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Metformin in Breast Cancer: Molecular Mechanisms, Preclinical Evidence and Clinical Implications

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Abstract
Background: Metformin, a first-line therapy for type 2 diabetes mellitus, has recently attracted attention for its potential anticancer properties. Preclinical and clinical evidence suggests that it modulates cancer cell metabolism, proliferation and survival pathways, indicating its possible role as an adjunct therapeutic agent, particularly in breast cancer.
Aim: To summarize current knowledge on the mechanisms of action, preclinical outcomes and clinical implications of metformin use in breast cancer.
Material and methods: A comprehensive literature search was conducted in PubMed, Scopus, Web of Science and Google Scholar databases, including publications up to 2025. Eligible sources encompassed preclinical studies, clinical trials, observational data, meta-analyses and reviews addressing metformin in breast cancer.

Results: Metformin demonstrates multifaceted antitumor activity, including inhibition of cell proliferation, reduced angiogenesis, downregulation of the PI3K/AKT/mTOR pathway, depletion of cancer stem cell populations and improved chemotherapy response. Clinical benefits are most evident in patients with type 2 diabetes and HER2-positive tumors, although findings in the general population remain inconsistent.
Conclusions: Metformin appears to be a promising supportive therapy in selected breast cancer subgroups, particularly in metabolically burdened patients. Further high-quality randomized trials are essential to clarify its clinical relevance and identify biomarkers predicting treatment response.

Keywords: metformin, breast cancer, AMPK, mTOR, cancer therapy, chemotherapy, T2DM

Introduction

Metformin, which belongs to the biguanide group, has been the cornerstone of pharmacotherapy for type 2 diabetes (T2DM) for many decades. It is the most commonly used oral hypoglycemic drug in the world and remains the first-line therapy in most international diabetes guidelines. It is estimated that more than 200 million patients currently use it, making it one of the most widely prescribed metabolic drugs [1].

The history of metformin dates back to the early 20th century. As early as 1918, it was observed that guanidine - a natural component of the plant Galega officinalis, used in traditional European medicine - has glucose-lowering properties. Research by Paton and Findlay showed that administering guanidine hydrochloride to rabbits caused hypoglycemia in most of the tested animals [2]. Based on these findings, the synthesis of guanidine derivatives was initiated, among which metformin distinguished itself by having the most favorable safety and efficacy profile. In the 1950s, it was introduced into the treatment of type 2 diabetes mellitus (T2DM) by Jean Sterne, and in the following decades, it established itself as the first-line drug of choice [3].

Chemically, metformin is a biguanide composed of two linked guanidine molecules. Despite its long-term use, its mechanism of action remains the subject of ongoing research, particularly due to its broad, pleiotropic biological effects. In addition to its hypoglycemic action, metformin also has a beneficial effect on body weight, lipid profile, blood pressure, inflammatory processes, and reduces the risk of cardiovascular complications [4-7]. A growing body of evidence also points to its potential role in the treatment of obesity, non-alcoholic fatty liver disease (NAFLD), and metabolic disorders associated with aging processes [8, 9]. In recent years, metformin has become the subject of intensive oncological research. Preclinical data indicate that this drug may modulate key cellular processes associated with tumor transformation, including energy metabolism, proliferation, apoptosis, and angiogenesis. Its antitumor effects involve both indirect mechanisms - resulting from the reduction of insulinemia and inhibition of insulin and IGF-1 signaling - and direct mechanisms, related to the activation of AMPK kinase and inhibition of the mTOR pathway. [10-12]. These mechanisms have prompted researchers to consider metformin as a potential adjunctive therapy in oncology.

Particular interest has focused on the potential role of metformin in the treatment of breast cancer - a malignancy that, according to GLOBOCAN 2022, remains the most commonly diagnosed cancer among women worldwide. In 2022, approximately 2.3 million new cases were reported, accounting for 23.8% of all cancer diagnoses in women. In that year, breast cancer also remained one of the leading causes of cancer-related mortality in this population, with an estimated 670,000 deaths, representing 15.4% of all cancer deaths among women [13]. Increasing evidence indicates that metabolic disorders play a significant role in its pathogenesis, and type 2 diabetes increases the risk of developing breast cancer by approximately 10–20% [14]. This phenomenon is primarily explained by the excessive activation of insulin, insulin-like growth factor (IGF), and estrogen receptor signaling pathways, which promote the proliferation and survival of cancer cells [15]. Metformin, as a drug that reduces insulin resistance and lowers insulin levels, may limit the activation of these pathways, which is one of the biological rationales for its potential anticancer effects.

The aim of this article is to provide a concise overview of the current state of knowledge regarding the potential significance of metformin in breast cancer - including the molecular mechanisms of its action, preclinical and epidemiological data, and the results of clinical studies - in order to assess whether this drug may serve as a valuable component of adjunctive therapy in oncology.

Materials and Methods

A comprehensive literature search was conducted to collect and analyze studies evaluating the role of metformin in breast cancer, with particular emphasis on its molecular mechanisms, preclinical evidence and clinical outcomes. Scientific databases PubMed, Scopus, Web of Science, and Google Scholar were searched to identify peer-reviewed publications available up to 2025.

The search strategy included the following keywords and their combinations:

"metformin", "breast cancer", "anti-cancer", "AMPK", "mTOR", "insulin-IGF-1", "HER2-positive", "ER-positive", "triple-negative breast cancer (TNBC)", "clinical trial", "pCR", "survival", "molecular mechanisms"

Studies were screened based on title, abstract and full-text relevance. Articles were included if they met the criteria of (1) examining the effects of metformin on breast cancer biology or treatment response, (2) presenting preclinical or clinical data, and (3) being published in English or Polish. Reviews, mechanistic reports, meta-analyses, randomized trials, observational studies, in vitro and in vivo experiments were all considered eligible.

Publications were excluded if they lacked oncologic relevance, reported insufficient data, or focused solely on glycemic control without mechanistic or clinical connection to cancer. Reference lists of included papers were additionally reviewed to ensure completeness of data collection.

Mechanisms of the Anticancer Action of Metformin

Metformin exhibits effects that go far beyond the classical regulation of carbohydrate metabolism, modulating numerous signaling, metabolic, and immunological processes important for the initiation and progression of cancers. Population data indicate that its use may reduce the risk of developing certain cancers in a dose-dependent manner, which results both from the drug's impact on the body's metabolic environment and its direct effects on cancer cells [16, 17].

The central site of metformin's action are the mitochondria. Inhibition of complex I of the respiratory chain leads to a decrease in ATP levels, an increase in the AMP/ATP ratio, and subsequent activation of AMPK kinase - a key cellular energy sensor [18, 19]. AMPK activation initiates a broad adaptive response, including inhibition of gluconeogenesis, increased glucose uptake, reduced lipogenesis, enhanced β-oxidation, and decreased glucose absorption in the gastrointestinal tract [20, 21]. These processes form the basis of metformin's metabolic effects and at the same time contribute to its anticancer properties.

In the oncological context, metformin operates through both indirect and direct mechanisms, with the former primarily driven by modulation of the insulin–IGF-1 axis. This insulin-dependent anticancer activity results from the inhibition of gluconeogenesis and enhanced glucose utilization in peripheral tissues, which lowers blood glucose levels and subsequently reduces circulating insulin and IGF-1. Under physiological conditions, insulin regulates cellular metabolism and growth, whereas IGF-1 supports proliferation, differentiation, and survival. Upon ligand binding, the insulin receptor (IR) and the insulin-like growth factor 1 receptor (IGF-1R) phosphorylate the IRS-1 and IRS-2 adaptor proteins, thereby triggering the activation of key pro-mitogenic signaling cascades, including the PI3K/AKT/mTOR and RAS/RAF/MAPK pathways, which are frequently hyperactivated in cancer cells [22]. Hyperinsulinemia and elevated IGF-1 levels further augment the expression of cyclin D1 and other key regulators of the cell cycle, thereby fostering a microenvironment conducive to tumor initiation and progression.

Of particular importance, breast cancer cells exhibit elevated expression of IR and IGF-1R compared to normal mammary epithelium, rendering them especially sensitive to insulin signaling. Metformin-induced reductions in insulin and IGF-1 levels limit IR/IGF-1R activation and IRS-1 phosphorylation, thereby suppressing the PI3K/AKT/mTOR and RAS/RAF/MAPK pathways and ultimately inhibiting cancer cell proliferation. Additionally, the attenuation of insulin–IGF-1 signaling reduces the production of pro-mitogenic mediators, including pro-inflammatory cytokines, sex hormones, and growth factors, further amplifying the metabolic anticancer effects of metformin [23].

In addition to its effects on the hormonal environment, metformin also acts directly on cancer cells, with suppression of mTOR signaling, which regulates proliferation, growth, and survival of cancer cells, being a key component of this action. Activation of AMPK inhibits the mTORC1 complex, leading to G1-phase cell cycle arrest, reduced cyclin D1 expression, and suppression of protein biosynthesis, thereby inhibiting cancer cell proliferation [24].

This mechanism is further reinforced by metformin's inhibition of mitochondrial complex I of the electron transport chain, which lowers ATP levels and increases the AMP/ATP ratio, thereby further activating AMPK. Inhibition of complex I also reduces hypoxia-induced activation of HIF-1, impairing cancer cells' adaptation to hypoxic conditions and shifting their metabolism toward glycolysis as the primary energy source, thereby reducing their survival [25].

Metformin also affects additional pathways regulating cell proliferation and survival. Through p53-dependent induction of the REDD1 protein (regulated in DNA damage and development 1), it enhances the inhibition of mTOR, thereby reinforcing cell cycle arrest [26]. Importantly, it may also promote ferroptosis - an iron-dependent form of cell death - by destabilizing the cystine transporter SLC7A11 and increasing the generation of lipid ROS. This mechanism is particularly important in eliminating cells that are resistant to apoptosis [27].

At the level of the tumor microenvironment, metformin exhibits immunomodulatory effects, including inhibition of immunosuppressive cell activity, reduction of inflammation, and - in breast cancer - limitation of estrogen synthesis in peripheral tissues. The combination of metabolic, cytotoxic, cytostatic, and immunological effects forms the rationale for considering metformin as a promising agent in multi-modal oncology therapies [28].

Preclinical Research on Metformin in Breast Cancer: Current Insights

Following the demonstration of metformin's potential anticancer properties, numerous research groups began investigating its use as an adjunctive therapy in breast cancer. Both in vitro and in vivo studies demonstrate its multifaceted activity across various tumor subtypes. Metformin inhibits breast cancer cell proliferation, limits clonogenic potential, and induces G1-phase cell-cycle arrest, characterized by reduced cyclin D1 and E2F1 levels and inhibition of the MAPK, AKT, and mTOR pathways [29]. Apoptotic induction is generally minimal at therapeutically relevant concentrations; however, in animal models, prolongation of tumor latency has been observed, along with greater efficacy in xenografts representing progressive disease [30].

An important and well-documented mechanism of metformin's action is its impact on the tumor microenvironment. In models of metastatic breast cancer, it normalized aberrant angiogenesis - reducing vessel density and leakiness, decreasing hypoxia, and enhancing vessel maturation. This effect was linked to a marked reduction in the expression of PDGF-B, a key regulator of vascular stabilization. The normalization of the microcirculation resulted in fewer metastases and improved chemotherapy effectiveness due to enhanced tumor perfusion [31].

Strong evidence also supports the synergistic activity of metformin with anticancer agents. In combination with paclitaxel, it enhanced AMPK activation, which resulted in more pronounced mTOR inhibition, an increased proportion of cells in the G2/M phase, and augmented apoptosis. In mouse models, the combined therapy inhibited tumor growth more effectively than monotherapy [32].

The effect of metformin on breast cancer stem cells (CSCs), which are responsible for treatment resistance and disease relapse, is of particular importance. Studies by Hirsch et al. demonstrated that low doses of metformin selectively eliminate CSCs and inhibit their transformation. The combination of metformin with doxorubicin exhibited strong synergistic activity - leading to the elimination of both CSCs and differentiated tumor cells, resulting in long-term remission in xenograft models, whereas doxorubicin monotherapy was associated with rapid relapse [33].

Metformin also exhibits synergism with tamoxifen in ER-positive tumors. The combination of both agents enhanced the inhibition of cell proliferation and migration, reduced clonogenic capacity, and more strongly induced apoptosis through modulation of the AMPK/mTOR/p70S6 pathway and the Bax/Bcl-2 ratio [34].

In studies on triple-negative breast cancer (TNBC), metformin inhibited cell proliferation, clonogenicity, and migration, induced S-phase cell cycle arrest, and enhanced the cytotoxic effect of cisplatin. Downregulation of RAD51 - a key protein involved in homologous DNA repair - further sensitized TNBC cells to cytotoxic treatment [35].

The strongest preclinical evidence indicates that metformin affects key biological processes involved in breast cancer development: it inhibits proliferation, normalizes angiogenesis, acts synergistically with chemotherapy and hormonal therapy, and reduces the population of cancer stem cells. According to the current state of knowledge, metformin represents a promising component of combination therapies, warranting further clinical validation.

The effect of metformin on breast cancer in humans

One of the first clinical studies suggesting the anticancer effects of metformin reported a higher rate of pathological complete response (pCR) in breast cancer patients receiving metformin concurrently with neoadjuvant chemotherapy. Among a cohort of 2,539 patients, pCR was achieved in 24% of diabetic women treated with metformin, compared to 8% of those receiving other hypoglycemic agents and 16% of non-diabetic patients. The difference between the metformin group and patients receiving other antidiabetic medications was statistically significant ($P = 0.007$). In multivariate analysis, metformin remained an independent predictor of pCR (odds ratio, OR 2.95; $P = 0.04$), indicating a potential anticancer effect that extends beyond its glucose-lowering action [36].

In the METTEN trial, the addition of metformin to neoadjuvant chemotherapy combined with trastuzumab in patients with early HER2-positive breast cancer resulted in a higher pCR rate in the metformin arm (65.5%) compared with the control group (58.6%), although this difference did not reach statistical significance ($P = 0.589$), likely due to the limited sample size. Breast-conserving surgery was more frequent in the metformin group (79.3% vs. 58.6%) [37]. Further analysis revealed a significant reduction in residual tumor proliferation, assessed by Ki-67 expression, in the metformin arm ($P = 0.025$), particularly among patients with high baseline Ki-67 levels [38].

As the presence of residual invasive disease correlates with an increased risk of recurrence, these findings may have important prognostic implications. Large meta-analyses suggest that metformin use reduces the overall risk of cancer-related death and cancer incidence (OR 0.65 and 0.73, respectively) [39]. This effect was confirmed in a study by Liuboty et al., in which metformin increased the rate of clinical response (77.5% vs 25%) as well as pCR (26.5% vs 6%) in patients with metabolic syndrome [40].

A meta-analysis by Hong Xu et al., including 5,464 patients with diabetes and breast cancer, demonstrated a higher rate of pCR and a 47% reduction in the risk of death (overall survival, OS; hazard ratio, HR 0.53). After accounting for hormone receptor status, the benefits were even more pronounced (OS; HR 0.35) [41]. Similar results were reported by Behrouzi et al., where metformin reduced the risk of death by 85% (HR 0.15) and the risk of recurrence by 77% (HR 0.23) in women with type 2 diabetes [42].

In a study by Azazy et al. involving 60 non-diabetic patients, the addition of metformin increased both clinical and pathological response rates, particularly in the luminal B subtype, although statistical significance was not reached due to the small sample size [43]. Similarly, in another randomized study including 80 patients, a slight advantage of metformin was observed in overall response rate (ORR), clinical complete response (cCR), and pathological complete response (pCR), along with a higher rate of breast-conserving surgeries [44].

In a large retrospective analysis involving 3,757 Chinese patients, five-year disease-free survival (DFS) and overall survival (OS) were the highest in the group receiving metformin (96.1% and 97.1%, respectively), surpassing outcomes observed both in non-diabetic women and in those treated with insulin [45].

Similarly, a meta-analysis by Zhonghua Wu et al. demonstrated an increase in overall response rate (ORR) following the addition of metformin in patients with advanced breast cancer, although no improvement was observed in progression-free survival (PFS) or overall survival (OS) [46].

Evidence further suggests that the effectiveness of metformin may vary by molecular subtype. In a subgroup analysis of the ALTTO trial, patients with HER2-positive breast cancer and diabetes treated with metformin achieved better DFS, distant disease-free survival (DDFS), and OS outcomes compared with those receiving insulin [47].

In patients with metastatic estrogen receptor–positive (ER-positive) breast cancer, the addition of metformin did not improve response rate, progression-free survival (PFS), or overall survival (OS) (HR 1.2) [48]. Similarly, in the MA.32 trial, metformin did not prolong invasive disease-free survival (IDFS) or OS in the overall study population, although a potential benefit was observed in the HER2-positive subgroup (HR 0.64) [49, 50].

In triple-negative breast cancer (TNBC), meta-analyses report a reduction in overall mortality (HR 0.55), with no effect on recurrence risk [51, 52]. Moreover, adding metformin to erlotinib therapy in patients with metastatic TNBC did not yield clinical benefit [53].

Clinical data suggest that metformin may improve prognosis in selected breast cancer patient groups, particularly those with type 2 diabetes and HER2-positive tumors. In contrast, outcomes in non-diabetic populations and in triple-negative breast cancer remain inconsistent. Although the current evidence is insufficient to support routine use of metformin in breast cancer treatment, the observed benefits in specific subgroups underscore the need for further clinical investigation.

DISCUSSION

Available evidence indicates that metformin - a long-established first-line therapy for type 2 diabetes - may also hold therapeutic relevance in oncology, particularly in breast cancer. Its activity is multidirectional, encompassing both systemic metabolic effects and direct modulation of proliferative signaling pathways within tumor cells. The most consistently described mechanisms include suppression of insulin–IGF-1 signaling and AMPK-mediated inhibition of the mTOR pathway, ultimately reducing proliferation, angiogenesis and tumor growth. These anticancer effects have been demonstrated across numerous in vitro and in vivo models.

Preclinical studies further show that metformin interferes with several critical stages of breast cancer progression: it decreases cell division, migration and clonogenic capacity, reduces the population of cancer stem cells (CSC), and improves tumor perfusion by normalizing pathological angiogenesis - a feature that may enhance chemotherapy delivery and response. Particularly noteworthy is the selective reduction of CSCs, which are responsible for therapeutic resistance and recurrence. These findings support the concept that metformin does not replace standard treatment, but may potentiate its efficacy when used as an adjunct.

Clinical results, however, are less uniform than laboratory data. Benefits appear more pronounced in patients with type 2 diabetes and in HER2-positive disease, whereas outcomes in non-diabetic populations, especially in triple-negative breast cancer (TNBC), remain inconsistent. This pattern suggests that therapeutic response may depend on metabolic status and intrinsic tumor biology, potentially shaped by factors such as AMPK activation, GLUT-1 expression or TP53 mutational status. Such variability underscores the need for individualized treatment strategies and identification of predictive biomarkers.

Given the current evidence, metformin should be regarded as a promising therapeutic candidate rather than a clinically established standard. Future research should focus on refining patient selection and delineating which molecular subgroups derive the greatest benefit. Priority directions include:

- identification of predictive biomarkers for treatment response
- clinical evaluation of combination strategies (especially HER2-targeted and immunotherapies)
- optimization of dosage, bioavailability and treatment duration
- multicenter randomized trials to validate clinical benefit

Metformin therefore remains an emerging yet highly compelling agent in breast cancer therapy - one whose integration into routine clinical practice will depend on the availability of further high-quality evidence and a more precise definition of therapeutic indications.

CONCLUSIONS

Metformin represents one of the most promising adjuvant agents in breast cancer therapy, particularly in patients with metabolic dysregulation and in the HER2-positive subtype. Preclinical findings consistently demonstrate antiproliferative and anti-angiogenic effects, as well as a reduction in cancer stem cell populations, although clinical outcomes remain variable. Therapeutic benefit appears to be strongly shaped by tumor biology and patient's metabolic phenotype, underscoring the need for precise patient selection. At this stage, metformin should not be regarded as standard of care but rather as a promising component of multimodal therapy. Successful clinical implementation will require large, multicenter randomized trials, biomarker-guided stratification, as well as optimized dosing and exposure strategies.

Disclosure

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