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Metformin in Oncology- Its Effect on Cancer Development and Progression

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ABSTRACT

Purpose: This review examines the mechanisms and role of action of metformin in oncology, highlighting its potential as an anti-cancer drug beyond its primary use in the treatment of type 2 diabetes. The article discusses the molecular pathways affected by metformin, as well as its clinical applications in various cancers, and synergistic effects with conventional therapies. Materials and Methods: The review synthesizes key preclinical and clinical studies on the anti-cancer properties of metformin, on its effects on metabolic pathways, induction of apoptosis, and modulation of the tumor microenvironment. We analyzed data on breast, colorectal, prostate, lung, pancreatic, and ovarian cancers. Results and discussion: Metformin exhibits multi-directional anti-cancer effects, including inhibition of tumor growth, inhibition of angiogenesis, and enhancement of response to chemotherapy and immunotherapy. Epidemiological studies have reported that cancer risk is reduced and prognosis improved in diabetes patients treated with metformin. Future work regarding dosing and patient selection is discussed. Conclusions: Metformin is a very interesting drug in the oncologic context, as it may be helpful not only for prevention, but also as adjuvant to treatment. Additional clinical studies should evaluate its integration with other existing therapies and its potential place in personalized cancer therapy.

Keywords: metformin, mTOR, oncology, IGF-1, tumor.

1. INTRODUCTION

Metformin is an anti-diabetic drug belonging to the biguanide group, and for many years it has remained one of the most widely used agents in the treatment of type 2 diabetes. Its main mechanism of action is to inhibit gluconeogenesis in the hepatocytes, resulting in decreased glucose production, and to increase the sensitivity of tissues, like skeletal muscle and adipose tissue, to insulin (Zhou et al., 2001). The effect on carbohydrate metabolism makes metformin effective in lowering blood glucose levels and reducing insulin resistance, a key component in

the treatment of type 2 diabetes. In addition, the drug has a favourable safety profile, with relatively low risk of hypoglycemia and a positive effect on patients' body weight, which distinguishes it from some other hypoglycemic drugs. In recent years, a growing number of studies have indicated that metformin may also exhibit anti-cancer effects. This mechanism is due to its ability to modulate metabolic and molecular pathways involved in the development and progression of cancer (Pollak, 2012). Epidemiological studies suggest that patients with type 2 diabetes taking metformin may have a lower risk of certain cancers, such as pancreatic, breast, ovarian, colorectal, lung, and prostate cancer, compared to patients treated with different drugs from this group.

Moreover, many clinical trials are ongoing for testing the possible use of metformin, as an adjuvant to classical treatments including chemotherapy and radiation, and as a preventive agent in at-risk populations with cancer. There are also theories on the potential of metformin in overcoming the resistance of cancer to treatment and the enhancement of immunotherapy. This review endeavors to provide an overview of the role and use of metformin in oncology, specifically in the context of its effect on cancer biology, the putative mechanisms of action it may impart, and its potential use in clinical practice as part of anti-cancer treatment.

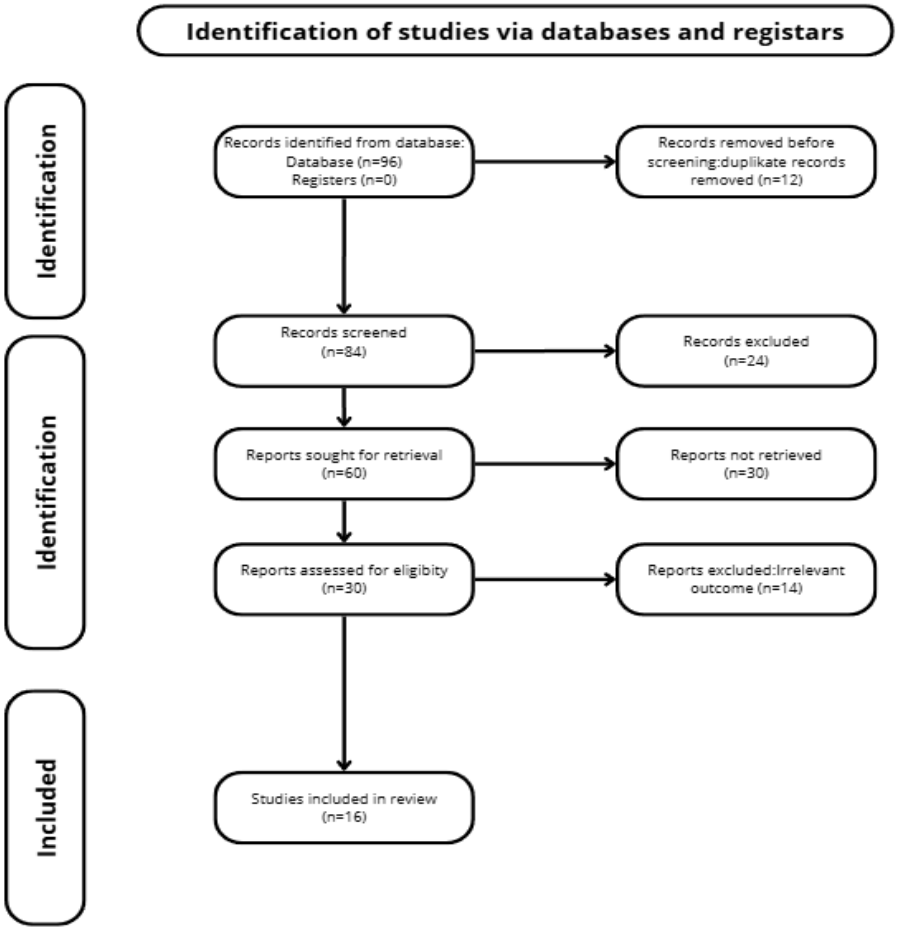

Figure 1 PRISMA consort chart of selected studies

2. REVIEW METHODS

A systematic literature search was performed using the following electronic databases: PubMed, Scopus, and Web of Science. The search was conducted using combinations of the following keywords and Medical Subject Headings (MeSH): “metformin,” “cancer,” “anti-tumor,” “anti-neoplastic.”

Inclusion Criteria:

Studies were included if they met the following criteria:

1. Publication type: Original research articles, randomized controlled trials (RCTs), cohort or case-control studies, systematic reviews, and meta-analyses.

2. Study focus: Investigated the effect of metformin on cancer incidence, progression, survival, or molecular mechanisms relevant to tumor biology.
3. Tumor types: Focused on colorectal, breast, prostate, pancreatic, ovarian
4. Language: Published in English.
5. Publication date: Between January 2000 and March 2025.
6. We included 16 articles in this systematic review study (Fig.1)

Exclusion Criteria:

Studies were excluded based on the following criteria:

1. Publication type: Editorial, letter to the editor, case report, conference abstract without full text, or narrative review that did not perform data synthesis.
2. Irrelevant outcomes: Articles focusing solely on the antidiabetic effects of metformin without reference to oncological endpoints.
3. Duplicated data: Research with the same data or with outcomes already present in wider meta-analyses.
4. Insufficient data: Articles lacking transparent methodology, statistical analysis, or full-text access.

3. RESULTS AND DISCUSSION

Mechanisms of action of metformin in oncological disease

Inhibition of the mTOR pathway

Metformin activates AMP-activated protein kinase (AMPK) by increasing the ratio of AMP to ATP in the cell, leading to metabolic energy stress (Shaw et al., 2005). The active form of AMPK has an inhibitory effect on the mTOR (mechanistic target of rapamycin) pathway, which is a key regulator of cancer cell proliferation, growth, and survival (Dowling et al., 2007). The mTOR signalling pathway regulates ribosome function, growth factor expression, and is central to the regulation of protein translation. Suppression of the mTOR pathway leads to impaired protein synthesis, which is required for cancer cell growth (Zakikhani et al., 2006). Moreover, suppression of mTOR signaling promotes the stop of cell cycle progression into GI phase, also inhibiting tumor progression. Metformin has also been shown to potentiate targeted therapies (e.g., PI3K inhibitors) and platinum-based chemotherapeutics through inhibition of the mTOR pathway.

Induction of apoptosis and inhibition of angiogenesis

Metformin induces apoptosis in cancer cells by generating reactive oxygen species (ROS), which cause DNA damage and oxidative stress. This pathway induces the activation of caspases and the mitochondrial-driven apoptotic-degradation pathway. Metformin also results in a reduction in the anti-apoptotic protein Bcl-2 and elevation in the pro-apoptotic Bax expression, inducing apoptosis-mediated cell death (Ben Sahra et al., 2008). Furthermore, metformin can modulate p53-dependent signalling pathways, both through upregulation of pro-apoptotic factors in cancer cells. Angiogenesis, the development of new blood vessels, is an essential component that facilitates tumorigenesis. Metformin also presents anti-angiogenic properties, which are mediated through the downregulation of vascular endothelial growth factor (VEGF) and HIF-1a, which is a protein involved in the cellular response to oxygen tension (Memmott et al., 2010) Reducing angiogenesis results in a reduced blood supply of oxygen and nutrients to the tumor, leading to tumor shrinkage. Moreover, metformin can inhibit the activity of MMPs, leading to the inability of neoplasia cells to invade and metastasize.

Effects on cancer cell metabolism

Cancer cells, due to their increased need for both energy and nutrients, frequently become addicted to their metabolism, utilizing the Warburg effect, which involves relying on glycolysis instead of oxidative phosphorylation, even in the presence of oxygen. Metformin decreases the glucose supply to cancer cells and inhibits their growth (Buzzai et al., 2007) The removal of glucose metabolism inhibitors compromises the lactate production and the pH of the tumour micro-environment. Metformin also reduces the production of fatty acids used to make cell walls in quickly proliferating cancer cells (Ben Sahra et al., 2008) When lipogenesis is blocked there is a deficiency of those phospholipids necessary for the growth of the cancer cells. Metformin also perturbs the metabolism of glutamine, which is an important amino acid that cancer cells use to make nucleotides and other molecules necessary for life. Glutamine deprivation also makes cancer cells more vulnerable, especially in a nutrient-poor environment.

Indirect effect - lowering insulin and IGF-1 levels

Insulin and insulin-like growth factor (IGF-1) are potent growth factors for cancer cells. In type 2 diabetes, there are high insulin levels, which can drive cancer. Activation of mitogenic pathways such as PI3K, Akt, and mTOR is inhibited by metformin (Decensi et al., 2010). Metformin may reduce insulin levels, and its anti-tumour effect may also directly affect tumour cells. Additionally, metformin may influence the tumour microenvironment by limiting the tumour's exposure to growth factors. IGF-1 is one of the most significant modulators of cancer cell proliferation and their resistance to anti-neoplastic treatments. By lowering IGF-1 levels, metformin limits its ability to trigger anti-apoptotic signalling.

Furthermore, metformin is reported to have a synergistic effect with the IGF-1 inhibitors. It potentiates the efficacy of most anti-cancer drugs. Furthermore, lowering insulin and IGF-1 could also act on the immune system, enhancing the capacity of lymphocytes to destroy cancer cells and impeding their escape from immune control.

Effects of metformin on different types of cancer

Breast cancer

It has recently been reported that metformin suppresses the proliferation of breast cancer cells by aiming the mTOR pathway and inducing apoptosis. It is considered that this drug may be applied as an adjuvant for hormone-dependent cancers (Dowling et al., 2007). Metformin's mechanism of action is also related to the metabolic activities of cells, which results in a lowered energy supply to dividing cancer cells. We found that in patients with type 2 diabetes treated with metformin, the incidence of pCR following NAC was higher than that in patients who had not received metformin. These data provide evidence that metformin can increase the sensitivity of esophageal cancer cells to cytostatics (Jiralerspong et al., 2009).

Furthermore, preclinical studies suggest that metformin has synergistic effects when combined with other classes of anti-cancer agents, such as inhibitors of the PI3K/AKT/mTOR pathway. Therefore, it may constitute an optimal partner in combination regimens. This is based on suppressing breast cancer cell proliferation by arresting mTOR signaling and reducing the expression of substances that promote cancer cell survival (Zakikhani et al., 2006). Furthermore, metformin may also benefit TME by decreasing insulin and growth factors, thereby reducing tumor proliferative stimulation. There is more and more evidence that metformin use reduces both the risk of breast cancer relapse and the prognosis of patients, particularly in receptor-positive cancers.

Colorectal cancer

Metformin has chemopreventive effects on cancer, making it a potential tool in cancer prevention, especially in high-risk individuals. Experimental findings have also revealed the preventive influence of metformin on the initiation phase of carcinogenesis, as short-term administration of metformin decreased the number of aberrant crypts in the colorectal mucosa. This is relevant because aberrant crypts are regarded as an early biomarker of colon carcinogenesis. Furthermore, metformin may induce antitumor effects by regulating the intestinal microenvironment, which includes modifying the composition of intestinal microbiota and reducing inflammation levels closely associated with colorectal cancer (Hosono et al., 2010). Additionally, FASN expression is reduced, and metformin can suppress the proliferation of tumor cells, thereby inhibiting the mechanism of colorectal cancer (Algier et al., 2010). FASN is an essential enzyme for de novo lipid synthesis in cancer cells. It is frequently overexpressed in aggressive tumors; reducing this pathway with metformin results in decreased growth and increased apoptosis of cancer cells. Metformin also modulates metabolic pathways related to AMP kinase (AMPK) activation, which, through inhibition of the mTOR pathway, decreases cell proliferation.

Clinical research has shown that the use of metformin in type 2 diabetes patients is associated with a decreased risk of cancer (Hosono et al., 2010). It has also been reported that people with diabetes who use metformin have a better prognosis if they develop cancer, which may be attributed to its well-documented anti-cancer action. Moreover, additional evidence suggests that metformin may enhance the antitumor effect of anti-cancer treatments, particularly cytotoxic drugs, by sensitizing cancer cells to cytotoxic therapy. Further studies are ongoing trying to identify the ideal doses and the best population, among those individuals affected by colorectal cancer proneness, to treat with metformin for prevention and treatment of CRC.

Prostate cancer

In vitro data have shown that metformin induces apoptosis in prostate cancer cells by regulating p53-dependent metabolic pathways (Ben Sahra et al., 2008). Key mediator of the p53/TP53 signal transduction pathway and modulates p53 activity, playing a role in the

regulation of the p53/TP53 response to DNA damage and the induction of apoptosis. Activation of this pathway by metformin inhibits growth and induces apoptosis of cancer cells.

Furthermore, metformin alters the mitochondrial energy metabolism of prostate cancer cells by inhibiting ATP synthesis, leading to decreased cancer cell survival under the harsh conditions of the tumor microenvironment. Furthermore, metformin suppresses the growth of prostate tumors in mice by downregulating fatty acid synthase (FASN), a rate-limiting enzyme in the synthesis of lipids required for the rapid development of cancer cells (Algier et al., 2010). FASN is over-expressed in aggressive prostate cancers and is correlated with a worse outcome for patients. This pathway is blocked by metformin, depriving the tumor of the lipids used to make cell membranes and for the stored energy it needs to grow. Metformin also presents anti-tumor activity through reprogramming the tumor microenvironment. Research has shown that the drug can lower insulin and insulin-like growth factors, which are believed to be responsible for promoting the progression of prostate cancer. High amounts of insulin and IGF-1 are connected with a higher risk of cancer progression and hormone therapy resistance. Metformin can directly or indirectly reduce these factors, thereby leading to the suppression of the activation of the PI3K/AKT/mTOR pathways, which subsequently inhibit tumor and invasion and metastasis capabilities.

Additionally, metformin therapy in patients with type 2 diabetes is linked with a lower chance of prostate cancer and reduced aggressiveness of the disease in clinical trials. It was also reported that men taking metformin seem to have a better response to hormone therapy, particularly in castration resistant prostate cancer. Metformin may enhance the effectiveness of anti-androgens by also blocking the resistance of cancer cells to hormone therapy. More investigation is required to identify suitable dosages and the subset of patients who may potentially benefit the most from metformin for prostate cancer.

Lung cancer

Lung cancer is one of the more frequent cancers seen worldwide, with its development closely associated with exposure to carcinogens, particularly present in tobacco smoke. Studies both in vitro and in vivo show that metformin has excellent potential in the chemoprevention and treatment of cancer. Metformin was found to block the formation of tobacco-specific nitrosamine-induced lung tumors in mice, implying its therapeutic value for lung cancer chemoprevention (Memmott et al., 2010). This finding might be explained by the potential effect of metformin in the mTOR pathway, a central pathway in the regulation of growth and proliferation of cancer cells. Therefore, by blocking this pathway, cells are unable to replicate due to metformin. The molecular cascades that drive the anti-tumor effect of metformin are through AMPK activation, which in turn phosphorylates cell-metabolism inhibitors as well as inhibits protein/lipid synthesis needed for cancer cells' proliferation.

Furthermore, metformin lowers both insulin and IGF-1 levels, which are linked to the development of lung cancer. Elevated levels of these factors facilitate the growth of cancer cells and make them less responsive to therapy. In this respect, metformin-induced reduction of insulin could be protective due to decreased activation of cancer cell proliferation. Metformin can also inhibit the tumor micro-environment that mediates the immune system's response. The drug is believed to enhance the activity of T lymphocytes and macrophages, which are crucial in attacking and destroying cancer cells, according to studies. Moreover, metformin is an anti-inflammatory agent that could lower chronic inflammation in the lungs, which is one of the conditions that predispose the lung cells to develop cancer. Furthermore, the drug has an impact on angiogenesis (the development of new blood vessels), which is necessary for the growth and spread of cancer.

Angiogenesis inhibition by metformin could reduce the nutrient and oxygen supply to cancer cells, thereby affecting their growth. Clinical investigations suggest that metformin may enhance the efficacy of chemotherapy in lung cancer. There is evidence that type 2 diabetics taking metformin have a decreased lung cancer incidence and better prognosis from cancer diagnosis. It might also make cancer cells more sensitive to chemotherapy and radiation therapy. More studies are still in progress to elucidate the optimal information itineraries, which, in the fight against lung cancer, may also involve taking metformin on boar.

Pancreatic cancer

Pancreatic cancer is among the most aggressive cancers, has a low survival rate, and current treatments have limited effects. An increasing number of reports suggest that metformin might be involved in the prevention and treatment of this tumor. The action of metformin is in the suppression of the IGF-l (insulin-like growth factor l) pathway, which is necessary for pancreatic cancer cells to proliferate and survive. IGF-1 and insulin activate the PI3K/AKT/mTOR axis, which is responsible for tumour growth and resistance to treatment. Blockade of this pathway by metformin leads to the suppression of anabolic process activation and slows down tumor

growth speed, as well as the capacity for resistance to apoptosis (Kisfalvi et al., 2009). Another anti-tumor action of metformin in pancreatic cancer is to promote tumor cell apoptosis. The drug is an activator of the AMPK kinase, resulting in attenuation of protein synthesis, inhibition of proliferation, and increased sensitivity to metabolic stress in cancer cells.

In addition, metformin modulates mitochondrial energy metabolism, decreasing ATP generation in cancer cells, which may lead to cancer cell death due to nutrient deprivation. Metformin has also been shown to block EMT, a crucial step in cancer cell migration and metastasis, according to preclinical evidence. Inhibition of EMT by metformin may be expected to decrease the aggressiveness of pancreatic cancer and metastatic spread. Clinical trials have shown that metformin may prolong survival in patients with pancreatic cancer. Patients with type 2 diabetes using metformin had superior survival rates to those receiving alternative hypoglycemic agents or no treatment at all. The beneficial effect of metformin on pancreatic cancer prognosis may result not only from its direct anti-tumor activity (TA) effect but also from its role in improving systemic metabolic homeostasis. This drug is used as a first-line treatment for pancreatic cancer. In addition to direct effects on cancer cells, metformin appears to impact the tumor microenvironment, which has been implicated in the pathogenesis of pancreatic cancer. Persistent inflammation and cross-talk with tumor stroma cells contribute to treatment resistance and the progression of rapidly growing tumors.

Metformin is anti-inflammatory and decreases the generation of pro-inflammatory cytokines (e.g., TNF-α and IL-6), an event that may have implications for the down-regulation of tumor growth. Additional clinical trials are underway in this field, aiming to determine the most effective treatment regimen that incorporates metformin as a component of chemotherapy in pancreatic cancer treatment, as well as to identify patients for whom it is most beneficial.

Ovarian cancer

Ovarian cancer is one of the main cause of death among gynecological malignancies, and the aggressive nature and advanced stage at the time of diagnosis restrict the efficacy of treatment. Nevertheless, according to emerging depictions, metformin may also have a significant treatment effect on the prognosis of patients with this cancer.

Metformin also exerts its anti-cancer effects by modulating the tumor microenvironment and suppressing the proliferation of ovarian cancer cells (Gotlieb et al., 2008). Tumor microenvironment has an essential role in the progression of ovarian cancer, such as the invasion of the immune response, drug resistance, and the formation of distant metastasis. Metformin may exert an anti-inflammatory effect by lowering the levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, which stimulate tumor growth. In the case of ovarian cancer, one of the significant effects of metformin is on cancer cell metabolic and proliferative-signaling pathways. The drug stimulates the AMPK kinase, a central metabolic regulator within cells. During AMPK activation, the mTOR pathway, which regulates cell growth and proliferation, is suppressed. Accordingly, metformin impairs the proliferation and survival of ovarian cancer cells in a tumor microenvironment.

Metformin also modulates the mitochondrial energy metabolism of the tumor, resulting in decreased ATP production and increased metabolic stress, which, in turn, induces apoptosis in the cancer cells. Clinical evidence indicates that metformin is beneficial in ovarian cancer (Zhang et al., 2011).

Vintage analyses demonstrated that time to death was longer in type 2 diabetes patients who were treated with metformin, when compared with those who were not treated with metformin. The reason for this amelioration may not be considered solely as an effect of metformin as an anti-diabetic agent, but also its simultaneous influence in inhibiting both insulin and IGF-1. Elevated blood insulin is linked to an increased risk of ovarian cancer progressing, as it encourages tumour cells to grow and resist chemotherapy. This effect is reduced by metformin, potentially leading to inhibition of tumor growth and an enhancement of the therapeutic effect.

There is also increasing evidence that metformin may sensitize ovarian cancer cells to conventional chemotherapy. It has been demonstrated that it could sensitize cancer cells to cytotoxic drugs, including cisplatin and paclitaxel, by enhancing the apoptosis and suppressing the resistant mechanisms in cancer cells. Metformin has also been shown to block EMT (epithelial to mesenchymal transition), which is critical to ovarian cancer invasiveness and metastasis. Through inhibition of EMT, metformin might restrict tumorigenesis and decrease the risk of relapse following therapy. Additional clinical trials are in progress to define the best regimen for the treatment that could involve metformin in combination therapy for ovarian cancer.

In summary, metformin appears to be a beneficial supplement to cancer treatment, as it not only has anti-diabetic effects but also exhibits multi-directional anti-tumor effects (Table 1). Its application in the clinic can improve the efficacy of treatment and the prognosis of patients.

Table 1. Summary of metformin's effects on different types of cancer.

Cancer Type	Mechanisms Involved	Clinical Benefit
Breast	AMPK activation, mTOR inhibition, apoptosis	Enhanced chemo sensitivity, lower recurrence
Colorectal	AMPK activation, FASN inhibition, microbiota modulation	Risk reduction, improved outcomes
Prostate	p53 activation, insulin/IGF-1 inhibition	Reduced progression, synergy with hormone therapy
Lung	AMPK activation, angiogenesis inhibition	Chemopreventive effect, immune activation
Pancreatic	IGF-1 inhibition, apoptosis induction	Improved survival in diabetic patients
Ovarian	mTOR inhibition, EMT suppression, apoptosis	Improved chemo response, reduced metastasis

4. CONCLUSION

Metformin exerts pleiotropic anti-neoplastic actions targeting metabolic, cancer cell proliferative and tumour micro-environmental pathways. Its ability to inhibit the mTOR pathway, induce apoptosis and inhibit angiogenesis renders it an appropriate drug for cancer therapy. Studies confirm the beneficial effects of metformin on the prognosis of patients with various cancers, including breast, colorectal, prostate, lung, pancreatic, and ovarian cancers. Metformin, in particular, can reduce the likelihood of cancer incidence, slow its growth, and enhance the effects of chemotherapy and radiation treatment. Metformin also exhibits a synergistic effect with other anti-cancer drugs, which improves the sensitivity of cancer cells while reducing their resistance to therapy. And that is especially crucial for fast-growing forms of cancer like pancreatic or ovarian cancer. Because of its metabolic and anti-inflammatory activities, metformin may be an agent for cancer prevention, particularly in high-risk populations, including those with type 2 diabetes, as encouraging as these findings are, more clinical trials are necessary to establish the correct therapeutic timing of metformin, the patient populations that will obtain greater advantage, and all molecular bases explaining the anti-neoplastic action of metformin.

Author's Contributions

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Writing review and editing: Maria Pawluczyk, Krzysztof Pawlikowski
Supervision: Mateusz Marciniak
All authors have read and agreed with the published version of the manuscript.

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Informed consent

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Ethical approval

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Conflict of interest
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Data and materials availability
All data associated with this work are present in the paper.

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