Journal of Oncology Research and Therapy
Ahsan M, et al. Oncol Res Ther 10: 10296.
www.doi.org/10.29011/2574-710X.10296
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Research Article

The Role of Metformin in cancer Prevention and Treatment: A Game Changer?

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Citation: Ahsan M, Khan A, Abbas S, Farooq T, Aziz S, et al. (2025) The Role of Metformin in cancer Prevention and Treatment: A Game Changer?. J Oncol Res Ther 10: 10296. DOI: 10.29011/2574-710X.10296.

Received Date: 11 July, 2025; **Accepted:** 24 July, 2025; **Published Date:** 28 July, 2025.

Abstract

Metformin, a commonly used drug to manage type 2 diabetes, is now gaining attention for its potential role in fighting cancer. Over the years, researchers have discovered that metformin can do more than just control blood sugar—it may also slow down or stop the growth of cancer cells. This review looks at how metformin might help prevent or treat cancer by exploring how it works in the body, what lab and clinical studies have found, and how it could be used for different types of cancer. Metformin exerts direct antitumor effects by inhibiting mitochondrial respiratory complex I, leading to reduced reactive oxygen species (ROS) generation and enhanced AMP-activated protein kinase (AMPK) activity. These processes disrupt cancer cell energetics, induce apoptosis, and modulate key regulatory pathways including mTOR and NF-κB.

Aside from its direct effects, metformin also works behind the scenes by lowering insulin levels and reducing the activity of a growth factor called IGF-1, both of which can fuel cancer growth. New research suggests that metformin may also help by targeting cancer stem cells, improving the balance of gut bacteria, and even influencing how genes behave and how the immune system responds to cancer. While these findings are encouraging, there are still some limitations to using metformin more widely in cancer care, such as a lack of sufficient randomized controlled trials (RCTs), variability in dosing and effectiveness, and uncertainty about its mechanisms in specific types of cancer. In conclusion, metformin presents a safe, affordable, and potentially effective adjunct in cancer management. While early findings are encouraging, large-scale clinical trials are warranted to validate its oncologic benefits and optimize its therapeutic use.

Keywords: Metformin; Cancer Prevention; Cancer Treatment; AMPK; Insulin Resistance; Colorectal Cancer; Breast Cancer; Anticancer Mechanisms;

Abbreviations:

T2DM – Type 2 Diabetes Mellitus

AMPK – AMP-Activated Protein Kinase

mTOR – Mammalian Target of Rapamycin

ATP – Adenosine Triphosphate

AMP – Adenosine Monophosphate

ROS – Reactive Oxygen Species

CRC – Colorectal Cancer

NF-κB – Nuclear Factor Kappa-light-chain-enhancer of Activated B cells

IGF-1 – Insulin-like Growth Factor 1

ETC – Electron Transport Chain

FAP – Familial Adenomatous Polyposis

PDAC – Pancreatic Ductal Adenocarcinoma

NSCLC – Non-Small Cell Lung Cancer

HER2 – Human Epidermal Growth Factor Receptor 2

VEGF – Vascular Endothelial Growth Factor

ERK – Extracellular Signal-Regulated Kinase

PI3K/Akt – Phosphoinositide 3-Kinase / Protein Kinase B Pathway

MAPK – Mitogen-Activated Protein Kinase

RCT – Randomized Controlled Trial

GC – Gastric Cancer

HCC – Hepatocellular Carcinoma

EMT – Epithelial-Mesenchymal Transition

SHH – Sonic Hedgehog

ACC – Acetyl-CoA Carboxylase

FAS – Fatty Acid Synthase

ACLY – ATP Citrate Lyase

pS6K – Phospho-serine 6 Kinase

ADME – Absorption, Distribution, Metabolism, and Excretion.

Introduction

Metformin, a widely recognized and essential medication for managing type 2 diabetes mellitus (T2DM), has garnered attention for its potential role in cancer prevention and treatment. It has been associated with a decreased risk and improved prognosis in the incidence and outcome of colorectal cancer in patients with T2DM [1]. Since 2019, metformin has been included on the World Health Organization's list of essential medicines due to its low cost, excellent tolerability, safety profile, and minimal risk of hypoglycemia. These attributes make it the preferred choice for managing millions of patients with T2DM, either alone or in combination with other medications [2]. Metformin is extensively distributed throughout the body, including the liver, kidney, brain, and intestines. It is not digested and is removed unaltered by renal excretion. Plasma membrane monoamine transporter (PMAT) or organic cation transporter 3 (OCT3) on the luminal side of enterocytes promote the first absorption of metformin in the intestine following oral dosing [3]. In the 1920s and 1930s, guanidine derivatives were used to treat diabetic mellitus (DM), but their usage was stopped because of their toxicity when insulin became available [4]. As an insulin sensitizer, metformin enhances insulin action and decreases insulin resistance, which greatly contributes to glucose oxidative decomposition and liver glycogen synthesis [5]. As we know, CRC exhibits a linear progression from normal colonic epithelium to adenoma initiation and malignant transformation to carcinoma and even to metastasis [6]. Cancer is a leading cause of death worldwide and represents a growing major public health problem. The data collected reported that, in 2020, there were 19.3 million new cases and 10 million deaths from cancer worldwide. Breast cancer is the most diagnosed cancer in the world, followed by lung cancer. Prostate cancer was the most frequently diagnosed cancer in males, followed by lung cancer, non-melanoma skin cancer (NMSC), lip and oral cavity cancer, and liver cancer [7].

Mechanism of Action of Metformin in Cancer

Direct Anticancer Effects

Metformin exerts its influence on cancerous cell metabolism through the inhibition of respiratory complex I (NADH-coenzyme Q oxidoreductase), a component of the electron transport chain (ETC) located in the mitochondria. This inhibition leads to a decrease in the flow of electrons to complex III, where reactive oxygen species (ROS) are generated. Reduced production of ROS, oxidative stress, and DNA damage, thereby lowering the risk of mutagenesis. Mitochondrial dysfunction and cellular energy stress, resulting in a depletion of adenosine triphosphate (ATP) and an increase in the AMP/ATP ratio [8].

Additionally, recent research has established that metformin can induce alternative forms of cell death, such as pyroptosis, which involves inflammatory, caspase-1-dependent programmed cell death. Metformin induces pyroptosis through AMPK-dependent activation of sirtuin 1 (a nicotinamide adenine dinucleotide [NAD+]-dependent deacetylase) and downstream nuclear factor kappa B (NF-kB) expression [4]. Moreover, metformin has been shown to activate the tumor suppressor p53 in vitro, which appears to be AMPK-dependent. This activation leads to cell cycle arrest, especially in pancreatic cancer models [9].

Indirect Effects on Cancer Metabolism

Insulin plays a significant role in cancer development and progression through its mitogenic properties, such as promoting cell proliferation, increasing glucose utilization, decreasing apoptosis, and enhancing the response to growth factors like insulin-like growth factor 1 (IGF-1). IGF-1 is a more potent mitogen than insulin, and it stimulates cell growth and anti-apoptotic activity via MAPK/ERK or Ras/Raf/MEK/ERK and PI3K/Akt/mTOR signaling [9]. Metformin counteracts these mitogenic effects by reducing insulin and IGF-1 signaling, thereby inhibiting cancer growth.

Epigenetic and Immunomodulatory Effects

Metformin has been shown to influence epigenetic mechanisms in cancer cells, potentially altering gene expression and modifying cellular behavior. Additionally, metformin may enhance immune responses, improving the body's ability to recognize and attack cancer cells.

Metformin's Effect on Cancer Stem Cells:

The critical role of cancer stem/initiating cells in tumorigenesis and cancer development has led to investigations into how metformin affects these cells. Studies have found that metformin (at concentrations of 1 mM) can activate hex ribonucleotide-binding protein 3 (FOX3) via AMPK activation, which is sufficient to promote the differentiation of glioma-initiating cells into non-tumorigenic cells [3].

Metformin and AMPK Activation:

AMPK activation is central to many of metformin's anticancer effects. AMPK is activated when adenosine monophosphate (AMP) binds to the ?-subunit, inducing structural changes that lead to phosphorylation of the a-subunit at Thr172. Metformin may mediate AMPK activation by increasing the AMP/ATP ratio, though it has also been suggested that metformin could directly bind to the γ-subunit of AMPK. The exact mechanism of this direct binding and its ability to activate AMPK remains unclear [3].

Metformin and Gut Microbiome Modulation:

The bioavailability of metformin in the gut is approximately 300 times higher than in plasma, which underscores its influence on gut microbiome modulation. Studies have shown that metformin can alter the composition of the gut microbiome by increasing the proportion of beneficial bacteria, such as Akkerman Sia municipia, Bacteroides, Butyric monas, Megasphaera, and Prevotella, while decreasing harmful bacteria like Anaerotruncus, Lactococcus, and Parabacteroides [3]. Dysbiosis of the gut microbiome has been implicated in various diseases, including cancer, glucose metabolism disorders, aging, and even acquired immunodeficiency syndrome (AIDS).

Epidemiology of Metformin Use And Cancer Reduction Risk

Cancer remains a leading global cause of morbidity and mortality, with a rising incidence in various populations. Epidemiological studies suggest that type 2 diabetes mellitus (T2DM) is associated with an increased risk of multiple cancers. Metformin, a first-line therapy for T2DM, has been postulated to reduce cancer risk through its effects on cellular metabolism, inflammation, and insulin signaling. Several observational studies and meta-analyses have explored this potential association, providing insights into metformin's role in cancer prevention.

A substantial body of research, including retrospective cohort studies, case-control studies, and meta-analyses, has investigated the link between metformin use and cancer risk reduction. Findings from these studies suggest that metformin users have a lower incidence of various cancers compared to those using other antidiabetic medications.

Meta-analysis by Gandini et al. (2014): A systematic review of 47 studies reported a 31% reduction in overall cancer risk among metformin users (relative risk [RR] = 0.69, 95% confidence interval [CI] = 0.52–0.90). [10]. Retrospective cohort study by Lee et al. (2012): Found that diabetic patients using metformin had a 37% lower cancer risk compared to those using insulin or sulfonylureas (hazard ratio [HR] = 0.63, 95% CI = 0.53–0.74) [11].Case-control study by Franciosi et al. (2013): Reported a significant association between metformin use and reduced colorectal cancer risk (odds ratio [OR] = 0.74, 95% CI = 0.61–0.88) [12].

Cancer-Specific Epidemiological Findings

The protective effect of metformin varies by cancer type. Key epidemiological findings include

Colorectal Cancer

Several meta-analyses suggest that people who use metformin may have a 20–40% lower risk of certain health outcomes compared to

non-users. For example, a study by Zhang et al. (2021) found that metformin users had a relative risk of 0.78 (95% CI: 0.66–0.91), indicating a meaningful reduction in risk and supporting the idea that metformin could have protective benefits beyond its role in managing blood sugar [13].

Breast Cancer

A study by DeCensi et al. (2015) reported a 25% reduction in risk among metformin users, with a hazard ratio (HR) of 0.75 (95% CI: 0.61–0.93). The findings also suggested potential survival benefits, highlighting metformin's possible role beyond glycemic control in contributing to improved breast cancer outcomes [14].

Pancreatic Cancer

Multiple large meta-analyses and systematic reviews have found that people with type 2 diabetes who use metformin have a lower risk of developing pancreatic cancer compared to those who do not use it or who are on other diabetes medications. These findings suggest a potential protective effect of metformin against one of the most aggressive forms of cancer [15].

Lung Cancer

Several large cohort studies and meta-analyses have suggested that metformin use may be linked to a reduced risk of developing lung cancer, especially among individuals with diabetes. Some evidence even points to a possible dose-response relationship, indicating that higher or prolonged use could be more protective [16, 17]. However, findings across the literature are not entirely consistent. While some studies report no significant overall reduction in lung cancer incidence among metformin users, certain subgroups-such as male smokers and female nonsmokers-appear to experience more pronounced benefits [18].

Prostate Cancer

Some studies and meta-analyses suggest that metformin use may be linked to a reduced risk of developing prostate cancer, particularly with long-term use. However, the evidence remains mixed. While certain analyses report a protective effect, others have found no significant association, and a few even suggest a potential increased risk in specific populations. These conflicting findings highlight the need for further research to clarify metformin's role in prostate cancer prevention [19, 20].

Preclinical & Clinical Studies (In Vitro And Animal Models)

Cancer cells (5×10^6^) were injected into the right flank of female nu/nu mice (Charles River Laboratories), all of which developed tumors in 10 days with a size of ~55 mm^3. For each experiment, mice were randomly distributed into equal groups (3–4 mice per group) that were untreated (NT) or treated by intra-tumoral injections every 5 days (four cycles) with 1 mg/kg or 4 mg/kg doxorubicin, 10 mg/kg paclitaxel, 20 mg/kg carboplatin, 200 μg/ml metformin (diluted in the drinking water and present throughout the experiment starting at day 10), or combinations that included metformin. Tumor volume (mean ± SD) (mm^3) was measured at various times after the initial injection. All the mouse experiments were performed in accordance with Institutional Animal Care and Use Committee procedures and guidelines of Tufts University [21].

Clinical Evidence with Metformin in Cancer Prevention and Treatment:

Several studies assessed the influence of metformin on metabolic status in cancer patients with and without diabetes. It was observed in nondiabetic women that, in early-stage breast cancer, metformin reduced fasting insulin by 22% and improved several metabolic parameters [22]. Running parallel regulatory programs has been proposed to increase confidence in new approaches and to enhance the transition to implement novel methods. This could facilitate a more human-centric approach for translational sciences by using human cell systems with varying degrees of complexity and combining them with in silico and in vivo studies to define PK parameters and potential toxic (side) effect. Multi-organ body-on-chips have already been developed to simulate whole-body (patho) physiology and also account for the absorption, distribution, metabolism, and excretion (ADME) of pharmacological compounds [23]. A multicenter randomized trial of metformin in individuals with Barrett's esophagus who were taking a proton pump inhibitor showed no significant change in phospho-serine 6 kinase (pS6K), a biomarker of insulin pathway activation, comparing baseline endoscopy biopsies with end-of-study biopsies [24]. Many clinical trials have shown that chemopreventive drugs can inhibit the growth of adenomatous polyps in patients with FAP. However, their long-term use is often limited by side effects. Metformin, a well-known first-line antidiabetic drug, has also been recognized for its antitumor effects [25].

Uses of Metformin in Different Types Of Cancer:

Breast Cancer:

Metformin has attracted considerable attention due to its potential impact on breast cancer. Previous studies have indicated that the long-term use of metformin can reduce the risk of breast cancer in diabetic women [26]. Additionally, it has been reported that long-term metformin treatment can decrease the risk of ER-positive breast cancer [27]. Metformin has been found to have various effects on breast cancer. In a study by Vazquez-Martin et al., it was discovered that metformin inhibits the growth of breast cancer cells by reducing the levels of HER2 through the modulation of the AMPK/mTOR/p70S6K1 axis [28]. Metformin was also found to reduce the serum levels of estradiol in patients, which may be a possible mechanism for its ability to resist breast

cancer development [29]. Furthermore, metformin inhibited the expression of cyclooxygenase (COX) 2, which is known to promote breast cancer proliferation and angiogenesis, thereby limiting the metastasis of breast cancer [30, 31]. Metformin also inhibits angiogenesis by targeting the HER2/HIF-1a/VEGF secretion axis [32].

Gastric Cancer:

Use of metformin has demonstrated significant positive effects in the management of gastric carcinoma across multiple clinical trials [33,34]. In addition, metformin has been found to induce apoptosis in patients with gastric cancer (GC). This process is mediated by AMPK, which inhibits mTOR and mitochondrial complexes, ultimately leading to the apoptotic death of GC cells while sparing normal functioning cells. Metformin has been found to attenuate metastasis in GC through its effects on different proteins. One such group of proteins is cadherins, which are involved in cell–cell communication. Metformin's influence on these proteins helps prevent the migration and growth of cells in other parts of the body, a process known as the EMT [33]. Another important aspect of cancer progression is the maintenance of cancer cell stemness. Metformin has been identified as a potential regulator of this process. One specific gene, known as sonic hedgehog (SHH), has been studied in relation to cancer and is considered a potential therapeutic target [34]. Despite extensive research on the interplay between GC and metformin, there are still numerous underlying mechanisms that remain unidentified. One innovative approach to comprehending the role of metformin in GC involves analyzing RNA sequences [33].

Colorectal Cancer (CRC)

When considered as an adjuvant therapy in CRC, metformin has been proven effective, as it decreases the CRC proliferation, stemness, and metastatic activity [35]. Metformin-induced apoptosis has been linked to Bcl-2, Bax, Caspase-3, Mcl-1, and TRAIL [36]. Although there are currently no approved therapeutic interventions targeting this pathway, metformin has been hypothesized to reduce the proliferation and stemness induced by this pathway. Experiments with metformin have demonstrated a decrease in ß-catenin levels, resulting in a reduction in the EMT. However, there is currently insufficient evidence to directly link metformin to the Wnt/B-catenin pathway [37].

Liver Cancer

Research has demonstrated that the administration of metformin, a medication used to treat diabetes, is associated with a reduced risk of HCC and exerts a protective effect against its development [38, 39]. Metformin has also been implicated in the prevention of liver metastasis [40]. One potential therapeutic agent that has shown promise in modulating these pathwaysis metformin. Upon activation by metformin, AMPK reduces the degradation of I?Ba, thereby attenuating NF-?B signaling, decreasing IL-6 expression, and inhibiting STAT3 signaling. This is supported by the observation that the inhibitory effect of metformin on proliferation is significantly reduced in cells transfected with p65 (a subunit of NF-?B) or IBSR (an inhibitor of I?B degradation) [41]. Furthermore, it is worth noting that liver tumors often exhibit increased lipogenesis and fatty acid production [42]. In this regard, Bhalla et al. demonstrated that metformin can decrease HCC by inhibiting de novo lipogenesis through the suppression of key enzymes involved in this process, such as ACC, fatty acid synthase (FAS), and ATP citrate lyase (ACLY), at both the mRNA and protein levels [43]. These findings highlight the multifaceted nature of metformin's potential therapeutic effects in HCC.

Lung Cancer

Numerous studies have highlighted the potential benefits of using metformin in the fight against lung cancer. For instance, Xiao et al. demonstrated that metformin treatment significantly reduced the incidence of Non-Small Cell Lung Carcinoma (NSCLC) [49]. Recent research has also shown that the use of metformin is associated with a lower risk of lung cancer and improved progression-free survival in patients with advanced lung adenocarcinoma when combined with EGFR-TKI therapy [50, 51]. Preclinical studies on NSCLC have demonstrated that the use of metformin activates AMPK, leading to the induction of p53, the suppression of mTOR, and the inhibition of tumor growth. This ultimately enhances the tumor's response to radiotherapy and chemotherapy [52, 53].

Ovarian Cancer

Metformin has demonstrated promising anticancer effects in research conducted on ovarian cancer. According to a recent cohort study, the prolonged use of metformin in ovarian cancer patients was linked to a decrease in mortality rates and improved overall survival [49]. Metformin has been shown to reduce the transcription of Axl and Tyro3, two receptor tyrosine kinases associated with cell survival and resistance to apoptosis, in ovarian cancer cells [50]. It also inhibits the activation of downstream signaling molecules, including Erkand STAT3, in triple-negative breast cancers [51]. Metformin has also been found to inhibit the growth of ovarian cancer cell lines and reduce angiogenesis, adhesion, and macrophage infiltration in both in-vitro and in-vivo models [52, 53, 54].

Pancreatic Cancer:

It is worth noting that pancreatic ductal adenocarcinoma (PDAC) comprises more than 90% of all pancreatic cancer cases [55]. Metformin exerts its effects on PDAC through two distinct mechanisms. Firstly, it can directly impact pancreatic cells, and

secondly, it can indirectly influence PDAC through systemic pathways [56, 57] Recent research has also demonstrated that metformin induces apoptosis in pancreatic cancer cells by downregulating PCAF proteins . However, the exact mechanism through which metformin affects human cells, particularly in the context of PDAC, is not yet fully understood [58]. For more precision, further research is necessary to fully comprehend the implications of metformin in PDAC progression and growth [59].

Limitation

Metformin, traditionally known as an antidiabetic medication, has garnered attention for its potential anticancer properties, largely due to its ability to activate AMP-activated protein kinase (AMPK) and inhibit the mTOR pathway [60]. These mechanisms are thought to suppress cell growth and proliferation, which could hinder cancer progression. However, the precise mechanism through which metformin exerts its anticancer effects remains unclear, and it likely varies across different types of cancer. While several studies have pointed to metformin's potential in cancer treatment and prevention, clinical evidence remains insufficient and somewhat contradictory. Some trials suggest a promising role for metformin in reducing cancer risk or improving outcomes, particularly in patients with diabetes, but other studies fail to support its effectiveness in cancer treatment [61]. Additionally, a significant challenge in translating preclinical findings to clinical practice is the dosing issue. Experimental studies often use much higher doses than those achievable in human patients, with plasma levels 10 to 100 times greater than those seen in typical therapeutic doses [62]. Furthermore, the anticancer effects of metformin seem to vary across different cancers, with some studies indicating its potential in cancers like breast and colorectal, while others show limited or no effect [63]. Thus, despite its promising preclinical data, the role of metformin in cancer treatment remains uncertain, and further research is necessary to fully understand its efficacy and optimal use in oncology.

Future Directions And Potential For Clinical Integration:

The future potential for integrating metformin into cancer treatment looks promising, with several key areas that warrant further exploration. Personalized medicine is playing a crucial role, as doctors increasingly identify specific biomarkers to classify patients into subgroups that are likely to benefit most from metformin. This not only boosts the drug's effectiveness but also helps reduce its adverse effects. Additionally, advances in drug formulations and delivery systems are improving how metformin works in oncology, making treatments more targeted and reducing systemic side effects. These newer delivery methods also improve patient adherence to treatment. Combining metformin with other therapies, such as immunotherapy, targeted therapy, and radiotherapy, has shown promising synergistic effects in early studies, suggesting that combining these approaches could further enhance cancer treatment. However, to truly understand the full potential of metformin in cancer care, large-scale, randomized controlled trials are essential. These trials will provide the solid evidence needed to confirm the drug's efficacy and safety in a broader clinical setting.

Conclusion

Metformin is broadly used as medication for type 2 diabetes and according to recent studies it's an important agent in cancer treatment and prevention. Metformin inhibits cancer cell proliferation, induces apoptosis and enhances the efficacy of conventional cancer therapy. The potential impact of metformin on cancer is diverse. When combined with radiotherapy and chemotherapy as an adjunct it may improve results. Metformin is an attractive option for long term use in cancer prevention due to its low cost and favorable safety profile. Clinical trials exploring its effects in a variety of cancer treatment Though the initial evidence shows metformin's role is effective, it's important to use it with caution in the concept of it being the" game changer". For knowing its clear efficacy and safety profiles more strong clinical trials are needed to be conducted further investigations are important for understanding its role in cancer treatment and prevention.

Declaration

Funding: Not applicable

Conflicts of interest/Competing interest: Not applicable

Ethics Approval: Not applicable

Consent to Participate: Not applicable

Written Consent for Publication: Not applicable

Availability of Data and Material: Not applicable

Code Availability: Not applicable

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