International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
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ARTICLE TITLE	OLD DRUG, NEW USES: A COMPREHENSIVE REVIEW OF THE EVOLVING ROLE OF METFORMIN IN ONCOLOGY
DOI	https://doi.org/10.31435/ijitss.1(49).2026.5067
RECEIVED	13 January 2025
ACCEPTED	09 March 2026
PUBLISHED	19 March 2026
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OLD DRUG, NEW USES: A COMPREHENSIVE REVIEW OF THE EVOLVING ROLE OF METFORMIN IN ONCOLOGY

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ABSTRACT

Background: Metformin is a first-line therapy for type 2 diabetes mellitus and a prominent candidate for oncology drug repurposing following observational associations with lower cancer incidence and mortality in diabetic cohorts.
Objective: To synthesise mechanistic rationale and clinical evidence for metformin in oncology, focusing on breast cancer and non-small cell lung cancer (NSCLC), and to identify major sources of heterogeneity and priorities for future research.
Methods: Targeted narrative review of peer-reviewed preclinical, translational, and clinical studies, prioritising randomised controlled trials, presurgical biomarker studies, and higher-quality observational analyses with clinically interpretable endpoints.
Results: Metformin is proposed to act through host-mediated mechanisms, including improved insulin sensitivity and reduced hyperinsulinaemia and inflammatory signalling, and tumour-cell effects, including mitochondrial complex I inhibition, energetic stress, and AMPK to mTOR modulation. In breast cancer, metformin consistently improves metabolic and inflammatory biomarkers. However, the large MA.32 adjuvant trial in non-diabetic patients showed no overall benefit in invasive disease-free survival or overall survival. Presurgical studies suggest antiproliferative effects such as Ki-67 reduction may be limited to insulin-resistant or otherwise biologically defined subgroups. In NSCLC, evidence is heterogeneous. Combination trials with EGFR tyrosine kinase inhibitors or chemotherapy report mixed efficacy, and gastrointestinal toxicity can limit adherence. Emerging supportive-care studies indicate possible reductions in selected chemotherapy-related toxicities.
Conclusions: Current evidence supports context-dependent, rather than universal, oncologic utility of metformin. Future trials should prospectively stratify by metabolic status and tumour biology, optimise dose and timing, and test biomarker-guided combinations and patient-centred supportive endpoints.

KEYWORDS

Metformin, Oncology, Breast Cancer, Lung Cancer, AMPK, Cancer Metabolism

CITATION

Bernard Myszewski, Maria Rajkowska, Aleksandra Włodarczyk, Norbert Grabias, Jędrzej Piotrowski, Paulina Jarząbek, Julia Weronika Mieszkowska, Radosław Gryko, Anna Kinga Tejchma, Łukasz Dominik Woźniak. (2026) Old Drug, New Uses: A Comprehensive Review of the Evolving Role of Metformin in Oncology. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.5067

1. Introduction

Metformin, a synthetic biguanide, has been used for decades as a first-line therapy for type 2 diabetes mellitus (T2DM). Its long clinical experience, favourable safety profile, and low cost have made it a leading candidate for drug repurposing, including potential applications in oncology (Bailey, 2017; Knowler et al., 2002; Nathan et al., 2009).

Oncologic interest was sparked by cohort studies in people with T2DM, in which metformin exposure was often associated with lower cancer incidence or cancer-related mortality compared with other glucose-lowering strategies (Evans et al., 2005; Libby et al., 2009; Landman et al., 2010). These signals are hypothesis-generating and can be influenced by confounding and time-related biases, but they motivated extensive mechanistic work linking metformin to insulin/IGF-1 signalling, inflammation, and cellular energy sensing pathways (Samuel et al., 2019; Mihaylova & Shaw, 2011; Foretz et al., 2023).

Clinical translation has been uneven. Randomised trials in non-diabetic oncology populations frequently report modest or null effects, suggesting that any benefit may depend on patient metabolic phenotype, tumour biology, exposure constraints, and treatment context. Breast cancer and non-small cell lung cancer (NSCLC) are therefore useful case studies: they include presurgical biomarker trials, large adjuvant studies, and combination strategies with targeted therapy or chemotherapy (Bonanni et al., 2012; DeCensi et al., 2014; Goodwin et al., 2015; Goodwin et al., 2022; Li et al., 2019; Arrieta et al., 2022; Verma et al., 2023).

Aim of the review. This narrative review synthesises evidence on metformin's evolving role in oncology, with emphasis on (i) proposed anticancer mechanisms, (ii) clinical findings in breast and lung cancer, and (iii) smaller bodies of evidence relevant to supportive oncology (e.g., chemotherapy toxicity mitigation). We highlight sources of heterogeneity and outline priorities for future research.

2. Methodology

This targeted narrative review synthesised peer reviewed evidence on metformin in oncology, focusing on breast cancer and non small cell lung cancer. Literature was identified through keyword searches of major biomedical databases and reference list screening. Records were screened by relevance at title and abstract level and, when eligible, assessed in full text, prioritising randomised trials and presurgical biomarker studies, with selected higher quality observational analyses. For included studies we extracted design, population and metabolic status, tumour biology when reported, metformin regimen, co treatments, safety, and main outcomes, then summarised findings descriptively by theme without combining results into a single pooled estimate.

3. Results: Evidence Synthesis

3.1. Metformin Exposure and Cancer Risk in Diabetic Populations

Multiple cohort studies in T2DM populations have reported associations between metformin exposure and lower cancer incidence or cancer-related mortality compared with other glucose-lowering approaches (Evans et al., 2005; Libby et al., 2009; Landman et al., 2010). For example, the ZODIAC-16 cohort reported lower cancer mortality in metformin users (Landman et al., 2010). Similar observational signals have been reported across tumour sites and settings, including associations with reduced colorectal cancer risk (Ioannou & Boyko, 2011) and improved outcomes in pancreatic cancer meta-analyses (Li et al., 2017).

However, observational pharmacoepidemiology has well-recognised threats to validity that are particularly relevant here. Confounding by indication is plausible because diabetes severity, obesity, renal function, and treatment escalation influence both the choice of glucose-lowering therapy and cancer outcomes. Time-related biases can also be substantial: immortal time bias may arise if patients must survive long enough to be classified as “metformin users,” and time-lag bias may occur if comparator therapies are typically used at later disease stages. These considerations help explain why observational signals may overestimate causal effects.

Systematic reviews and meta-analyses have extended observational evidence to additional cancer sites, including endometrial cancer (Xie et al., 2024). Importantly, effect sizes vary across tumour types and study designs, and some associations attenuate after adjustment for biases and confounders. This pattern—promising signals in observational research but mixed results in randomised oncology trials—frames the need to interpret metformin’s oncologic potential as context-dependent rather than universal.

3.2. Mechanistic Rationale for Anticancer Activity

Metformin’s proposed anticancer activity is multidirectional, encompassing both indirect host-mediated mechanisms and direct tumour-cell effects. These mechanisms are not mutually exclusive and may interact: improved systemic insulin sensitivity can reduce mitogenic signalling in insulin-responsive tumours, while direct metabolic stress may alter tumour susceptibility to cytotoxic or targeted therapies (Samuel et al., 2019; Foretz et al., 2023).

Indirect (host-mediated) mechanisms. Hyperinsulinaemia and elevated IGF signalling can promote proliferation and survival pathways in multiple tumour types. By improving insulin sensitivity and reducing circulating insulin levels, metformin may attenuate insulin/IGF-driven activation of PI3K/AKT/mTOR signalling (Samuel et al., 2019). In addition, metformin can change inflammatory and adipokine profiles; in breast cancer trial populations, reductions in high-sensitivity C-reactive protein and leptin have been observed, linking metabolic control to inflammation-associated pathways (Goodwin et al., 2015).

Direct (tumour-cell) mechanisms. At the cellular level, metformin is strongly linked to mitochondrial and energetic regulation. Mechanistic work indicates that metformin can inhibit mitochondrial respiratory-chain complex I, thereby increasing the AMP/ATP ratio and activating AMPK, a central energy-sensing kinase (Mihaylova & Shaw, 2011; Foretz et al., 2023). AMPK activation can suppress mTORC1 signalling through several routes, including regulation of TSC2 and effects on raptor, thereby restraining anabolic growth programmes and proliferation.

Genotype and pathway context. The upstream kinase LKB1 (encoded by STK11) is a key activator of AMPK and a tumour suppressor gene implicated in Peutz-Jeghers syndrome (Hemminki et al., 1998). STK11 alterations occur in lung adenocarcinoma and shape tumour metabolism and treatment responses (Ding et al., 2008). In experimental systems, LKB1 status influences sensitivity to metabolic interventions, including biguanides; for example, phenformin showed activity in LKB1-deficient contexts in preclinical lung cancer models (Shackelford et al., 2013). p53-family signalling also intersects with metabolic stress responses, and

metformin-induced energetic stress has been proposed to affect p53-related pathways influencing cell-cycle arrest and apoptosis (Yi et al., 2019).

Metformin has additionally been linked to processes relevant to tumour progression and therapy resistance. In EGFR-mutant NSCLC models, metformin has been shown to sensitise resistant cells to EGFR inhibitors, potentially via suppression of IL-6 signalling and modulation of epithelial-mesenchymal transition (Li et al., 2014). Preclinical and translational work also suggests that dietary interventions and metformin can interact with tumour genotype to modulate response to immune checkpoint blockade, particularly in STK11-mutant NSCLC (Ndembe et al., 2024). In triple-negative breast cancer models, metformin has been reported to suppress cancer stem-cell phenotypes by promoting degradation of KLF5 (Shi et al., 2017).

Taken together, mechanistic evidence supports a plausible anticancer rationale but also predicts context dependence. Effects should vary with (i) host metabolic state, (ii) tumour genotype and pathway dependence, and (iii) achievable drug exposure in tumour tissue, which may differ from concentrations used in some preclinical models (Foretz et al., 2023).

3.3. Breast Cancer: Biomarkers, Diabetes Context, and Randomised Evidence

Breast cancer is influenced by genetic, hormonal, and lifestyle-related factors, and metabolic dysregulation is common and prognostically relevant. From a repurposing perspective, breast cancer is a rational setting to evaluate metformin because presurgical trial designs allow rapid assessment of biological activity through tissue biomarkers.

Presurgical biomarker trials. Ki-67 is a proliferation marker with prognostic value in early breast cancer (de Azambuja et al., 2007). In a randomised presurgical trial, metformin exposure was associated with changes in tumour proliferation that varied by insulin resistance and anthropometric factors, with the most consistent signals observed in subgroups with higher baseline insulin resistance (Bonanni et al., 2012). A subsequent presurgical study reported that metformin's effect on Ki-67 depended on baseline insulin resistance (HOMA index) and tumour subtype; a reduction in Ki-67 was observed in insulin-resistant individuals, while an opposite trend was noted in non-insulin-resistant participants (DeCensi et al., 2014). These findings align with the hypothesis that metformin's anticancer activity may be strongest in metabolically defined subgroups.

Systemic metabolic effects and biomarker modulation. The MA.32 programme provides rigorous evidence of metformin's systemic effects in non-diabetic breast cancer populations. In the MA.32 metabolic analysis, metformin reduced body weight and improved several metabolic and inflammatory biomarkers (including insulin, HOMA index, leptin, and high-sensitivity C-reactive protein) compared with placebo (Goodwin et al., 2015). These changes are consistent with host-mediated mechanisms and may be relevant for long-term cardiometabolic risk in cancer survivors.

Clinical outcomes in adjuvant therapy. The phase 3 MA.32 randomised clinical trial evaluated metformin (850 mg twice daily) versus placebo as adjuvant therapy in patients with high-risk operable breast cancer without diabetes. Metformin did not significantly improve invasive disease-free survival compared with placebo and did not improve overall survival (Goodwin et al., 2022). Exploratory analyses in MA.32 suggested potential benefit in certain subgroups, including participants with ERBB2-positive disease and carriers of the rs11212617 C allele, but these findings were hypothesis-generating and require independent confirmation. Notably, metformin was associated with a higher frequency of some non-haematologic grade 3 adverse events (Goodwin et al., 2022). The MA.32 survival results provide strong evidence that routine addition of metformin to adjuvant therapy in non-diabetic breast cancer patients is not supported in an unselected population.

Diabetes context and observational subgroup hypotheses. Diabetes is associated with poorer breast cancer outcomes, potentially through hyperinsulinaemia, inflammation, and comorbidity-related treatment differences. In the ALTTO trial analysis of HER2-positive breast cancer, diabetes without metformin was associated with worse outcomes than in non-diabetic participants, whereas metformin use among participants with diabetes was associated with outcomes more similar to those of non-diabetic participants (Sonnenblick et al., 2017). Because this evidence is observational, it cannot establish causality, but it supports further investigation of metformin in diabetes-associated risk contexts or in metabolically selected populations.

Combination strategies and advanced disease. Preclinical rationale suggests that metformin could modulate downstream signalling nodes relevant to EGFR/MAPK and PI3K/mTOR pathways. In metastatic triple-negative breast cancer, a phase 1 study evaluated metformin combined with erlotinib to establish safety and feasibility; conclusions about efficacy were limited by the early-phase design and small sample size (Fenn et al., 2020). In locally advanced breast cancer, a randomised trial integrating metformin with neoadjuvant chemotherapy reported non-significant trends toward improved clinical and pathological response endpoints

and suggested reduced neuropathy and musculoskeletal pain, albeit with worsened gastrointestinal adverse events (Barakat et al., 2022).

Overall interpretation. Breast cancer evidence supports biological activity and favourable systemic metabolic effects of metformin, while demonstrating that meaningful survival improvements are not evident in large randomised adjuvant data in non-diabetic patients overall. The evidence therefore points toward more targeted hypotheses: metformin may be most relevant in metabolically defined subgroups, in diabetes-associated contexts, or as an adjunct in carefully designed combination regimens where mechanistic synergy and tolerability can be demonstrated.

3.4. Lung Cancer: Observational Signals, Combination Trials, and Biomarker Questions

Lung cancer remains a leading cause of cancer mortality worldwide. In NSCLC, targeted therapies and immunotherapy have transformed outcomes in molecularly selected subgroups, but resistance and heterogeneity remain persistent challenges. Metabolic interventions such as metformin have been investigated as potential adjuncts, motivated by both epidemiological observations and preclinical work on metabolic stress and resistance pathways.

Observational and cohort evidence. Retrospective analyses in NSCLC have suggested that patients with diabetes treated with metformin may have improved outcomes compared with diabetic patients receiving other antidiabetic therapies (Lin et al., 2015). Such findings are consistent with a host-mediated hypothesis but remain susceptible to confounding and treatment-selection biases. In addition, observational designs do not clarify whether benefits reflect metabolic control, direct tumour effects, or differences in comorbidity management.

Preclinical evidence and resistance modulation. Experimental studies have reported that metformin can inhibit tumourigenesis in mouse models and modulate tumour growth pathways involving LKB1-AMPK signalling (Huang et al., 2008). In EGFR-mutant NSCLC models, metformin has been shown to sensitise EGFR-TKI-resistant cells in vitro and in vivo, potentially through suppression of IL-6 signalling and reversal of epithelial-mesenchymal transition (EMT) (Li et al., 2014). These mechanistic findings provide a rationale for combination strategies with EGFR inhibitors.

Combination studies with EGFR-TKIs. The METAL programme assessed metformin combined with erlotinib in stage IV NSCLC, reporting feasibility and tolerability in an early-phase safety run-in (Fasano et al., 2015; Morgillo et al., 2017). However, subsequent controlled data have tempered expectations. In a randomised, double-blind phase II trial in non-diabetic advanced NSCLC with EGFR mutations, the addition of metformin to gefitinib did not significantly improve progression-free survival and increased gastrointestinal toxicity, including a higher incidence of diarrhoea (Li et al., 2019).

Metabolic phenotype and subgroup signals. A secondary analysis of a phase 2 randomised trial suggested that BMI may modify the association between metformin added to EGFR-TKI therapy and outcomes in advanced lung adenocarcinoma, with a signal of improved overall survival among participants with higher BMI but not among those with lower BMI (Arrieta et al., 2022). Subgroup signals require cautious interpretation, but they align with the broader theme that metabolic status may be an effect modifier.

Chemotherapy-based strategies and STK11 questions. Metformin has also been tested as an adjunct to platinum-based chemotherapy. A randomised phase II study evaluated metformin and dietary restriction combined with cisplatin in NSCLC, illustrating the translational interest in metabolic co-interventions (Lee et al., 2021). The METALUNG phase II study evaluated metformin with pemetrexed and carboplatin in non-squamous NSCLC but was terminated for futility at interim analysis; the 6-month progression-free survival rate was modest and outcomes in STK11-mutant tumours were unexpectedly poor (Verma et al., 2023). These findings emphasise the risk of generalising metformin's potential benefit without precise biological selection.

Overall interpretation. The lung cancer literature suggests that metformin is unlikely to be a universally effective anticancer adjunct in NSCLC. The most defensible interpretation is that metformin may have value in carefully selected settings—potentially defined by metabolic phenotype, tumour genotype (including STK11/LKB1 status), and combination strategy—provided tolerability and dosing constraints are addressed.

3.5. Supportive Oncology and Other Clinical Contexts

Supportive-care outcomes can be clinically meaningful even when tumour control is unchanged, because they can improve adherence to effective therapy and quality of life. Several studies suggest that metformin may influence chemotherapy-induced toxicities.

Chemotherapy-induced peripheral neuropathy and other toxicities. Peripheral neuropathy is a common and dose-limiting adverse effect of chemotherapy, especially with platinum agents and taxanes. In a randomised controlled study in stage III colorectal cancer patients receiving oxaliplatin, metformin was associated with a lower proportion of patients experiencing grade 2–3 neuropathy at later cycles compared with control (El-Fatatry et al., 2018). In breast cancer, a randomised controlled trial in non-diabetic patients receiving neoadjuvant AC-T chemotherapy reported that metformin was associated with reduced incidence and severity of peripheral neuropathy, oral mucositis, and fatigue, and with lower rates of some organ toxicities (Serageldin et al., 2023). In another breast cancer neoadjuvant trial, metformin decreased the incidence of peripheral neuropathy, bone pain, and arthralgia but worsened gastrointestinal adverse events (Barakat et al., 2022). These mixed tolerability findings highlight that supportive-care benefit must be weighed against gastrointestinal side effects, particularly when metformin is added to regimens already associated with nausea or diarrhoea.

Benign breast disease. Fibroadenomas are common benign breast lesions influenced by hormonal factors. In a randomised clinical trial, metformin (1000 mg daily for six months) was associated with a greater reduction in fibroadenoma size compared with placebo (Alipour et al., 2021). While this does not directly establish cancer-preventive benefit, it is consistent with broader antiproliferative effects and supports the concept that metformin can influence breast tissue biology.

Metformin, cellular senescence, and aging-related pathways. Metformin has been studied as a potential modulator of aging-related biology, including cellular senescence and oxidative stress responses. Experimental work suggests metformin can influence stress-response pathways (including Nrf2-related regulation) and alter cellular aging phenotypes (Fang et al., 2018). In model organisms, metformin-associated lifespan extension has been linked to metabolic rewiring and lipid pathway modulation, although findings can be strain-dependent and context-specific (Cedillo et al., 2023). These aging-related observations intersect conceptually with cancer biology because senescence, metabolic stress responses, and immune surveillance contribute to both ageing and tumour progression.

3.6. Safety and Practical Considerations

Metformin is generally well tolerated in diabetes care, but oncology populations may experience different tolerability profiles due to concurrent therapies and comorbidities. Gastrointestinal adverse events—particularly diarrhoea, nausea, and abdominal discomfort—are common and can be clinically important when metformin is combined with targeted therapy or chemotherapy (Li et al., 2019; Barakat et al., 2022).

Long-term metformin exposure is associated with an increased risk of vitamin B12 deficiency, which may contribute to anaemia or neuropathy in susceptible individuals. In a placebo-controlled setting in non-diabetic breast cancer patients, metformin altered vitamin B12 metabolism compared with placebo, supporting the importance of monitoring during prolonged use (Lohmann et al., 2017). Lactic acidosis is rare but serious and is primarily a risk in patients with advanced renal impairment; appropriate patient selection and renal function monitoring remain essential, particularly in oncology settings where dehydration or nephrotoxic agents may occur (Foretz et al., 2023).

Because tolerability can constrain dosing, oncology use requires careful consideration of dose escalation, timing relative to systemic therapy, and proactive management of gastrointestinal side effects. These practical considerations are especially relevant in combination studies where the intended mechanism may depend on sustained exposure.

4. Discussion

The evidence reviewed in this paper is easier to interpret if metformin is treated as a context-sensitive metabolic intervention rather than a universal anticancer drug. Across tumour types, mechanistic plausibility and observational signals are common, yet randomised trials often show modest or no benefit. This pattern suggests that who is treated (metabolic phenotype), what is being treated (tumour biology), and when and how metformin is delivered (exposure and combinations) materially shape outcomes.

4.1. Reconciling epidemiology with trial outcomes

The initial enthusiasm for metformin in oncology was driven by population studies in people with T2DM, where metformin exposure frequently correlated with lower cancer incidence or mortality. These studies remain valuable for hypothesis generation, but their effect estimates can be distorted by confounding (e.g., differences in baseline health status or diabetes severity), time-related biases, and the choice of comparator drugs. In addition, epidemiologic cohorts typically reflect long-term exposure and metabolic comorbidity, whereas many oncology trials evaluate metformin over shorter windows in non-diabetic populations. As a result, discrepant findings between observational studies and trials should not be read simply as 'metformin works' versus 'metformin does not work'; they more often indicate that the mechanism being leveraged differs across settings.

4.2. Metabolic phenotype as an effect modifier

Clinical data indicate that any oncologic signal of metformin is shaped by the host metabolic phenotype. In presurgical breast cancer trials, Ki-67 fell mainly in participants with higher insulin resistance (Bonanni et al., 2012; DeCensi et al., 2014). In MA.32, weight and metabolic biomarkers improved, but invasive disease-free survival did not in the overall non-diabetic population (Goodwin et al., 2015; Goodwin et al., 2022). In lung adenocarcinoma, a benefit signal with EGFR-targeted therapy appeared concentrated in higher BMI groups (Arrieta et al., 2022). Future trials should therefore stratify patients a priori by insulin resistance and related markers rather than rely on post hoc subgroup findings.

4.3. Tumour biology and biomarker strategy

Tumour biology may further determine response. STK11/LKB1 alterations, common in NSCLC, affect metabolic control and can reshape microenvironmental features. Preclinical and translational studies link biguanide sensitivity and treatment interactions to LKB1 status and dietary context (Shackelford et al., 2013; Ndembe et al., 2024). However, METALUNG, conducted without biomarker selection, was stopped for lack of efficacy and outcomes were poor in STK11-mutant cases in that setting (Verma et al., 2023). Overall, the field needs biomarker-led trials with prospective validation before clinical adoption is considered.

4.4. Exposure, tolerability, and translational pharmacology

Pharmacology is a recurring obstacle. Experimental work often uses concentrations above those typically achieved in humans, and tumour uptake depends on transporters and the microenvironment (Foretz et al., 2023). In trials, gastrointestinal toxicity, especially diarrhoea, can reduce adherence and effective exposure in combination regimens (Li et al., 2019; Barakat et al., 2022). Because long-term use can lower vitamin B12, neuropathy-focused studies should monitor and correct deficiency (Lohmann et al., 2017). Future studies should plan titration and toxicity management and, where feasible, confirm pathway engagement with translational biomarkers.

4.5. Where metformin may have nearer-term clinical value

While disease-modifying effects remain uncertain in many oncology settings, supportive-care endpoints may represent a more tractable clinical niche. Randomised studies suggest metformin may reduce chemotherapy-induced peripheral neuropathy and other toxicities (El-Fatatry et al., 2018; Serageldin et al., 2023), outcomes that are meaningful to patients and may enable delivery of planned anticancer therapy. Metformin has also shown signals in benign breast disease, such as fibroadenoma size reduction (Alipour et al., 2021). These areas warrant confirmatory trials with robust patient-reported endpoints and careful safety monitoring, rather than broad extrapolation to anticancer efficacy.

4.6. Research priorities

Based on the evidence reviewed, priorities for future work include: (i) prospective stratification by metabolic phenotype (insulin resistance, BMI, diabetes status) and tumour biology (e.g., receptor status in breast cancer; STK11/LKB1 and related alterations in NSCLC); (ii) mechanistically informed combination trials with pre-specified interaction analyses and explicit exposure/tolerability management; (iii) integration of translational biomarkers to confirm target engagement and to distinguish systemic metabolic effects from direct tumour effects; (iv) dedicated evaluation of supportive-care outcomes using clinically meaningful and patient-reported measures; and (v) strengthened observational methodology with transparent handling of time-related biases and confounding.

Finally, repurposing has an important equity dimension. Metformin is inexpensive and widely available, which makes it attractive in health systems with constrained access to novel oncology agents. At the same time, low cost is not a substitute for evidence: current data support continued research, but do not support routine off-label oncologic use outside clinical trials or established diabetes management.

5. Conclusions

Metformin has a plausible biological rationale and an attractive safety/cost profile, but its clinical utility in oncology is context-dependent. Mechanistic data support both host-mediated and tumour-cell effects, and observational studies in diabetes cohorts often suggest improved cancer outcomes among metformin users. However, large randomised trials in non-diabetic oncology populations have not demonstrated broad survival benefits, particularly in early breast cancer, and NSCLC trials show inconsistent efficacy with notable gastrointestinal toxicity.

Future progress is most likely to come from precision approaches rather than broad unselected use. Trials should stratify by metabolic state and tumour biology, optimise dose and timing, and evaluate biomarker-guided combinations and supportive-care endpoints. Within these constraints, metformin remains a credible candidate for continued investigation as a repurposed adjunct that could deliver scalable benefits if efficacy is confirmed in well-defined patient groups.

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Funding: The authors received no external funding for this work.

Institutional Review Board Statement: Not applicable; this review included only published data.

Informed Consent Statement: Not applicable.

Data Availability Statement: All supporting data are available within the cited peer-reviewed literature.

Acknowledgments: The authors acknowledge the contribution of investigators whose work underpins the advances reviewed in this article.

Conflicts of Interest: No conflicts of interest to declare.

Declaration of the use of generative AI and AI-assisted technologies in the writing process: In preparing this work, the authors used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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