI3K/Akt and MAPK pathways, and thus might contribute to promoting cancer cell proliferation, survival, metastasis, and drug resistance [151]. High levels of insulin led to an elevation in the expression of IGF-binding proteins 1 and 2, which facilitated IGF transport in the serum [152]. It was discovered that IGF-binding protein 2 was associated with enhanced non-homologous end joining repair, which promoted DNA damage repair and cell survival [152]. Upon activation, the IR phosphorylated its substrates and the adaptor protein Src homology and collagen domain protein (Shc). This led to the stimulation of downstream pathways, including the PI3K–AKT–mTOR axis and the MAPK pathway, which activated transcription factors such as ETS-like knowledge 1 (Elk1), thereby promoting cell survival, proliferation, and migration [153]. Additionally, insulin might promote cancer progression through chronic inflammation, as insulin resistance fostered a low-grade inflammatory state by upregulating proinflammatory cytokines such as IL-6 and TNFα [154].

Conversely, it was recently discovered that insulin could inhibit cancer growth by activating transcription factor 4, which would promote cell survival or induce apoptosis in different situations of ERS [155] (Table 1).

Preclinical evidence

Insulin exerted dual effects on cancer growth. A study demonstrated that insulin induced cell proliferation and metastasis in human colon cancer cell lines [156]. In contrast, another study

found that insulin inhibited melanoma tumor growth through up-regulating the expression of activating transcription factor 4 [155] (Table 2).

Clinical evidence

Although some clinical studies found a significant association between cancer and serum insulin levels or insulin resistance [157–159], insulin as an anti-diabetic treatment was not associated with overall risk of cancer. A retrospective cohort study found no links between insulin glargine and overall cancer risk or multiple specific cancers, including mouth and pharynx, stomach, non-melanoma skin, breast, cervical, ovarian, and central nervous system cancer [151]. Notably, two meta-analyses revealed that insulin treatment was associated with a reduced risk of breast and prostate cancer but conferred an elevated risk of liver, pancreatic, and colorectal cancer [160, 161]. A retrospective study showed that insulin would not improve overall survival and disease-free survival of patients with pancreatic cancer [162] (Table 3).

Prospects and challenges

There are still many unsolved issues to be addressed in this field. First, it remains to be elucidated whether glycemic control or weight loss could lower the risk of new-onset cancer or improve cancer survival in patients with diabetes. Moreover, the long-term effects of anti-diabetic medications on cancer are still inconclusive. Concerning the current studies, multiple confounders remain to be adjusted, such as the change in blood glucose and body weight along with treatment with anti-diabetic medications, as well as the use of multiple anti-diabetic medications. Therefore, the current evidence derived from real-world studies and *post hoc* analyses should be interpreted with caution and be regarded as exploratory. In the future, more large-scale clinical studies should aim to elucidate the impact of glycemic control or weight loss effects mediated by anti-diabetic medications on cancers in more diverse population. Furthermore, potential biomarkers should be identified to predict the risk of cancer in patients with T2DM. Further mechanistic studies are still needed to explore the molecular pathways underlying the association between diabetes, anti-diabetic medications, and cancer.

Multiple mechanisms have been revealed underlying the associations between anti-diabetic medications and cancer beyond glycemic and body weight control, including modifying cell proliferation, regulating metabolism, alleviating inflammation, inducing autophagy and apoptosis, inhibiting metastasis, modulating intestinal flora, regulating angiogenesis, and EMT. These mechanisms support the potential of these drugs as adjuncts to conventional therapies. Additionally, drug-specific and cancer-type-dependent effects underscore the need for precise treatment strategies. Further investigations are still needed to explore the diverse roles of anti-diabetic medications in cancer.

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Author contributions

Meng Cao (Writing—original draft, Writing—review & editing), Chu Lin (Conceptualization, Writing—original draft, Writing—review & editing), Xiaoling Cai (Conceptualization, Writing—original draft, Writing—review & editing), Fang Lv (Investigation), Wenjia Yang (Investigation), and Linong Ji (Investigation).

Conflict of interest

L.J. has received fees for lecture presentations and for consulting from Merck, Metabasis, AstraZeneca, MSD, Novartis, Roche, Eli Lilly, Sanofi-Aventis, and Takeda. No other support from any organization for the submitted work has been received other than that described. The other authors declare no conflict of interest.

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