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REVIEW

Dual Benefits of Antidiabetic Drugs: Mechanistic Insights into Blood Glucose Control and Cancer Suppression

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Abstract

Background: Antidiabetic medications, including metformin, SGLT2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs), thiazolidinediones (TZDs), and DPP-4 inhibitors, exhibit potential anticancer properties beyond glycemic control. This review synthesizes their mechanisms, evaluates the strength of evidence across cancer types, and addresses key controversies in the field. This review introduces a novel evidence classification framework and discusses emerging implications for combination immunotherapy, offering a structured appraisal of the field. **Materials and Methods:** A narrative review was conducted using PubMed, Scopus, and Google Scholar (January 2015–April 2025). Evidence strength was classified as strong, moderate, suggestive, or conflicting based on study design and consistency of findings. **Results:** Metformin demonstrates moderate observational evidence supporting reduced incidence and mortality in breast, colorectal, and liver cancers, primarily through AMPK/mTOR modulation and insulin/IGF-1 axis suppression. SGLT2 inhibitors show promising preclinical activity in lung and hepatocellular carcinomas via glucose restriction and AMPK activation, though sex-specific adverse effects observed in colorectal cancer models warrant caution. GLP-1 RAs exhibit moderate preclinical and observational support in breast and colorectal cancers, with clinical trials confirming no excess cancer risk. TZDs present a paradox: preclinical models suggest possible cancer-promotive stromal effects, while epidemiological studies indicate neutral or protective outcomes, highlighting their context-dependent actions. DPP-4 inhibitors show conflicting evidence: although preclinical studies raised concerns about pancreatic safety, meta-analyses of randomized trials show no increased cancer risk. A new critical appraisal table reconciles these discrepancies. **Conclusion:** Antidiabetic drugs exert anticancer effects mainly through indirect metabolic and immunomodulatory mechanisms rather than direct cytotoxicity. The strength of evidence varies substantially across drug classes and cancer types, with metformin having the broadest support. Key limitations include residual confounding, preclinical-clinical translational gaps, and insufficient long-term data. Future research should prioritize cancer-specific trials, combination immunotherapy strategies, and mechanistic studies in relevant human models. In this review, we propose a structured evidence-classification framework integrating preclinical, epidemiological, and clinical trial data to comparatively evaluate the anticancer potential of major antidiabetic drug classes. In addition, we critically assess emerging immunomodulatory mechanisms and discuss their translational relevance in the context of cancer immunotherapy.

Keywords: Antidiabetic drug- Cancer therapy- Metformin- SGLT2 inhibitors- GLP-1 agonists- Glucose metabolism

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Introduction

Glucose metabolism is a fundamental aspect of cancer biology, as recognized by the Warburg effect, the dependence of cancer cells on aerobic glycolysis even in the presence of sufficient oxygen [1].

Antidiabetic medications, initially formulated to regulate blood glucose levels in individuals with diabetes, are crucial for metabolic control via various mechanisms, including the reduction of hepatic glucose production (metformin) [2], inhibition of renal glucose reabsorption (SGLT2 inhibitors like dapagliflozin and empagliflozin) [3], enhancement of glucose-dependent insulin secretion (GLP-1 agonists such as liraglutide and exenatide) [4], activation of the PPARγ receptor (thiazolidinediones like pioglitazone) [5], and elevation of GLP-1 levels through DPP-4 enzyme inhibition (DPP-4 inhibitors such as sitagliptin) [6]. However, growing evidence suggests that these drugs may also exert anticancer effects beyond their primary glycemic purpose [7].

These effects are mediated through modulation of central growth-regulatory and metabolic pathways, attenuation of chronic inflammation, and disruption of cancer-associated glucose metabolism. For example, metformin has been shown to reduce the incidence of liver and breast cancer by inhibiting mTOR and increasing insulin sensitivity. At the same time, SGLT2 inhibitors disrupt the metabolism of glucose-dependent cancer cells by inducing glucose restriction [8].

This dual potential positions the repurposing of these inexpensive and well-tolerated drugs as a promising therapeutic strategy in oncology, with the potential to revolutionize treatment approaches [8]. Despite these promising findings, significant challenges still exist. Study results frequently contradict each other; for instance, the anticancer effects of thiazolidinediones in breast and prostate cancer remain inconclusive [9].

Additionally, the limited specificity for cancer cells, the requirement for doses exceeding the therapeutic range for diabetes, and methodological constraints like small sample sizes, inadequate follow-up, and poor adjustment for confounding factors such as obesity and diet have restricted their generalizability and broader clinical application [10]. Additionally, the evidence for certain drugs, such as DPP-4 inhibitors, remains limited and preliminary [11].

Figure 1 provides a conceptual overview of the shared and distinct anticancer mechanisms of major antidiabetic drug classes. While all five classes converge on core pathways such as glucose metabolism inhibition and inflammation reduction, their primary molecular targets and downstream effects vary significantly, influencing their cancer-type-specific efficacy and clinical translation potential.

Table 1 summarizes the distinct mechanistic pathways through which major classes of antidiabetic drugs may influence cancer biology. Understanding these mechanisms is critical for interpreting both preclinical and clinical findings, as the same drug may exert cancer-suppressive or -promoting effects depending on cellular context, signaling pathway engagement, and tissue-specific responses.

Although various antidiabetic drugs target metabolic stress pathways such as AMPK and mTOR signaling, their upstream targets and main mechanisms of action vary greatly.

Metformin primarily induces mitochondrial energetic stress, leading to AMPK activation; SGLT2 inhibitors reduce glucose availability with effects that depend on the context; GLP-1 receptor agonists activate incretin-mediated cAMP–PKA pathways; thiazolidinediones modulate transcriptional programs through PPAR-γ; and DPP-4 inhibitors indirectly extend endogenous GLP-1 activity. Recognizing these mechanistic differences is essential for accurately evaluating their anticancer potential. While the activation of AMPK and inhibition of mTOR play roles in the anticancer effects of some antidiabetic drugs, the underlying mechanisms differ considerably among drug classes (Table 1).

Despite the rapidly growing body of preclinical, epidemiological, and clinical evidence suggesting anticancer effects of antidiabetic drugs, the existing literature remains characterized by several critical gaps. Prior reviews have largely focused on individual drug classes or specific cancer types, with limited efforts to systematically compare the strength and translational relevance of evidence across different antidiabetic agents.

Moreover, the links between reported molecular mechanisms and clinically meaningful outcomes, particularly in terms of patient stratification and trial design, have not been sufficiently elucidated. Importantly, the potential role of antidiabetic drugs in modulating the tumor microenvironment and shaping responses in the era of cancer immunotherapy has not yet been comprehensively examined using a structured evidence-based framework.

To address these gaps, the present review applies a systematic evidence-classification approach to integrate mechanistic insights with clinical data and to delineate priorities for future translational and clinical research.

This schematic summarizes the major antidiabetic drug classes (Biguanides, TZDs, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors) and their proposed anticancer mechanisms. These include inhibition of glucose metabolism, suppression of mTOR/PI3K/Akt signaling, reduction of inflammation, induction of apoptosis or cell cycle arrest, and activation of AMPK. While each drug class may preferentially target specific pathways, collectively they modulate key metabolic and proliferative signals relevant to cancer proliferation.

Materials and Methods

This narrative review aims to consolidate current evidence regarding the anticancer effects of antidiabetic medications, including metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitors (e.g., dapagliflozin and empagliflozin), glucagon-like peptide-1 (GLP-1) receptor agonists (including liraglutide and exenatide), thiazolidinediones (e.g., pioglitazone), and dipeptidyl

peptidase-4 (DPP-4) inhibitors (such as sitagliptin).

Relevant literature was collected from peer-reviewed databases, including PubMed, Scopus, and Google Scholar, focusing on studies published between January 2015 and April 2025 to ensure up-to-date coverage and reflect recent developments.

Results and Discussion

In this section, epidemiological and observational data are distinguished from evidence derived from in vitro and preclinical models. We acknowledge the potential for publication bias, wherein positive preclinical findings may be reported more frequently than negative results.

To ensure a balanced synthesis, meta-analyses are prioritized over individual studies when available.

Evidence Classification Framework

To ensure consistency in interpreting the available data, we employ the following evidence classification terminology throughout this review:

• Evidence Classification: The following terms are used to indicate the strength of evidence:

• Strong evidence: Supported by multiple randomized controlled trials (RCTs), meta-analyses, or consistent high-quality observational studies.

• Moderate evidence: Supported by observational studies with mechanistic validation, or by robust preclinical data.

• Suggestive evidence: Primarily based on preclinical studies or limited human data.

• Conflicting evidence: Inconsistent findings across study types.

Biguanide (Metformin)

In 2005, Evans et al. first documented the anticancer potential of metformin, observing a reduced cancer incidence among diabetic patients receiving the drug [12].

Subsequent observational studies and meta-analyses support that metformin lowers cancer incidence and improves outcomes in both diabetic and non-diabetic populations [13, 14].

While some trials have failed to confirm this benefit, limitations such as small sample sizes, short follow-up, and residual confounding (e.g., obesity, diet) preclude definitive conclusions [15, 16].

Metformin's preventive effects extend to precancerous conditions in non-diabetic individuals, inhibiting oral tumor progression [17] and colorectal adenoma recurrence [18].

These benefits are linked to its modulation of the insulin/IGF-1 axis and key aging-related pathways, including SIRT1 activation and NF-κB suppression. However, its impact on oxidative stress and cellular aging in cancer contexts can be paradoxical [19, 20].

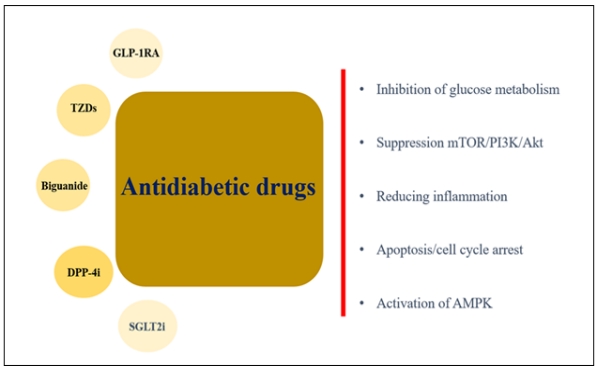

Figure 1- Mechanistic Overview of Antidiabetic Drugs in Cancer Modulation

Breast cancer

Breast cancer (BC) ranks among the most prevalent cancers globally and was responsible for the highest number of cases and deaths in 2020 [19]. Studies have shown that long-term use of metformin reduces the risk of breast cancer in women with diabetes and reduces the risk of ER-positive cancer [21].

This clinical benefit is mechanistically supported by metformin's activation of AMPK and subsequent inhibition of the mTOR pathway, which converges on key tumor-promoting processes. Specifically, AMPK/mTOR inhibition leads to (1) cell cycle arrest (e.g., G1 arrest in combination with fulvestrant), (2) reduced angiogenesis via suppression of the HER2/HIF-1α/VEGF axis, and (3) downregulation of pro-inflammatory mediators like COX-2 [22, 23].

Synergistic effects with fulvestrant or paclitaxel involve cell cycle arrest at G1 or G2/M phases, respectively. Metformin, when combined with fulvestrant, arrests the cell cycle in G1 in ER-positive cancer [21, 24, 25].

Collectively, these actions dampen tumor proliferation and metastatic potential, providing a plausible biological pathway for the observed reduction in cancer incidence and mortality in epidemiological studies.

Colorectal cancer (CRC)

Colorectal cancer (CRC) is the third most prevalent cancer globally and ranks as the second leading cause of cancer-related deaths [26].

Metformin is effective as adjuvant therapy in CRC,

Table 1. Distinct Mechanistic Pathways of Antidiabetic Drugs in Cancer Therapy

Drug Class	Primary Mechanism	AMPK/mTOR Role
Metformin	Mitochondrial dysfunction	Direct AMPK activation, mTOR inhibition
SGLT2 inhibitors	Glucose uptake inhibition	AMPK is indirect, cell-type dependent
GLP-1 RAs	Activation of cAMP-PKA signaling	AMPK secondary
TZDs	PPAR-γ transcriptional control	No direct AMPK
DPP-4 inhibitors	GLP-1 prolongation	AMPK not direct

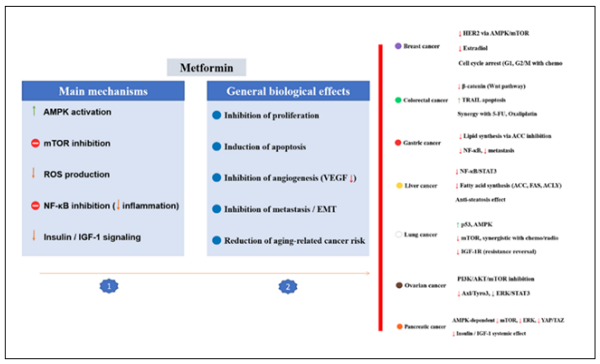

Figure 2. Multimodal Anticancer Mechanisms of Metformin Across Different Cancer Types. Metformin exerts its anticancer effects primarily through AMPK activation, leading to downstream inhibition of mTOR signaling, reduction of ROS production, suppression of NF-κB-mediated inflammation, and modulation of the insulin/IGF-1 axis. These pathways collectively contribute to key biological outcomes such as inhibition of proliferation, induction of apoptosis, suppression of angiogenesis and metastasis, and reduction of cancer risk associated with metabolic aging. The figure also highlights cancer-specific mechanisms, including modulation of HER2 and estrogen signaling in breast cancer, β-catenin/Wnt pathway in colorectal cancer, lipid synthesis in liver cancer, p53 and IGF-1R in lung cancer, and AMPK/mTOR/ERK/YAP pathways in pancreatic cancer. Synergistic interactions with conventional chemotherapy and radiotherapy are indicated where relevant.

reducing proliferation, stemness, and metastasis [27]. In ACF-positive mice, metformin treatment led to a reduction in lesion numbers and suppressed the expression of S6 kinase, phosphorylated mTOR (p-mTOR), and S6 protein [28].

Metformin promotes apoptosis by modulating Bcl-2 family proteins and sensitizes cells to TRAIL-induced death. It also potentiates the effect of cisplatin by activating the PI3K/Akt pathway [29]. In resistant CT-26 cells, it improves angiogenesis in combination with cyclophosphamide [30].

AMPK activation and mTOR inhibition by metformin reduce cellular proliferation and enhance the response to chemotherapy, as reported in observational studies, leading to decreased disease recurrence and increased survival. Simultaneously, reductions in insulin and IGF-1 levels inhibit PI3K/Akt pathway activation. Collectively, these mechanisms provide a compelling biological rationale for the improved clinical outcomes in patients treated with metformin [2, 10, 27].

Gastric cancer

Gastric cancer (GC) ranks among the most prevalent malignancies globally and remains a leading cause of cancer-related mortality [31, 32].

Epidemiological data indicate that metformin use improves prognosis and reduces recurrence after gastrectomy in diabetic patients with gastric adenocarcinoma [31]. In vitro, it inhibits GC cell proliferation by decreasing p-mTOR and p-AKT levels, inducing intrinsic apoptosis [33]. Combined with cisplatin, metformin slows metastasis, an effect linked to the suppression of NF-κB signaling [34, 35].

In summary, Metformin enhances gastric cancer outcomes by activating AMPK-driven suppression of mTOR/AKT signaling and promoting intrinsic apoptosis. Its synergy with cisplatin, through NF-κB inhibition, decreases metastatic potential. These effects are linked to lower recurrence rates and better survival after gastrectomy.

Liver cancer

In type 2 diabetes, metformin use is associated with a 2–3-fold lower risk of hepatocellular carcinoma (HCC) [36].

It exerts protective effects by inhibiting NF-κB/STAT3-driven inflammation and IL-6 production [37]. Furthermore, metformin targets hepatic lipogenesis by downregulating key enzymes (ACC, FAS, ACLY), thereby reducing the steatotic microenvironment conducive to HCC [38].

Metformin protects against hepatocellular carcinoma through AMPK-mediated mTOR inhibition and suppression of NF-κB/STAT3 inflammation. Simultaneous modulation of hepatic lipogenesis via ACC/FAS/ACLY downregulation reduces steatosis-driven carcinogenesis, explaining the reduced HCC risk in clinical studies.

Lung cancer

Recent studies have shown that metformin reduces the risk of lung cancer and improves progression-free survival in advanced lung adenocarcinoma [39].

Metformin may reduce lung cancer risk and improve progression-free survival in advanced lung adenocarcinoma [40]. Preclinical studies show it enhances tumor response to radiation and chemotherapy, partly through p53 upregulation [41].

While metformin can synergize with cisplatin or reverse crizotinib resistance, a meta-analysis found no overall survival benefit in diabetic NSCLC patients, highlighting inconsistent clinical translation [42].

In summary, AMPK activation and mTOR inhibition by metformin reduce cancer cell proliferation and enhance tumor response to radiation and chemotherapy, which has been reported in clinical studies as improved progression-free survival in advanced lung adenocarcinoma. Simultaneously, metformin's systemic reduction of insulin and IGF-1 levels attenuates PI3K/Akt pathway activation in non-small cell lung cancer (NSCLC).

Ovarian cancer

Long-term metformin use is linked to reduced mortality and improved overall survival in ovarian cancer patients [43].

It inhibits growth by inducing G2/M cell cycle arrest and downregulating tyrosine kinase receptors (Axl, Tyro3) involved in survival and chemoresistance [44, 45].

Metformin also impairs metastatic potential by reducing angiogenesis, cancer cell adhesion, and macrophage infiltration in the tumor microenvironment [44, 46].

Collectively, Metformin improves ovarian cancer outcomes through AMPK-driven cell-cycle arrest and attenuation of Axl/Tyro3-mediated chemoresistance. Simultaneously lowering insulin/IGF-1 and remodeling the tumor microenvironment, it delays recurrence and enhances platinum sensitivity, aligning with observed survival benefits in clinical cohorts.

Pancreatic Cancer

The evidence for metformin in pancreatic ductal adenocarcinoma (PDAC) remains debated. A large meta-analysis suggested a 46% risk reduction associated with its use [47].

Direct mechanisms include AMPK-mediated inhibition of KRAS-downstream effectors (PI3K/AKT, ERK, YAP/TAZ) and induction of apoptosis [48, 49]. Indirect effects involve lowering insulin/IGF-1 levels and modulating the gut microbiome [50].

As illustrated in Figure 2, metformin's multimodal action supports its potential as an adjunctive therapy in various cancers, particularly those driven by metabolic dysregulation or hyperinsulinemia.

Collectively, Metformin influences pancreatic cancer by suppressing KRAS effector pathways (PI3K/AKT, ERK, YAP/TAZ) through AMPK activation. Systemic insulin/IGF 1 reduction further modulates the tumor microenvironment. These mechanisms provide a rationale for the potential protective effects observed in meta-analyses.

SGLT2 inhibitor drug

Beyond glycemic control, SGLT2 inhibitors exert systemic effects with potential relevance to cancer biology. These include weight loss, reduced visceral adiposity, and a metabolic shift toward ketogenesis [51, 52].

Crucially, SGLT2 inhibitors possess documented antioxidant and anti-inflammatory properties, such as reducing reactive oxygen species and pro-inflammatory cytokine release from macrophages [53]. These mechanisms may contribute to their emerging anticancer potential, as discussed below.

Lung cancer

Preclinical studies suggest SGLT2 inhibitors hold promise in lung adenocarcinoma (LUAD). Canagliflozin reduced cancer proliferation and improved survival in SGLT2-expressing models, an effect linked to direct inhibition of glucose uptake [54].

However, prolonged treatment may promote tumor dedifferentiation via a glucose-deprivation-induced epigenetic mechanism involving α-ketoglutarate and EZH2 dysregulation [55].

Intriguingly, canagliflozin also shows efficacy in SGLT2-negative squamous cell carcinoma and can potentiate radiotherapy, indicating off-target or context-dependent mechanisms.

Collectively, SGLT2 inhibitors impair glucose uptake in lung adenocarcinoma, inducing AMPK-dependent metabolic stress and HIF-1α destabilization. This dual action suppresses tumor growth and enhances radiotherapy sensitivity, offering a mechanistic basis for their emerging role in glucose-dependent thoracic malignancies [56].

Breast cancer

SGLT2 inhibitors can suppress the in vivo proliferation of estrogen-dependent and triple-negative breast cancer cells[57, 58]. The impact on triple-negative breast cancer is proposed to be systemic through the reduction of circulating insulin levels [59, 60].

SGLT2 inhibitors reduce breast cancer proliferation by limiting glucose availability and lowering systemic insulin levels. This metabolic modulation attenuates PI3K/Akt signaling and downstream proliferative pathways, particularly in insulin-sensitive and triple-negative subtypes. These mechanisms support their potential role in metabolically driven breast malignancies [58].

Hepatocellular Carcinoma

In hepatocellular carcinoma (HCC), SGLT2 inhibitors demonstrate preclinical efficacy. Canagliflozin suppresses cancer proliferation and extends survival in xenograft models by inhibiting β-catenin signaling, proliferation, and angiogenesis [61].

This effect was absent in an SGLT2-negative cell line, indicating a direct impact of SGLT2 inhibitors on the tumor [62]. SGLT2 inhibitors have also been proposed to reduce hepatocarcinogenesis in models of metabolic dysfunction-associated steatohepatitis (MASH) [63].

Notably, combination therapy with empagliflozin and metformin shows synergistic benefits, improving survival and reducing disease markers in a carcinogen-induced HCC model [64].

SGLT2 inhibitors suppress hepatocellular carcinoma progression through direct inhibition of tumor glucose uptake and β-catenin signaling. By reducing hepatic steatosis and downregulating Akt/HIF 1α activity, they disrupt the metabolic tumor microenvironment. These mechanisms position SGLT2 inhibitors as potential adjuncts in metabolic dysfunction-associated HCC.

Pancreatic cancer

The effectiveness of SGLT2 inhibitors in pancreatic cancer has solely been evaluated in xenograft models [65, 66].

SGLT2 inhibitors demonstrate preclinical efficacy in pancreatic cancer by suppressing glucose transporter-1 (GLUT-1) expression and lactate dehydrogenase A activity, thereby disrupting glycolytic metabolism. This metabolic interference inhibits tumor growth and may enhance chemosensitivity in pancreatic ductal adenocarcinoma models [66].

Prostate cancer

In prostate cancer, canagliflozin was shown to suppress cancer proliferation and improve survival in mice using an androgen-independent xenograft model, demonstrating efficacy both as a single agent and when combined with 5 Gy radiotherapy [67].

SGLT2 inhibitors suppress prostate cancer growth by inhibiting glycolysis and HIF-1α stabilization via the PI3K/

Akt/mTOR axis. This metabolic interference enhances radiotherapy sensitivity and reduces tumor proliferation in androgen-independent models, supporting their potential role in advanced prostate cancer management [68].

Colorectal cancer

Unexpectedly, a sex-specific adverse effect was observed in a preclinical model of colorectal cancer. Female mice fed a canagliflozin-enriched diet showed an increased intestinal adenoma burden.

This effect may be attributed to high intraluminal drug concentrations inhibiting intestinal SGLT1, thereby elevating luminal glucose levels that subsequently fuel adenoma growth.

This critical finding underscores the potential limitations of translating preclinical results directly to humans and highlights the necessity for sex-specific analyses and cautious interpretation when evaluating SGLT2 inhibitors for oncology applications [69].

Emerging evidence suggests that the effects of SGLT2 inhibitors in colorectal cancer (CRC) may be context-dependent and potentially influenced by biological sex, highlighting the need for cautious interpretation and stratified clinical investigation. Preclinical studies have demonstrated that pharmacological inhibition of SGLT2 can alter tumor glucose availability and metabolic signaling pathways in colorectal tumor models; however, divergent outcomes have been reported between male and female experimental systems.

In particular, sex-specific differences in intestinal glucose handling, hormonal regulation, and tumor metabolism have been proposed as potential modifiers of SGLT2 inhibitor–mediated effects in CRC. These findings are clinically relevant, as they raise the possibility that metabolic interventions targeting glucose transport may not uniformly confer anticancer benefits across patient subgroups [70, 71].

Importantly, current human data remain limited and largely observational, underscoring the need for biomarker-driven and sex-stratified clinical trials to clarify both efficacy and safety signals before broader oncologic application of SGLT2 inhibitors in colorectal cancer can be justified [8, 72].

Mechanistic Insights from In Vitro Studies on SGLT2 Inhibitors

In vitro investigations reveal that SGLT2 inhibitors exert anticancer effects through diverse metabolic disruptions. A key mechanism involves the inhibition of mitochondrial complex I, leading to AMPK activation and subsequent mTOR pathway suppression, as demonstrated by canagliflozin in prostate, lung, liver, and breast cancer cells [73].

In lung, colon, prostate, and pancreatic cancers, SGLT2 inhibitors, such as canagliflozin and dapagliflozin, can lower cell proliferation and enhance the effect of doxorubicin [74].

In lung cancer, canagliflozin slows cell proliferation in vitro but not in vivo, possibly via an off-target effect on mutant EGFR[75]. This metabolic interference halts cell cycle progression and reduces viability, particularly in breast cancer models [76].

It also boosts doxorubicin's effect, potentially reducing its heart-related side effects [77-79].

Beyond core metabolism, SGLT2 inhibitors target oncogenic signaling hubs. In hepatocellular carcinoma (HCC), canagliflozin suppresses growth by downregulating Akt and HIF-1α activity [80].

Notably, efficacy in certain models, like HCC, appears dependent on SGLT2 expression, though off-target effects via GLUT inhibition may occur at high concentrations [61, 62].

SGLT2 inhibitors also aid in combination therapies, reducing cisplatin resistance or enhancing the effects of radiation [81]. In prostate cancer, it inhibits glycolysis and HIF-1α via the PI3K/Akt/mTOR axis [67, 68].

A significant translational promise lies in their role as chemosensitizers and radiosensitizers. SGLT2 inhibitors enhance the efficacy of doxorubicin in several cancer types and can overcome cisplatin resistance or potentiate radiotherapy [74, 81, 82].

Notably, some in vitro effects, such as canagliflozin's activity in certain lung cancer models, may involve off-target actions (e.g., on mutant EGFR), highlighting a potential disconnect from in vivo outcomes that warrants further investigation [75].

GLP-1 receptor agonists (GLP-1 RAs) drug

Beyond their established metabolic and cardiovascular benefits, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exhibit properties directly relevant to oncology.

Their cardioprotective action, demonstrated by reduced adverse cardiovascular events in high-risk patients[83-85], is partly mediated through the reduction of systemic inflammation, a key driver of carcinogenesis [86, 87].

Complementing this indirect mechanism, direct preclinical evidence confirms that GLP-1R activation can inhibit cancer cell proliferation and induce apoptosis [88].

Breast cancer

Preclinical studies on GLP-1 receptor agonists (GLP-1 RAs) in breast cancer yield mixed but insightful findings. In vitro and in vivo, exenatide-4 inhibits breast cancer cell proliferation by blocking NF-κB nuclear translocation and activity, an effect mediated by the GLP-1 receptor (GLP-1R) [89].

Liraglutide also demonstrates anticancer effects, altering gene activity and reducing cell proliferation and motility; in mouse models, it reduces tumor proliferation both alone and in combination with chemotherapies [90]. However, context is critical. In triple-negative breast cancer (TNBC) models, high-dose liraglutide may paradoxically promote growth via pathways such as NOX4/ROS/VEGF [91].

Reassuringly, this preclinical complexity has not translated into increased risk at the population level. Large-scale clinical data and meta-analyses indicate no increased breast cancer risk associated with GLP-1 RA use in diabetic populations [92, 93].

Collectively, GLP-1RAs modulate breast cancer biology through receptor-mediated suppression of NF-κB and cAMP/PKA pathways. While preclinical models show context-dependent effects, clinical data confirm no elevated breast cancer risk, reflecting their overall metabolic safety and potential indirect benefits in obesity-associated malignancies.

Prostate cancer

Research indicates that GLP-1 receptor (GLP-1R) activation exerts inhibitory effects on prostate cancer. The receptor is expressed in prostate tumor tissue, and its agonism suppresses growth both in vitro and in vivo.

Exenatide-4 (Ex-4) reduces the proliferation of prostate cancer cell lines (notably LNCaP) and inhibits tumor growth in mouse xenograft models, an effect mediated through the cAMP-PKA pathway [94].

Liraglutide also demonstrates anticancer activity, slowing LNCaP cell proliferation and inducing apoptosis via p38 MAPK signaling [88]. Furthermore, it acts as a chemosensitizer; combined with docetaxel, liraglutide enhances cell cycle arrest and apoptosis through the ERK/MAPK and PI3K/Akt pathways, suggesting a potential to improve therapeutic efficacy [95].

Supporting the therapeutic relevance of this target, forced overexpression of GLP-1R in prostate cancer cells (ALVA-41) significantly attenuates proliferation in vitro and in vivo by inducing cell cycle arrest. These collective findings position GLP-1R as a promising molecular target in prostate cancer therapy [96].

Collectively, GLP-1R activation inhibits prostate cancer growth via cAMP-PKA and p38 MAPK signaling, inducing cell-cycle arrest and apoptosis. The receptor's expression in tumor tissue and its ability to enhance docetaxel efficacy position GLP-1R as a promising therapeutic target in advanced prostate cancer.

Pancreatic cancer

The epidemiological safety profile of GLP-1 receptor agonists (GLP-1 RAs) regarding pancreatic cancer risk appears reassuring, with recent reviews and meta-analyses finding no clear association[97].

Preclinically, their role is complex. While human pancreatic tumors often exhibit reduced or absent GLP-1R expression a feature correlating with poorer prognosis pharmacological activation of the receptor demonstrates anticancer effects [98]. Liraglutide inhibits pancreatic cancer cell proliferation primarily by blocking the PI3K/Akt pathway [98].

Furthermore, GLP-1R signaling via cAMP leads to the suppression of Akt and ERK1/2 activity, resulting in growth inhibition and apoptosis [99].

A promising therapeutic application lies in overcoming chemoresistance; liraglutide modulates the NF-κB pathway and the efflux transporter ABCG2, thereby restoring sensitivity to gemcitabine in resistant cell lines and animal models [100].

These mechanistic insights suggest potential utility in pancreatic cancer management, particularly in modulating treatment response, despite the endogenous downregulation of its target receptor in advanced disease.

Colorectal cancer

Preclinical research indicates that GLP-1 receptor (GLP-1R) activation exerts inhibitory effects on colorectal cancer (CRC) cells through multiple pathways.

In murine CT26 colon carcinoma cells, GLP-1R agonism reduces proliferation and survival by elevating intracellular cAMP and inhibiting the activity of glycogen synthase kinase 3β (GSK-3β) and ERK1/2. Furthermore, it enhances the cytotoxic effect of irinotecan, a topoisomerase I inhibitor [101].

Liraglutide, a clinically used GLP-1 RA, suppresses CRC cell proliferation, migration, and invasion while inducing apoptosis, primarily by inhibiting the PI3K/Akt/mTOR signaling axis[102]. These effects are associated with the downregulation of key proliferative (cyclin D1) and invasive (MMP-11) proteins [102].

Interestingly, GLP-1R-mediated signaling via the SIRT3 pathway has also been shown to inhibit survival and invasion in other malignancies, such as glioma, suggesting potential cross-cancer applicability of its mechanism [103].

GLP-1 Receptor Agonists and Gynecological Cancers

Emerging preclinical evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may hold therapeutic potential in gynecological cancers. In endometrial cancer, GLP-1R activation inhibits the growth of cancer cell lines via the cAMP/PKA pathway [104].

Liraglutide exerts anticancer effects, which appear to be modulated by hormone receptor status and autophagy-related mechanisms [105]. In ovarian cancer, the GLP-1R agonist exendin-4 (Ex-4) suppresses proliferation, migration, and invasion while inducing apoptosis through inhibition of the PI3K/Akt pathway [106].

Ex-4 also modulates the expression of key metastasis-related enzymes (e.g., MMP-2, MMP-9, TIMPs) and impairs endothelial cell survival. In cervical cancer associated with type 2 diabetes, GLP-1 RAs may indirectly hinder tumor progression by ameliorating hyperglycemia, a known tumor-promoting factor [107, 108].

These findings highlight the diverse mechanisms both direct (receptor-mediated) and indirect (metabolic) through which GLP-1 RAs may influence gynecological malignancies.

Thiazolidinedione

Thiazolidinediones (TZDs) are oral antidiabetic drugs that act as ligands for PPAR-α and PPAR-γ, nuclear receptors that regulate glucose and lipid metabolism, inflammation, and cell proliferation [109].

TZDs are used therapeutically to treat type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NASH), and several types of cancer [110, 111].

Breast cancer

Studies show that pioglitazone, a drug, does not significantly increase breast cancer (BC) risk [112].

In BC cells, levels of PPAR-γ, a protein, are lower,

and its gene promoter is more methylated, suggesting that it may contribute to worsening cancer proliferation. However, in triple-negative breast cancer (TNBC), pioglitazone helps when used with doxorubicin by reducing cancer cell movement and invasiveness, a common problem with doxorubicin alone. It also boosts the cell-killing effects of cisplatin in lab tests [113, 114].

PPAR-γ plays a crucial role in regulating processes such as activating the CXCR4 and CXCR7 genes, inhibiting eIF2α, and controlling glucose metabolism, all of which impact cancer cell migration [82, 115]. Even with these findings, pioglitazone is not yet used in clinical treatments for BC [116].

First, the differential impact of PPAR-γ activation must be interpreted in a cell-type–specific manner. In vitro studies have demonstrated that activation of PPAR-γ in cancer-associated stromal cells, including fibroblasts and adipocytes, can promote proliferative and pro-tumorigenic signaling pathways that support breast cancer progression [117].

In contrast, in vivo TZD exposure is associated with systemic metabolic improvements, including weight reduction, decreased circulating insulin levels, and attenuation of chronic inflammation, which are known to suppress tumor-promoting metabolic signaling [118].

The clinical outcome observed in population-based studies likely reflects the net balance between these localized stromal effects and broader systemic metabolic benefits.

Second, dosing considerations represent a critical determinant of translational relevance. Many in vitro investigations employ supraphysiological concentrations of pioglitazone, often in the micromolar range, to elicit phenotypic effects on stromal or cancer cells.

However, standard therapeutic dosing for diabetes management results in substantially lower plasma and tissue concentrations, raising concerns regarding the physiological applicability of in vitro tumor-promotive findings to clinical contexts [119].

Third, differences in tumor microenvironment complexity further contribute to the discordance between experimental and clinical observations. Murine models and cell culture systems represent simplified tumor environments, whereas human breast tumors exhibit extensive immune cell infiltration, pronounced stromal heterogeneity, and complex paracrine signaling networks.

These features may attenuate or counterbalance pro-tumor stromal signaling induced by PPAR-γ activation in experimental systems [120].

Finally, epidemiological evidence provides the most clinically relevant framework for risk assessment. A comprehensive meta-analysis by Tseng (2022), encompassing a large diabetic population, demonstrated no significant increase in breast cancer risk associated with TZD use [112].

This population-level evidence takes precedence over isolated preclinical observations when informing clinical decision-making. Nevertheless, the observed mechanistic discrepancies underscore the need for further studies using human-derived tumor models to clarify the context-dependent effects of PPAR-γ modulation in breast cancer [9].

Overall, the dual effects of TZDs highlight the importance of integrating mechanistic, preclinical, and clinical evidence when evaluating cancer risk.

Lung cancer

The role of PPAR-γ agonists like pioglitazone in lung cancer is complex and context-dependent. In preclinical models, pioglitazone inhibits NSCLC growth and metastasis by modulating proliferative and inflammatory pathways, including the suppression of prostaglandin E2 (PGE2). It may also overcome resistance to EGFR inhibitors by upregulating PTEN [121].

However, these anticancer effects contrast with chemoprevention trials, where pioglitazone showed minimal efficacy in high-risk individuals [122].

Furthermore, combining pioglitazone with metformin did not enhance prevention in animal models, while its pairing with celecoxib demonstrated synergistic anticancer activity [123]. Notably, PPAR-γ activation can paradoxically promote tumorigenesis in certain murine models, underscoring its dual and microenvironment-dependent nature [124, 125].

In summary, TZDs modulate lung cancer progression through PPAR-γ-mediated transcriptional regulation, suppressing prostaglandin E2 (PGE2) and inflammatory pathways. While preclinical models demonstrate reduced NSCLC growth and restored PTEN expression, clinical chemoprevention trials show limited efficacy, highlighting the context-dependent nature of PPAR-γ activation in lung oncogenesis.

Liver cancer

Research suggests that pioglitazone, a type 2 diabetes drug (TZD), may protect against liver cancer, according to a meta-analysis [126]. Rodent studies also show it prevents liver fibrosis and cancer after cirrhosis [127].

Preclinical tests highlight pioglitazone's ability to fight cancer. In hepatocellular carcinoma, high levels of the receptor for advanced glycation end products (RAGE) signal worse outcomes, like increased invasion. Pioglitazone lowers RAGE, along with HMGB1, NF-κB, and p38 MAPK, thereby reducing cancer cell proliferation, spread, and invasion [128].

Additionally, pioglitazone causes changes in lipid metabolism, leading to the death of HepG2 liver cancer cells under low-oxygen conditions due to oxidative stress [129].

In summary, TZDs exert protective effects in hepatocellular carcinoma through PPAR-γ-mediated suppression of RAGE/NF-κB signaling and modulation of hepatic lipid metabolism. These actions attenuate fibrosis-driven carcinogenesis and reduce oxidative stress in steatotic microenvironments, aligning with clinical observations of lowered HCC risk in diabetic patients receiving pioglitazone.

Colorectal cancer

Research indicates that thiazolidinediones (TZDs), such as pioglitazone, reduce the risk of colorectal cancer in patients with type 2 diabetes, according to a meta-analysis involving approximately 2.5 million individuals [130].

In vitro experiments using pioglitazone and its derivative, Δ2-pioglitazone, on HCT116 and HT29 cells inhibited proliferation and promoted cellular differentiation. Pioglitazone arrested the cell cycle in the S phase, whereas Δ2-pioglitazone induced a G0/G1 phase arrest [131].

In vivo rodent studies employing HT29 and SW480 cell lines demonstrated that pioglitazone suppressed tumor growth and liver metastasis [130]. Moreover, pioglitazone enhances immunotherapy efficacy by promoting PPAR-γ-mediated degradation of PD-L1, a mechanism similarly observed in lung cancer [132, 133].

It also aids immunotherapy by breaking down PD-L1 through PPAR-γ, a process boosted by pioglitazone, similar to its effect in lung cancer. To improve the low solubility of pioglitazone, combining it with capecitabine, a common colorectal cancer drug in nanoparticle form, increased its availability and enhanced its ability to kill HT29 and HCT119 cells [134].

Pancreatic cancer

The evidence regarding pioglitazone, a diabetes medication, and its association with pancreatic cancer risk is mixed, leaving its true impact unclear [135].

However, research has shown that DPP-4 inhibitors exert anticancer effects in pancreatic cancer cell lines such as Capan-1, AsPC-1, BxPC-3, PANC-1, and MIA PaCa-2. In rodent studies using BxPC-3 cells, pioglitazone reduced tumor growth and lymph node metastasis.

It also enhances the efficacy of gemcitabine, a standard chemotherapy agent, by inhibiting the NF-κB pathway, inducing apoptosis, and potentiating the action of HDAC inhibitors. Pioglitazone shows promise in slowing cancer progression and improving therapeutic outcomes in preclinical studies [136, 137].

DPP-4 Inhibitors

DPP-4 inhibitors are oral antidiabetic agents that work by inhibiting the enzyme DPP-4, thereby preventing the degradation of the incretin hormones GLP-1 and GIP [138].

GIP, secreted by enteroendocrine K cells, enhances glucose-dependent insulin secretion. Additionally, it stimulates pancreatic beta-cell proliferation, upregulates proinsulin gene transcription and translation, and suppresses hepatic glucose production.

GIP receptors are abundantly expressed in adipocytes, where they promote glucose uptake and fatty acid synthesis[139]. A growing body of research suggests that DPP-4 inhibitors may possess anticancer properties [140, 141].

Tumorigenesis

DPP-4 inhibitors exhibit complex and context-dependent impacts on tumor biology [140].

In breast cancer, findings indicate that stromal CD26 (DPP-4) expression is reduced in malignant tissues, while adjacent non-cancerous regions often show preserved staining. This loss of stromal CD26 correlates with poorer patient prognosis [142].

Notably, a discrepancy exists between preclinical and clinical data: while inhibition of DPP-4 in mouse models can promote epithelial-mesenchymal transition (EMT) and metastasis via the CXCL12/CXCR4/mTOR axis, large human epidemiological studies have not shown an associated increased risk of breast cancer incidence.

This divergence may arise from species-specific differences, variations in drug exposure duration and dosing, or the distinct tumor microenvironment, underscoring that preclinical findings do not always directly translate to clinical outcomes [143].

In contrast, evidence suggests a potential benefit in colorectal cancer (CRC). A retrospective analysis by Ng et al. reported that CRC patients treated with DPP-4 inhibitors had a significantly higher 5-year disease-free survival rate [141].

However, the relationship appears dose-dependent. Chou et al. found a J-shaped association, where a lower cumulative dose of DPP-4 inhibitors was linked to a decreased CRC risk, but a higher cumulative dose was associated with an increased risk, highlighting the need for further investigation into the underlying mechanisms [141].

The role of DPP-4 in hepatocellular carcinoma (HCC) is also complex. Yu et al. observed that low DPP-4 expression in human HCC patients correlated with poorer survival, whereas Nishina et al. reported that high CD26 expression in a mouse model led to more aggressive tumors and reduced survival, suggesting opposing roles in different contexts [144, 145].

Analyses of large patient databases indicate potential survival benefits associated with DPP-4 inhibitor use in other malignancies. Studies of the SEER-Medicare database found improved overall survival in patients with colorectal and lung cancers [146], and another study linked DPP-4 inhibitor use to improved progression-free survival in advanced colorectal and lung cancers [147].

Overall, the impact of DPP-4 inhibition on cancer is not uniform. Its effects appear to be significantly influenced by the specific tumor type, dosage, and the local microenvironment. While some human data are encouraging for certain cancers, the conflicting preclinical evidence, particularly regarding metastasis, necessitates careful interpretation and further research to clarify its precise role in oncology.

Pancreatic cancer

GLP-1 promotes pancreatic cell proliferation, which may lead to the development of premalignant alterations [148]. DPP-4 breaks down GLP-1, inactivating it [138], and DPP-4 inhibitors extend GLP-1's half-life in serum [58]. Elashoff et al. found an increased pancreatic cancer risk with sitagliptin in a review of an FDA database [149].

In an animal study, Matveyenko et al. demonstrated that sitagliptin administration increased the likelihood

Table 2. Critical Appraisal of Preclinical and Clinical Evidence on DPP-4 Inhibitors and Pancreatic Cancer Risk

Author (s)	Year	Study Type	Population/ Model	N (if applicable)	Intervention	Follow-up	Primary Outcome	Finding	Bias Risk
Elashoff et al. [151]	2011	Database review	FDA MedWatch	Large	Sitagliptin	2–3 years	Pancreatic cancer incidence	↑ Risk	High (reporting bias)
Engel et al. [152]	2013	Cohort study	German insurance claims	1.3M	Various DPP-4i	Mean 2 years	Pancreatic cancer incidence	No ↑ Risk	Moderate
Matveyenko et al. [153]	2009	Preclinical	Mice	N/A	Sitagliptin	9 months	Pancreatitis/ dysplasia	↑ Dysplasia	Moderate (animal model)
Butler et al. [154]	2013	Preclinical	Organ donors (deceased)	N/A	Sitagliptin + Ex-4	Post-mortem	Pancreatic changes	↑ Changes	High (retrospective)
Gokhale et al. [155]	2016	Meta-analysis	Multiple RCTs	100K+	DPP-4i	2–5 years	Pancreatic cancer incidence	No ↑ Risk	Low

of developing pancreatitis and ductal metaplasia [150].

Butler et al. similarly observed that treatment with sitagliptin and exenatide was associated with comparable pancreatic alterations in brain-dead organ donors [154]. However, Gokhale et al. reported no significant increase in pancreatic cancer risk associated with DPP-4 inhibitor use, although the study's short follow-up period and limited sample size constrained the reliability of its conclusions [156].

Engel et al. concluded that sitagliptin was safe and did not correlate with an elevated risk of malignancy [152]. To systematically evaluate these conflicting findings, we present a critical appraisal of key preclinical and clinical studies on DPP-4 inhibitors and pancreatic cancer risk (Table 2).

As summarized in Table 2, the conflicting preclinical and clinical evidence for DPP-4 inhibitors in pancreatic cancer highlights the need for cautious interpretation. Preclinical studies consistently demonstrated increased pancreatic dysplasia or inflammation following DPP-4 inhibitor exposure [153, 154].

These findings are largely attributed to species-specific differences; rodents have distinct pancreatic islet architecture and proliferative responses compared to humans, which may exaggerate drug-induced pancreatic effects.

Additionally, many preclinical experiments use supraphysiologic doses or long-term exposure that exceed typical human therapeutic regimens, potentially amplifying risk signals.

In contrast, clinical trials and large cohort studies have not confirmed an increased risk of pancreatic cancer [152, 155].

Shorter duration of exposure in randomized controlled trials, coupled with rigorous monitoring and patient selection, reduces the likelihood of detecting rare or long-latency adverse events. Observational studies and database analyses, such as FDA MedWatch reports, are prone to reporting and surveillance biases, which can overestimate associations due to heightened awareness or selective reporting [151].

Current consensus suggests that DPP-4 inhibitors do not meaningfully increase pancreatic cancer risk in humans. Clinicians should continue to monitor patients according to standard guidelines, but may be reassured by the absence of consistent evidence from well-conducted trials.

Preclinical findings underscore the need for ongoing pharmacovigilance but should be interpreted in the context of interspecies differences and methodological limitations.

To systematically summarize the preclinical and clinical evidence of antidiabetic drugs across various cancer types, an evidence strength matrix is provided (Table 3). This allows comparison of the consistency and robustness of findings across different drug classes and malignancies.

Metformin shows the strongest evidence across multiple cancer types, with moderate evidence from observational studies and mechanistic support.

SGLT2 inhibitors show promising preclinical data, particularly in lung and liver cancers, but lack long-term clinical trials; a sex-specific adverse effect was noted in preclinical colorectal models.

GLP-1 RAs show a balanced profile, with moderate

Table 3. Evidence Strength Matrix: Antidiabetic Drugs Across Cancer Types

Drug Class	Breast Cancer	Colorectal Cancer	Lung Cancer	Hepatocellular Carcinoma	Pancreatic Cancer	Ovarian Cancer
Metformin	Moderate*	Moderate*	Moderate*	Moderate*	Conflicting†	Suggestive‡
SGLT2 inhibitors	Suggestive‡	Adverse §	Moderate‡	Moderate‡	Preclinical‡	–
GLP-1 RA	Moderate‡	Moderate ‡	Suggestive ‡	Conflicting†	Safe (no excess risk)	Moderate‡
TZD	Conflicting†	Moderate*	Moderate*	Moderate*	Conflicting†	–
DPP-4i	Conflicting†	Moderate*	Moderate*	Conflicting†	Conflicting†§	–

* Observational/epidemiological evidence. ‡ Predominantly preclinical evidence. † Conflicting preclinical and clinical findings. § Negative or adverse findings. – Insufficient evidence.

preclinical evidence and clinical safety data confirming no excess cancer risk.

Thiazolidinediones (TZDs) have context-dependent effects; epidemiological data support moderate protection in colorectal, lung, and liver cancers, but findings are conflicting in breast and pancreatic cancers.

DPP-4 inhibitors present conflicting evidence across several cancer types, reflecting species-specific and context-dependent effects; some human data suggest potential benefit in colorectal cancer, while pancreatic and breast cancer findings remain inconclusive.

Immune Checkpoint Modulation and Implications for Combination Immunotherapy

Beyond their direct metabolic and antiproliferative effects, antidiabetic drugs modulate the tumor immune microenvironment, a critical determinant of cancer progression and response to immunotherapy. Understanding these immunomodulatory properties is essential for designing rational combination therapies.

Metformin

Metformin activates AMPK, which inhibits mTOR signaling, reducing tumor proliferation and cancer stem cell activity. These effects are linked to improved disease-free and overall survival in breast cancer patients, especially those with insulin resistance or obesity. AMPK activation also modulates the tumor microenvironment, reducing insulin-driven growth signals and enhancing anticancer immunity, supporting the translational relevance of metformin in clinical outcomes [157].

Metformin enhances anticancer immunity through multiple mechanisms. It increases CD8+ T cell infiltration and function while reducing immunosuppressive regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in preclinical models [158]. Metformin also downregulates PD-L1 expression on cancer cells via AMPK activation and inhibits the HIF 1α/PD-L1 axis [159].

These effects potentially sensitize tumors to immune checkpoint inhibitors (ICIs). Clinically, retrospective analyses suggest diabetic cancer patients on metformin may have improved responses to anti PD-1/PD-L1 therapy, though prospective validation is needed [160].

SGLT2 inhibitors

SGLT2 inhibitors appear to reduce systemic inflammation and may decrease levels of pro-inflammatory cytokines (e.g., IL-6, TNF-α) that contribute to an immunosuppressive microenvironment [161]. Preclinical data indicate that canagliflozin can inhibit M2 macrophage polarization and reduce PD-L1 expression in certain cancer models [162].

A large population-based cohort study demonstrated a significantly lower incidence of gastric cancer among patients with type 2 diabetes treated with SGLT2 inhibitors compared with other glucose-lowering agents [163].

In parallel, a recent systematic review and meta-analysis reported a reduced overall cancer risk associated with SGLT2 inhibitor use when compared with DPP-4 inhibitors, supporting a potential class-specific protective effect beyond glycaemic control [164].

SGLT2 inhibitors limit glucose availability to cancer cells, activating AMPK and inhibiting mTOR in a context-dependent manner. These metabolic effects reduce proliferation and enhance chemosensitivity in lung, liver, and prostate cancers. Preclinical findings suggest that sex and tumor SGLT2 expression may influence efficacy, highlighting the need for stratified clinical evaluation [165].

Collectively, these findings suggest that SGLT2 inhibitors may exert clinically meaningful anticancer effects that warrant further prospective evaluation.

GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists demonstrate a favorable safety profile in cancer risk assessment, with recent clinical reviews reporting no significant increase in overall cancer incidence and possible protective effects against several malignancies, including gastrointestinal cancers.

Large observational evidence further suggests that GLP-1RA use may be associated with reduced cancer risk in adults with obesity, with notable implications for translational oncology research. However, dose-specific signals such as increased colorectal tumor incidence at high semaglutide doses warrant further investigation [166, 167].

More recent meta-analytic and real-world evidence have refined the understanding of the oncological implications of GLP-1 receptor agonists. A systematic review and meta-analysis published in 2024–2025 reported a significantly lower risk of colorectal cancer among GLP-1 receptor agonist users with type 2 diabetes [168].

Furthermore, a large cohort study demonstrated that combined use of GLP-1 receptor agonists and metformin was associated with a reduced incidence of obesity-related cancers, highlighting the importance of metabolic modulation in cancer prevention strategies [169].

These findings support the potential role of GLP-1 receptor agonists beyond glycemic control, particularly in metabolically driven malignancies.

Thiazolidinediones (TZDs)

Thiazolidinediones primarily activate PPAR-γ, leading to cell cycle arrest, apoptosis, and differentiation in cancer cells. Mechanistically, TZDs inhibit pro-tumorigenic signaling pathways such as PI3K/AKT and reduce inflammatory cytokine expression, which in turn limits angiogenesis and tumor invasion. Clinically, these mechanisms translate to observed benefits in colorectal and liver cancers, where long-term epidemiological studies suggest a reduced incidence or slower tumor progression in TZD users. Conversely, the noted bladder cancer risk with pioglitazone may reflect tissue-specific off-target effects of PPAR-γ activation, emphasizing the need to integrate mechanistic insight with patient-specific factors [170].

Thiazolidinediones, via PPAR-γ activation, have

Table 4. Comparative Overview of Antidiabetic Drug Classes: Mechanisms and Clinical Implications

Drug class	Primary mechanism of action	Cancer types with the most substantial evidence	Level of clinical evidence	Key limitations and contradictions	Recommendations for future research
Metformin	AMPK activation, mTOR inhibition, and reduced insulin/IGF-1 signaling	Breast, colorectal, and liver.	Observational studies; limited RCTs.	Confounding by BMI and lifestyle; limited data on non-diabetics	Large RCTs in non-diabetic high-risk populations
SGLT2 inhibitors	Glucose uptake inhibition; indirect metabolic stress	Lung, colorectal	Preclinical; observational	Supraphysiological doses; sex-specific animal findings	Translational studies with clinically relevant dosing
GLP-1 receptor agonists	Incretin signaling (cAMP/PKA); indirect metabolic effects	Breast, pancreatic (limited)	Observational preclinical	In vitro concentrations are not achievable in vivo	Mechanistic studies linking incretin signaling to tumor biology
Thiazolidinediones (TZDs)	PPAR-γ–mediated transcriptional regulation	Breast (conflicting)	Meta-analyses; preclinical	In vitro tumor promotion vs epidemiological protection	Context-specific evaluation by cancer subtype
DPP-4 inhibitors	Prolongation of endogenous GLP-1 signaling	Pancreatic, breast (controversial)	Observational; animal models	Species differences; conflicting metastatic data	Long-term prospective studies with cancer-specific endpoints

complex effects on inflammation and immunity. They can polarize macrophages toward an anti-inflammatory M2 phenotype (which may be contextually pro- or anticancer) and modulate T cell differentiation[171].

Notably, pioglitazone has been shown to promote PD-L1 degradation through PPAR γ mediated pathways, suggesting potential synergy with ICIs, particularly in cancers where PD-L1 is stabilized by oncogenic signals [172].

DPP-4 Inhibitors

DPP-4 inhibitors influence the tumor microenvironment through modulation of chemokine signaling, immune cell trafficking, and inflammatory pathways, mechanisms that may variably affect tumor progression across contexts. Updated meta-analyses of randomized controlled trials demonstrate that DPP-4 inhibitor use is not associated with a significantly increased risk of pancreatic cancer relative to comparators, and may even be linked to reduced pancreatitis risk in some subgroup analyses, reflecting a complex clinical safety profile. Mechanistic evidence from preclinical models indicates that DPP-4 inhibition can reprogram immune infiltration and cytokine expression; however, the net translational impact appears modest, consistent with largely neutral cancer risk outcomes in clinical settings [173].

DPP-4 (CD26) is itself expressed on immune cells and regulates T cell activation and migration. DPP-4 inhibitors may therefore have direct immunomodulatory consequences, though their net effect in cancer remains unclear and likely context dependent [144].

Some studies suggest DPP4 inhibition can enhance T cell chemotaxis and anticancer activity, while others indicate possible suppression of effective immune surveillance.

Combination Therapy Considerations

The immunomodulatory profiles of these drugs create opportunities for combination with modern immunotherapies [72].

Metformin and TZDs, with their potential to reduce PD-L1 and alter immune cell populations, are particularly interesting candidates for combination with anti-PD 1/ PD 1/PD L1 agents.

However, timing and sequencing are crucial; metabolic reprogramming of the tumor microenvironment may be necessary before or during ICI administration for optimal effect.

Future research must focus on identifying predictive biomarkers (e.g., obesity, insulin resistance, specific tumor mutations) to select patients most likely to benefit from such combinations and delineate optimal dosing schedules in clinical trials.

After discussing the immunomodulatory and anticancer effects of individual antidiabetic drug classes, it is useful to provide a comparative overview summarizing their primary mechanisms, the cancer types with the most substantial evidence, the strength of clinical data, key limitations, and directions for future research (Table 4). This synthesis can serve as a practical reference for clinicians and researchers.

As shown in Table 4, each antidiabetic drug class exhibits distinct mechanistic profiles and varying levels of evidence across different cancer types. Notably, metformin demonstrates the strongest clinical support across multiple malignancies, whereas the effects of TZDs and DPP-4 inhibitors remain context-dependent.

These summaries highlight critical gaps in knowledge and emphasize the need for mechanistic and clinical studies to guide safe and effective use in oncology settings. Further emphasizing the translational relevance of antidiabetic agents, Table 5 provides a comprehensive overview of representative drugs from each class, including their studied cancer types, trial phases, preclinical and clinical findings, key mechanisms, and references.

Only metformin has completed clinical trials in cancer; other agents (SGLT2 inhibitors, GLP-1 RAs, TZDs) currently have preclinical or observational evidence. Trial phases refer to the highest level of evidence available for

Table 5. Preclinical Studies and Ongoing Clinical Trials of Representative Antidiabetic Drugs in Cancer

Drug Class	Representative Drug	Cancer Type	Trial Phase	Trial Status	NCT Number	Study Design / Combination Therapy	Key Translational Rationale / Outcome	Reference
Biguanide	Metformin	Breast cancer	Phase III	Completed / Follow-up	NCT01101438	Randomized, adjuvant	Metabolic reprogramming; AMPK activation	[172]
Biguanide	Metformin	Colorectal cancer	Phase IIa	Completed	NCT01312467	Neoadjuvant metabolic study	AMPK activation; proliferation inhibition	[174]
SGLT2 inhibitors	Dapagliflozin	Colorectal cancer	Preclinical	Recruiting	N/A	In vitro and metabolic studies	Antiproliferative effects; glucose uptake modulation	[175]
SGLT2 inhibitors	Empagliflozin	Prostate cancer	Preclinical	Exploratory / Early phase	N/A	Mechanistic cancer cell studies	Glucose uptake inhibition; mitochondrial effects	[176]
GLP-1 receptor agonists	Liraglutide	Breast cancer	Preclinical	In vitro / In vivo	N/A	In vitro and in vivo breast cancer models; monotherapy	Reduction of tumor growth in vivo; decreased proliferation in vitro; apoptosis induction; epigenetic modulation	[90]
GLP-1 receptor agonists	Semaglutide	Oral squamous cell carcinoma / Breast cancer / Thyroid carcinoma	Preclinical	In vivo immune-modulatory models	N/A	In vitro and in vivo tumor models; immune modulation studies	Obesity-linked cancer risk reduction	[177]
Thiazolidinediones (TZDs)	Pioglitazone	Prostate cancer	Preclinical	Experimental	N/A	Xenograft and cell proliferation studies	PPARγ activation; metabolic reprogramming	[178]
Thiazolidinediones (TZDs)	Rosiglitazone	Bladder cancer	Preclinical	Experimental	N/A	Rosiglitazone + trametinib in a mouse model	Potent anti-tumor activity; tumor volume reduction	[179]

each drug class. References correspond to studies listed in the final column.

Conclusion, Study Limitations, and Future Research

As summarized in Table 4, antidiabetic drug classes differ considerably in their mechanisms of action, strength of evidence, and potential for cancer-specific translation.

According to current literature, metformin emerges as the most reliably supported candidate for further clinical research, particularly in estrogen receptor-positive breast cancer and colorectal cancer, with the strongest rationale for use in obese or insulin-resistant populations, including non-diabetic individuals at high metabolic risk.

SGLT2 inhibitors show promise in glucose-dependent tumors like lung cancer, but their preclinical findings, especially regarding sex-specific effects, necessitate caution and further validation at clinically relevant doses.

Evidence for GLP-1 receptor agonists remains suggestive but limited, especially in breast and pancreatic cancers, and future studies should examine achievable in vivo concentrations. Conversely, evidence for DPP-4 inhibitors in pancreatic and breast cancer remains inconclusive, and their evaluation awaits more comprehensive, cancer-specific prospective data.

Across different drug classes, anticancer effects are primarily achieved through indirect metabolic modulation rather than direct, consistent cytotoxicity. Common mechanisms involve decreasing insulin/IGF-1 signaling, modifying cellular energy balance, and reducing chronic inflammatory signaling.

Importantly, these mechanisms are distinct across drug classes: metformin mainly influences mitochondrial energetics, SGLT2 inhibitors reduce glucose availability, GLP-1 receptor agonists work through incretin-mediated signaling, TZDs regulate transcription via PPAR-γ, and DPP-4 inhibitors indirectly enhance GLP-1 activity by prolonging its effects. Hence, the anticancer effectiveness of these drugs depends on the context and varies according to tumor type and metabolic phenotype, rather than being a uniform class effect.

A clear distinction is essential between mechanisms involved in cancer prevention and those in treatment. In clinical populations, particularly individuals with diabetes or insulin resistance, lower cancer risk is primarily linked to systemic metabolic improvements, like decreased circulating insulin and IGF-1 levels.

Conversely, preclinical cancer models often focus on inducing apoptosis and halting the cell cycle, which calls for caution when applying experimental results to clinical settings.

The existing evidence is limited due to varied study designs, short follow-up periods, and remaining confounding factors such as obesity, diet, and lifestyle. Conflicting results, like the uncertain link between DPP-4 inhibitors and pancreatic cancer risk or the context-specific effects of TZDs, emphasize the need for carefully designed, cancer-specific clinical trials.

Additionally, while inhibiting chronic inflammatory pathways like NF-κB may help prevent tumor formation, excessive or long-term suppression could weaken anticancer immune responses, especially with

immunotherapy advances. Future research should focus on systematically exploring how metabolism and immunity interact when using antidiabetic drugs alongside modern cancer treatments.

Future research must pivot from broad, observational approaches to targeted, mechanism-informed clinical strategies. The following priorities are critical to realize the therapeutic potential of antidiabetic drugs in oncology:

Precision Trial Design

Conduct biomarker-driven, phase II/III trials that stratify patients by validated metabolic or molecular signatures. Prime candidates for enrichment include elevated plasma insulin/C-peptide, tumor phospho-AMPK/low pS6 status, or transcriptomic signatures of glycolysis and lipogenesis. Master protocols (e.g., basket trials) could efficiently test a single agent like metformin across multiple obesity-associated cancers (endometrial, colorectal, hepatocellular) sharing a common metabolic driver [53, 73].

Rational Immunometabolic Combinations

Prioritize combination therapy with immune checkpoint inhibitors (ICIs), particularly in immunologically cold tumors fueled by metabolic dysfunction. Preclinical evidence strongly supports evaluating metformin or pioglitazone with anti-PD-1 therapy in clear cell renal cell carcinoma or microsatellite-stable colorectal cancer, where metabolic reprogramming may overcome primary resistance. Trial endpoints should include immunologic correlates (e.g., CD8+/Treg ratio, myeloid cell infiltration) alongside traditional efficacy measures [132, 159, 160].

Focus on High-Risk, Non-Diabetic Cohorts:

Expand investigation into cancer prevention and treatment in non-diabetic populations with insulin resistance. Key cohorts include patients with metabolic syndrome, non-alcoholic steatohepatitis (NASH), or BRCA mutations and obesity. Proof-of-concept window-of-opportunity trials in the perioperative setting can provide rapid biomarker and pharmacodynamic validation in these populations [36, 163].

Leverage Advanced Human-Relevant Models

Deploy patient-derived organoids (PDOs) and organ-on-a-chip co-culture systems to preclinically identify synergistic drug combinations and biomarkers of response specific to human tumor biology, minimizing the translational gap from animal models [72].

Collectively, Future research should prioritize biomarker-driven clinical trial designs to identify metabolically responsive patient subgroups most likely to benefit from antidiabetic agents. In particular, window-of-opportunity and neoadjuvant trial settings may enable direct assessment of metabolic and immune modulation within the tumor microenvironment. Combination strategies integrating antidiabetic drugs with immunotherapy warrant focused investigation, especially given the emerging links between metabolic reprogramming and immune checkpoint responsiveness. Importantly, non-diabetic cancer patients as well as individuals with obesity or metabolic syndrome should be considered priority populations, as metabolic dysregulation may represent a modifiable determinant of therapeutic response rather than a mere comorbidity.

In conclusion, antidiabetic drugs, particularly metformin, demonstrate significant potential in cancer prevention and treatment, although their effects are context-dependent, varying by tumor type and patients' metabolic profiles. Future research should prioritize biomarker-driven clinical trials, integration with immunotherapy, and investigation in high-risk non-diabetic populations. Leveraging advanced human-relevant models and exploring the interplay between metabolism and immunity will be critical for translating preclinical findings into effective clinical applications.

Declarations

Ethics approval

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Conflict and interest

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