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Original Research Article

Interlinked Epidemics: Unraveling the Association Between Diabetes and Cancer

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Abstract: Diabetes mellitus and cancer represent two major global health challenges whose rising prevalence has created a significant clinical and public health burden. Increasing epidemiological evidence indicates that diabetes, particularly type 2 diabetes, is associated with an elevated risk of several cancers, including liver, pancreatic, colorectal, breast, and endometrial malignancies. The mechanistic interplay between these interlinked epidemics is complex and involves chronic hyperglycemia, hyperinsulinemia, insulin resistance, inflammation, oxidative stress, and dysregulated adipokine signaling. These metabolic disturbances converge on key oncogenic pathways such as PI3K/Akt/mTOR, AMPK, Wnt/β-catenin, and O-GlcNAcylation, driving cellular proliferation, metabolic reprogramming, angiogenesis, and resistance to apoptosis. Furthermore, antidiabetic therapies, including metformin and insulin analogues, may differentially influence cancer risk and therapeutic outcomes, highlighting the need for integrated treatment strategies. This review synthesizes current epidemiological, molecular, and clinical evidence to elucidate the bidirectional relationship between diabetes and cancer and discusses emerging therapeutic approaches targeting shared metabolic and signaling networks. Understanding these interconnected mechanisms is essential for developing precision-based interventions aimed at reducing cancer burden in diabetic populations.

Keywords: Diabetes, Cancer, PI3K/Akt/mTOR, Oxidative stress, Signaling, Insulin resistance.

INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent metabolic disorders worldwide, characterized primarily by chronic hyperglycemia and associated metabolic abnormalities [1]. Over the past few decades, the global incidence of both type 1 and type 2 diabetes has risen dramatically, paralleling a surge in non-communicable diseases, including various forms of cancer [2]. Increasing epidemiological evidence has revealed that individuals with diabetes are at a significantly elevated risk of developing certain malignancies, such as liver, pancreatic, colorectal, breast, and endometrial cancers [1-3]. This convergence of two major public health burdens has sparked growing interest in understanding the biological and clinical interconnections between diabetes and cancer [4,5].

The pathophysiological mechanisms linking diabetes to oncogenesis are complex and multifactorial [6]. Chronic hyperinsulinemia, insulin resistance, and elevated levels of insulin-like growth factors (IGFs) can create a pro-mitogenic and anti-apoptotic environment that promotes tumor initiation and progression [7]. Persistent hyperglycemia contributes to oxidative stress, DNA damage, and epigenetic modifications, while low-grade chronic inflammation, a hallmark of diabetes, fosters a tumor-promoting microenvironment [8]. Furthermore, shared lifestyle risk factors such as obesity, sedentary behavior, and poor dietary patterns exacerbate this interplay [6]. Understanding these mechanisms is crucial, as they not only shed light on cancer risk in diabetic populations but also highlight potential targets for preventive and therapeutic interventions.

Given the growing burden of both diabetes and cancer on global health systems, it is imperative to comprehensively understand their interrelationship. This review aims to integrate current epidemiological data, molecular and cellular mechanisms, and clinical evidence that elucidate how diabetes acts as a driving risk factor for cancer [3]. By synthesizing findings from experimental studies and clinical observations,

we seek to highlight the biological pathways linking metabolic dysregulation to tumorigenesis, identify cancer types most strongly associated with diabetes, and discuss potential preventive and therapeutic strategies to mitigate cancer risk in diabetic individuals [3,6]. This integrative approach may provide valuable insights for developing targeted interventions and inform future research directions at the intersection of metabolic and oncological diseases.

EPIDEMIOLOGICAL EVIDENCE LINKING DIABETES AND CANCER

Over the past two decades, a growing body of epidemiological studies has provided compelling evidence that diabetes, particularly type 2 diabetes mellitus (T2DM), is associated with an increased risk of developing several malignancies [9]. Large-scale cohort and case–control studies have consistently reported higher incidence and mortality rates for certain cancers among individuals with diabetes compared to non-diabetic populations [9,10]. The most robust associations have been observed for cancers of the liver, pancreas, endometrium, colon, breast, and bladder. Meta-analyses have estimated that T2DM confers approximately a 20–30% higher overall cancer risk, with site-specific risk varying widely depending on cancer type and study population [3-4].

Several factors contribute to this observed association. The long duration of diabetes and poor glycemic control appear to magnify cancer risk, suggesting a dose–response relationship. Additionally, the age-related rise in both diabetes and cancer prevalence amplifies their co- occurrence, as older adults are disproportionately affected by both conditions [10,11]. Gender differences have also been reported; for example, women with diabetes show a relatively higher risk for endometrial and postmenopausal breast cancers, while men exhibit stronger associations with liver and pancreatic cancers [1-3,11]. Importantly, some studies have demonstrated that the increased risk persists even after adjusting for shared risk factors such as obesity, physical inactivity, and smoking, indicating that diabetes itself contributes independently to carcinogenesis.

While observational studies cannot establish direct causality, the consistent associations across diverse populations, combined with biological plausibility, strongly support diabetes as a significant risk factor for cancer [2]. This epidemiological link underscores the urgency to explore the mechanistic pathways underlying this relationship, which may provide novel avenues for cancer prevention and management in diabetic patients.

Etiology and Pathogenesis

The etiology of diabetes-associated cancer is rooted in a convergence of metabolic, hormonal, and inflammatory disturbances that arise from chronic diabetic states [10,11]. Type 2 diabetes mellitus (T2DM), which accounts for the majority of diabetes cases, is primarily driven by insulin resistance, compensatory hyperinsulinemia, and persistent hyperglycemia—all of which play pivotal roles in promoting oncogenesis [7]. Hyperinsulinemia stimulates insulin and insulin-like growth factor-1 (IGF-1) receptors on various tissues, activating proliferative signaling cascades such as the PI3K/Akt/mTOR and MAPK/ERK pathways, thereby fostering uncontrolled cell growth and inhibiting apoptosis [12,13]. Concurrently, chronic hyperglycemia induces oxidative stress through the overproduction of reactive oxygen species (ROS), resulting in DNA damage, mutagenesis, and genomic instability—key initiators of malignant transformation [8].

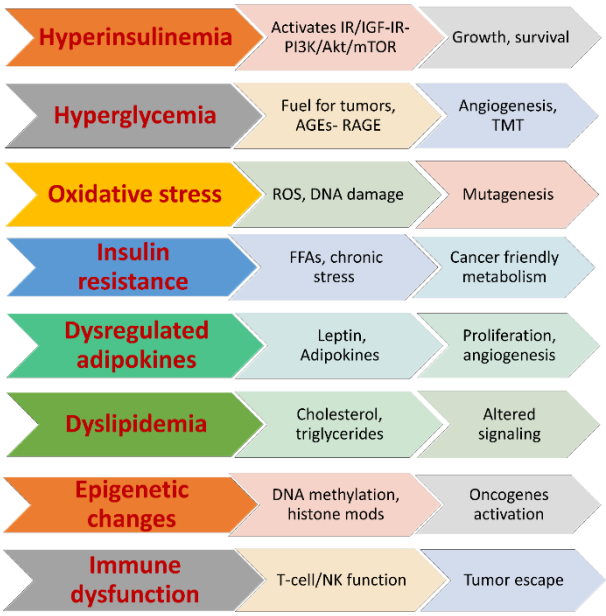

Figure 1: Pathological factors which create pre-tumorigenic environment

Moreover, both T2DM and obesity are associated with a state of chronic low-grade inflammation, marked by increased levels of pro-inflammatory cytokines (TNF-α, IL-6, CRP) that activate nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) pathways, enhancing tumor-promoting processes such as angiogenesis, invasion, and metastasis **[14,15]**. Dysregulated adipokines, such as reduced adiponectin and elevated leptin, further contribute to cancer development by promoting cellular proliferation and inflammatory signaling. Epigenetic alterations triggered by hyperglycemia—such as aberrant DNA methylation, histone modification, and microRNA dysregulation—can silence tumor suppressor genes or activate oncogenes, establishing a molecular environment conducive to cancer initiation and progression [16-18]. Collectively, these interlinked pathophysiological mechanisms create a pro-tumorigenic milieu that explains the elevated cancer risk observed in individuals with diabetes.

Pathophysiological Factors Involved in Diabetes-Induced Cancer

A. Hyperinsulinemia and Insulin Resistance

- Excess insulin (due to insulin resistance) acts as a growth factor.
- Activates insulin receptors (IR) and IGF-1 receptors, promoting:
  - PI3K/Akt/mTOR signaling
  - Cell proliferation
  - Anti-apoptotic effects
- Increases risk especially for breast, colorectal, and endometrial cancers.
- Drives both hyperglycemia and hyperinsulinemia.
- Results in increased free fatty acids (FFAs), which:
  - Contribute to lipotoxicity, inflammation, and cancer-promoting environments [7,19,20].

Type 2 diabetes is characterized by insulin resistance, which leads to compensatory hyperinsulinemia. Elevated circulating insulin can activate the insulin receptor (IR) and insulin- like growth factor-1 receptor (IGF-1R) signaling pathways, both of which promote cellular proliferation, inhibit apoptosis, and enhance survival of pre-malignant and malignant cells [19,21]. Activation of the PI3K/Akt/mTOR and MAPK/ERK pathways downstream of IR and IGF-1R contributes to uncontrolled cell cycle progression and tumor growth [22].

B. Chronic Hyperglycemia and Oxidative Stress

- High glucose levels directly:
  - Fuel aerobic glycolysis (Warburg effect) in cancer cells [18].
  - Promote advanced glycation end products (AGEs) → bind to RAGE → trigger inflammation and oxidative stress [23].
  - Enhance Wnt/β-catenin signaling, increasing oncogene expression [24].
- Persistent hyperglycemia causes excess reactive oxygen species (ROS).
- ROS damage DNA, proteins, and lipids:
  - Leads to mutations and genomic instability.
  - Triggers pro-survival pathways (PKC, MAPK) [8,25].

Persistent hyperglycemia drives the overproduction of reactive oxygen species (ROS), causing oxidative stress, DNA damage, and genomic instability—hallmarks of cancer initiation. High glucose levels can also lead to the formation of advanced glycation end products (AGEs) that interact with their receptor (RAGE), triggering inflammatory and pro-survival signaling cascades [8,23]. In addition, hyperglycemia alters cellular metabolism by promoting glycolytic flux, which supports the metabolic demands of rapidly dividing cancer cells.

C. Chronic Inflammation and Cytokine Signaling

- Diabetes is a low-grade inflammatory state.
- Elevated cytokines (e.g., IL-6, TNF-α) and C-reactive protein (CRP) activate: o NF-κB and JAK/STAT3 pathways → promote tumor initiation and progression.
  - Induce epithelial-to-mesenchymal transition (EMT) and angiogenesis [15, 26].

Diabetes is associated with low-grade systemic inflammation characterized by elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and CRP. These inflammatory mediators can induce activation of transcription factors like NF-κB and STAT3, which regulate genes involved in proliferation, angiogenesis, invasion, and metastasis [15, 26]. The chronic inflammatory milieu also contributes to immune evasion by tumor cells and fosters a tumor-supportive microenvironment.

D. Adipokine Dysregulation and Obesity-Linked Pathways

- ❖ Leptin is increased: promotes angiogenesis, cell proliferation.
- ❖ Adiponectin is decreased: removes its protective anti-inflammatory effect.
- ❖ Elevated cholesterol and triglycerides alter membrane fluidity, hormone synthesis, and activate pro-carcinogenic signaling [14, 27].

Obesity, which frequently coexists with type 2 diabetes, further amplifies cancer risk through dysregulation of adipokines [20, 28]. Decreased adiponectin and elevated leptin levels promote cell proliferation, angiogenesis, and inflammatory signaling. Increased circulating free fatty acids and lipid metabolites can also activate oncogenic pathways and induce insulin resistance, creating a feed-forward loop that enhances tumorigenesis.

E. Epigenetic Alterations and Genetic Susceptibility

- ❖ Diabetes induces epigenetic alterations (e.g., DNA methylation, histone acetylation) in oncogenes and tumor suppressor genes [29].
- ❖ T2DM compromises T-cell and NK cell function, allowing immune evasion by tumors [30].

Table: Etiological Factors in Clinical Trials for Diabetes-Induced Cancer

Etiological Factor	Targeting Strategy	Drug/Agent Examples	Cancer Type(s)	Trial Status
Hyperinsulinemia	Reduce insulin levels and receptor signaling	Metformin, Pioglitazone, GLP-1 agonists	Breast, Colorectal, Endometrial	Phase II/III, completed or ongoing
Hyperglycemia	Improve glycemic control	SGLT2 inhibitors (e.g., Dapagliflozin), Insulin sensitizers	Pancreatic, Breast (T2DM patients)	Early to mid-phase trials
Chronic Inflammation	Anti-inflammatory, cytokine inhibition	NSAIDs, IL-6 inhibitors, Curcumin	Colon, Pancreatic, Prostate	Pilot/observational trials
Oxidative Stress	ROS scavengers, Nrf2 activation	N-acetylcysteine, Resveratrol, Sulforaphane	Liver, Colon, Breast	Phase I/II nutraceutical trials
IGF/Insulin Signaling	Block receptor or downstream cascade	Everolimus, Linsitinib (IGF1R inhibitor)	Breast, Prostate, Pancreatic	Advanced phase or completed trials
Obesity/Adipokines	Weight reduction, modulate leptin/adiponectin	Bariatric surgery, Leptin inhibitors, Liraglutide	Endometrial, Liver, Breast	Interventional trials ongoing
Lipotoxicity	Fatty acid oxidation support, lipid-lowering	Fenofibrate, omega-3 fatty acids	Liver (NAFLD-associated), Colon	Small trials (Phase I/II)
Epigenetic Alterations	Reverse DNA methylation, HDAC inhibition	Vorinostat, DNMT inhibitors	Colon, Breast, Pancreatic	Experimental/early trials
Immune Dysfunction	Immunotherapy, checkpoint blockade	Anti-PD-1/PD-L1, metformin as adjuvant	Multiple cancers in T2DM context	Immuno-metabolic trials ongoing
Gut Microbiome Dysbiosis	Restore microbiota balance	Probiotics, FMT, Metformin	Colorectal, Liver	Emerging area, Phase I/II

Hyperglycemic and hyperinsulinemic conditions can influence gene expression through epigenetic mechanisms such as DNA methylation, histone modifications, and altered microRNA profiles [31]. These changes may disrupt tumor suppressor gene function or enhance oncogene activation, thereby predisposing diabetic individuals to malignant transformation. Genetic polymorphisms in insulin signaling or glucose metabolism pathways may further modulate individual susceptibility to both diabetes and cancer.

MOLECULAR AND CELLULAR MECHANISMS LINKING DIABETES TO CANCER

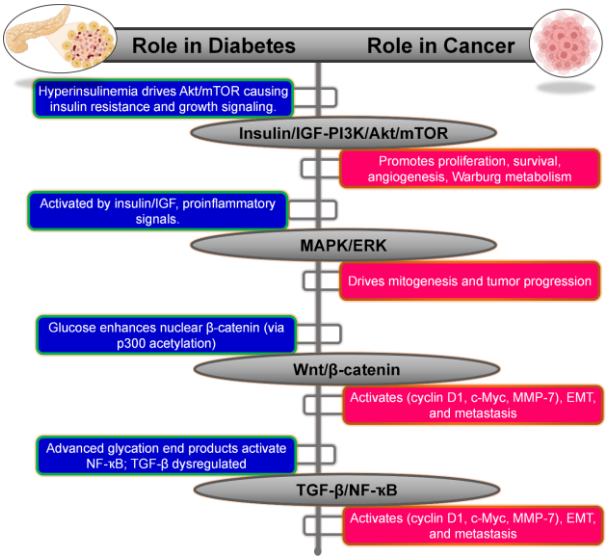

Figure 2: Role of Signalings in Diabetes and Cancer

The molecular crosstalk between diabetes and cancer involves a complex interplay of metabolic and growth-signaling networks. Chronic hyperglycemia and hyperinsulinemia dysregulate:

- ❖ PI3K/Akt/mTOR and MAPK/ERK for growth and survival
- ❖ Wnt/β-catenin for proliferation and EMT
- ❖ AMPK suppression removing growth brakes
- ❖ ROS/NF-κB to drive inflammation and mutation
- ❖ RAGE/TGF-β pathways fostering immunosuppression and angiogenesis [7,23,24].

These signaling axes not only explain higher cancer risks in diabetic patients but also suggest actionable drug targets (e.g., metformin, pathway inhibitors) [32].

The biological interplay between diabetes and cancer is multifaceted, involving a complex network of metabolic, hormonal, inflammatory, and genetic pathways that collectively create a pro-tumorigenic environment. Several key mechanisms have been identified that may explain how chronic diabetic states contribute to the initiation and progression of malignancies.

The molecular interplay between diabetes and cancer involves a complex network of signaling pathways and cellular processes that synergistically promote oncogenesis. Central to this link is insulin resistance, which drives chronic hyperinsulinemia—a hallmark of type 2 diabetes. Excess insulin activates the insulin receptor (IR) and insulin-like growth factor-1 receptor (IGF-1R) on epithelial and stromal cells, triggering downstream PI3K/Akt/mTOR and RAS/RAF/MEK/ERK (MAPK) signaling cascades [12,19,33]. These pathways enhance cellular proliferation, protein synthesis, and survival while suppressing apoptosis, thereby creating a proliferative advantage for premalignant cells. Concurrently, hyperglycemia increases intracellular glucose uptake, fueling the Warburg effect (aerobic glycolysis) which supports rapid tumor growth by providing biosynthetic precursors and ATP. Excess glucose also enhances the formation of advanced glycation end products (AGEs), which bind to their receptor RAGE and activate NF-κB signaling, leading to transcription of genes involved in inflammation, angiogenesis, and metastasis [13,23,34].

Additionally, chronic high glucose induces mitochondrial dysfunction and reactive oxygen species (ROS) overproduction, resulting in oxidative DNA damage, double-strand breaks, and genomic instability—critical drivers of mutagenesis and malignant transformation. The diabetic state is also characterized by chronic low-grade inflammation, with elevated IL-6, TNF- α, and CRP promoting activation of STAT3, NF-κB, and COX-2 pathways, which stimulate angiogenesis, immune evasion, and epithelial-to-mesenchymal transition (EMT) [35, 36]. Adipokine dysregulation further contributes to tumorigenesis: leptin activates JAK/STAT and MAPK pathways to promote proliferation and

angiogenesis, while reduced adiponectin removes inhibitory signals on AMPK, allowing unchecked mTOR activation. Finally, epigenetic reprogramming induced by hyperglycemia—including aberrant DNA methylati, histone acetylation, and altered microRNA expression—can silence tumor suppressors and activate oncogenes, cementing the malignant phenotype [27,37,38]. Together, these interwoven molecular events explain how the diabetic milieu acts as a potent driver of cancer initiation, progression, and metastasis.

A. Hyperglycemia-driven signaling bridges diabetes and cancer

Chronic hyperglycemia activates key oncogenic signaling pathways, including PI3K/Akt/mTOR, Wnt/β-catenin, and O-GlcNAcylation, leading to enhanced cell proliferation and survival. Persistent high glucose also promotes metabolic reprogramming, oxidative stress, and pro- inflammatory cytokine production, creating a tumor-promoting microenvironment [39,40]. Collectively, these molecular alterations establish a mechanistic link between diabetes and increased cancer risk, progression, and therapeutic resistance.

B. Insulin–PI3K signalling: a metabolic driver of cancer

Chronic hyperinsulinemia enhances activation of the insulin receptor–PI3K/Akt pathway, stimulating downstream mTOR signaling and promoting cell growth and survival. This persistent signaling accelerates anabolic metabolism, increases glucose uptake, and supports biosynthetic processes essential for tumor development [7,12,41]. Sustained insulin–PI3K activation therefore acts as a metabolic driver linking type 2 diabetes with cancer progression and reduced therapeutic responsiveness.

C. Integrating metabolic and molecular circuits in diabetes, obesity and cancer

Diabetes and obesity disrupt systemic metabolic homeostasis, leading to chronic hyperglycemia, hyperinsulinemia, and altered adipokine signaling. These metabolic disturbances converge on shared molecular circuits such as PI3K/Akt/mTOR, AMPK, and inflammatory pathways that regulate cell growth, survival, and energy balance [42,43].

The integration of these metabolic and oncogenic networks establishes a mechanistic framework linking metabolic disorders with cancer initiation, progression, and therapeutic outcomes.

D. Molecular basis of carcinogenesis in diabetic patients

Chronic hyperglycemia and hyperinsulinemia activate oncogenic signaling pathways such as PI3K/Akt/mTOR and MAPK, promoting uncontrolled cell proliferation and survival. Increased oxidative stress, advanced glycation end products (AGEs), and persistent low-grade inflammation further induce DNA damage and genomic instability [12,20]. Together, these metabolic and molecular alterations create a pro-tumorigenic environment that enhances cancer initiation, progression, and resistance to therapy in diabetic patients.

E. Metabolic and hormonal remodeling of colorectal cancer signaling by diabetes

Diabetes-associated hyperglycemia and hyperinsulinemia reshape colorectal cancer signaling by persistently activating PI3K/Akt/mTOR and Wnt/β-catenin pathways. Altered insulin, IGF-1, and adipokine profiles further enhance proliferative, anti-apoptotic, and pro-angiogenic signaling within the tumor microenvironment. This metabolic and hormonal reprogramming promotes tumor growth, invasion, and therapeutic resistance in colorectal cancer patients with diabetes [44,45].

F. mTOR complexes in diabetes-cancer interplay

mTOR exists as two functionally distinct complexes, mTORC1 and mTORC2, which integrate nutrient, insulin, and growth factor signals to regulate cell growth and metabolism. In diabetes, chronic hyperinsulinemia and nutrient excess lead to sustained activation of mTOR signaling, promoting anabolic processes and inhibiting autophagy [12,13]. This persistent mTOR dysregulation fosters tumor initiation, progression, and metabolic reprogramming, thereby linking diabetic metabolic imbalance with cancer development.

Table 2: Major Signaling Pathways in Diabetes-Induced Cancer

Pathway	Role in Diabetes	Role in Cancer
PI3K/Akt/mTOR	Activated by high insulin/IGF levels due to insulin resistance	Promotes cell growth, survival, angiogenesis, and inhibits apoptosis
MAPK/ERK	Triggered by insulin and inflammatory cytokines	Enhances cell proliferation, invasion, and metastasis
Wnt/β-Catenin	Hyperglycemia enhances β-catenin nuclear activity via p300 acetylation	Upregulates oncogenes like **c-Myc**, **cyclin D1**, and promotes epithelial-to-mesenchymal transition (EMT)

AMPK	Inhibited in high glucose/nutrient overload conditions	Normally tumor-suppressive; loss of AMPK leads to unchecked mTOR activation and cell growth
NF-κB	Activated by AGEs, ROS, and proinflammatory cytokines	Promotes inflammation, survival signals, angiogenesis, and immune evasion
JAK/STAT3	Upregulated in chronic inflammatory states (IL-6 signaling)	Promotes tumor growth, immune suppression, and stem cell-like traits
RAGE/AGE	Activated by advanced glycation end-products (AGEs)	Sustains oxidative stress and inflammation; supportstumor microenvironment
TGF-β Signaling	Dysregulated in insulin-resistant tissues	Drives fibrosis, EMT, immunosuppression, and metastasis
Hexosamine Biosynthetic Pathway (HBP)	Increased O-GlcNAcylation in hyperglycemia	Modifies transcription factors, oncogenes, and epigenetic regulators, promoting tumorigenesis
Oxidative Stress (ROS/PKC)	Elevated in diabetes due to mitochondrial dysfunction and hyperglycemia	CausesDNA damage,activates oncogenic signaling (e.g., PKC, MAPK), and promotes mutation

5. Drugs in Clinical Trials for Diabetes-Induced Cancer

Emerging evidence highlighting the interplay between diabetes and cancer has prompted several clinical trials investigating pharmacological interventions that may simultaneously target metabolic dysregulation and tumor progression.

Table 3: Drugs in Clinical Trials for Diabetes-Induced Cancer

Drug Name	Mechanism of Action	Target/Pathway	Cancer Type(s)	Trial Status
Metformin	AMPK activator; reduces hepatic glucose output	AMPK → mTOR inhibition	Breast, Colorectal, Endometrial	Multiple Phase II/III completed
Pioglitazone	PPAR-γ agonist; insulin sensitizer	PPAR-γ, anti-inflammatory	Bladder, Prostate	Mixed results, bladder cancer risk
Dapagliflozin	SGLT2 inhibitor; lowers glucose	Glucose-lowering, IGF axis	Breast, Pancreatic (experimental)	Early phase trials (I/II)
Exenatide	GLP-1 receptor agonist; improves insulin response	Insulin/IGF1 modulation	Pancreatic, Colorectal (T2DM pts)	Observational, pilot trials
Everolimus	mTOR inhibitor	PI3K/Akt/mTOR	Breast, Pancreatic, Renal	Approved; trials in diabetic subsets
Temsirolimus	mTORC1 inhibitor	mTOR	Renal, Endometrial	Phase II/III completed
Resveratrol	SIRT1 activator, antioxidant, AMPK booster	AMPK, NF-κB	Colon, Breast	Early trials; nutraceutical form
Berberine	AMPK activator, ROS scavenger	AMPK, oxidative stress	Colorectal, Liver (T2DM)	Phase I/II trials in Asia
Liraglutide	GLP-1 analog; improves insulin	Incretin pathway	Colon, Pancreatic	Ongoing studies

	secretion			
Sulforaphane	Nrf2 activator; antioxidant enzyme inducer	ROS detox, NF- κB suppression	Breast, Prostate	Phase I trials
Dasatinib + Quercetin	Senolytic combo; clears senescent cells	Inflammation, aging factors	Liver, Pancreas (obese/diabetic)	Pilot trials ongoing

Metformin, a first-line antidiabetic agent, is one of the most extensively studied drugs, with numerous trials evaluating its potential to reduce cancer incidence and improve survival outcomes by activating AMPK, inhibiting mTOR signaling, and suppressing cancer cell proliferation. Thiazolidinediones, such as pioglitazone, are also under investigation for their ability to modulate PPAR-γ activity, thereby exerting anti-inflammatory and antiproliferative effects in certain malignancies. Additionally, newer classes of antidiabetic drugs, including GLP-1 receptor agonists and SGLT2 inhibitors [46-51], are being evaluated in clinical settings to determine their impact on tumor metabolism, angiogenesis, and metastatic behavior. Combination therapies involving conventional chemotherapeutics with metabolic modulators are another focus, aiming to improve treatment efficacy and minimize cancer recurrence in diabetic populations [52,53]. These ongoing trials could provide crucial insights into repurposing existing antidiabetic medications or developing novel agents for preventing and managing diabetes-associated cancers.

Table 4: Registered Clinical Trials Investigating the Interplay Between Diabetes, Antidiabetic Therapies, and Cancer Outcomes

NCT / ref	Short title (trial)	Intervention / exposure	Cancer type / focus	Diabetes status of participants	Phase / design	Status (registry)	Key outcome(s) / notes
NCT01101438. ClinicalTrials.gov	Metformin vs placebo in early breast cancer (MA.32)	Metformin vs placebo (added to standard therapy)	Early, high-risk breast cancer	Non-diabetic patients (adjuvant setting)	Phase III RCT	Completed / published	Primary: invasive disease-free survival. Reported no significant improvement in IDFS overall; subgroup/exploratory analyses published. PubMed+1
NCT01312467. ClinicalTrials.gov	Metformin for colorectal cancer risk (biopsy	Metformin (short presurgical exposure)	Colorectal (risk / biomarkers)	Non-diabetics / pre-op patients	Phase II (PD)	Completed / active	PD endpoints: effect on tissue proliferation markers (e.g., Ki- 67)

	PD markers)						
NCT03359681. ClinicalTrials.gov+1	Metformin in colon cancer (placebo-controlled)	Metformin vs placebo	Colon cancer (adjuvant / biomarker)	Often non-diabetic cohorts	Randomized, double-blind	Active / Completed (check registry)	Cell-growth / proliferation biomarkers, translational endpoints
NCT01210911. ClinicalTrials.gov	Metformin + chemotherapy in pancreatic cancer	Metformin + chemo vs chemo	Pancreatic adenocarcinoma	Mixed (mostly non-diabetic/oncology patients)	Phase II	Completed / terminated (varies by arm)	Several pancreatic trials with metformin showed mixed efficacy; many small/negative.
NCT02186847. ClinicalTrials.gov	Chemoradiation ± metformin in rectal / other cancers	Metformin adjunct to chemoradiation	Various solid tumours (rectal, etc.)	Non-diabetic cancer patients	Phase II RCT	Completed / active	Safety and radiosensitization endpoints studied.
NCT01997775. ClinicalTrials.gov	Metformin in Stage IV lung adenocarcinoma	Metformin + standard therapy	NSCLC (adenocarcinoma)	Cancer patients (mostly non-diabetic)	Phase II	Completed / active	Evaluated response rates / survival signals with metformin add-on. ClinicalTrials.gov
NCT01981525. ClinicalTrials.gov	Pilot: Metformin in patients at high cancer risk	Metformin chemoprevention pilot	Varies (pre-malignant lesions)	Diabetic & non-diabetic cohorts	Pilot / Phase II	Completed / active	Safety/tolerability & biomarker endpoints
NCT05536037. ClinicalTrials.gov	Metformin for prevention of oral cancer transformation	Metformin topical/oral for oral precancer	Oral precancerous lesions → cancer prevention	Non-diabetic (precancer cohort)	Phase I/II	Recruiting / Active	Endpoint: rate of malignant transformation of oral lesions
NCT00099021. ClinicalTrials.	Pioglitazone to prevent	Pioglitazone (PPARγ	Oral leukoplakia →	Non-diabetic (premalign	Phase II	Completed / terminated	Studied whether pioglitazon

gov	head & neck cancer	agonist)	head/neck cancer prevention	ant lesions)			e reduces malignant progression of OPLs
NCT01838317. ClinicalTrials.gov	Pioglitazone in cancer patients (various)	Pioglitazone (Actos)	Several solid tumours (pilot/phase II)	Cancer patients (mixed diabetic status)	Phase II	Completed / active	Small phase II testing antitumour activity; varied outcomes.
NCT01637935 (results). ClinicalTrials.gov	Cohort: Pioglitazone and bladder cancer incidence	Pioglitazone exposure cohort	Bladder cancer incidence	Patients with type 2 diabetes (exposed vs unexposed)	Observational cohort (safety surveillance)	Completed / results posted	Focus: association between pioglitazone use and bladder cancer incidence (post-marketing safety analyses).
NCT02695121. ClinicalTrials.gov	Cancer in patients on dapagliflozin	SGLT2 inhibitor exposure cohort	Breast cancer (and other site analyses)	Type 2 diabetes patients	Observational cohort / pharmacoepidemiology	Completed / active	Assess incidence differences by prior insulin or drug exposure
NCT04572165. ClinicalTrials.gov	Semaglutide exposure & pancreatic cancer risk	Semaglutide (GLP-1 RA) safety surveillance	Pancreatic cancer risk	Type 2 diabetes patients on semaglutide	Observational / regulatory safety study	Recruiting / Active	Regulatory safety signal evaluation (pancreatic cancer risk).
NCT02347813. ClinicalTrials.gov	Preventing squamous cell skin cancer (pioglitazone basis)	PPARγ agonist mechanisms, prevention	Cutaneous squamous cell carcinoma (SCC)	Non-diabetic high-risk cohorts	Interventional / prevention	Completed / Active	Based on preclinical anti- SCC effects of pioglitazone

CONCLUSION

Diabetes, particularly Type 2 diabetes mellitus (T2DM), is associated with an increased risk of several types of cancer (e.g., liver, pancreatic, colorectal, breast, and endometrial cancers). This link is driven by pathophysiological factors that create a pro-tumorigenic environment. The intricate and bidirectional relationship between diabetes and cancer represents a growing public health challenge, underscoring the need for integrated research and clinical strategies. Accumulating evidence suggests that chronic hyperglycemia, insulin resistance, systemic inflammation, and shared genetic and environmental factors create a biological milieu conducive to tumor initiation and progression in individuals with diabetes.

While epidemiological studies have strengthened the link between these two conditions, mechanistic insights are gradually unraveling the molecular pathways that bridge metabolic dysregulation and oncogenesis. Recognizing diabetes as a significant risk factor for cancer opens opportunities for early screening, precision prevention, and therapeutic interventions tailored to this high-risk population. Future research must focus on elucidating the causal mechanisms, identifying predictive biomarkers, and evaluating the long-term safety and efficacy of antidiabetic drugs in cancer prevention and treatment. A comprehensive and multidisciplinary approach will be essential to mitigate the dual burden of diabetes and cancer, ultimately improving patient outcomes and reducing global disease burden.

Conflict of Interest

The authors declare no conflict of interest financial or otherwise.

Acknowledgment

Declared none.

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