Clinical benefits of metformin in gynecologic oncology (Review)

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Abstract. Evidence has suggested that diabetes may contribute to the initiation and progression of specific types of cancer. Metformin, a biguanide, has become the preferred first-line therapy for the treatment of type 2 diabetes. Metformin is inexpensive, has a proven safety profile and is able to be safely combined with additional antidiabetic agents. In addition to the well-established antidiabetic effects of metformin, there has also been notable interest in its antitumor properties. The present review discusses the emerging role of metformin as an example of an existing drug, used worldwide in the treatment of diabetes, which has been demonstrated to exert significant *in vitro* and *in vivo* anticancer activities and has thus been investigated in clinical trials. In gynecologic oncology, metformin has been suggested to exhibit significant treatment efficacy against endometrial cancer. Three studies have demonstrated the potential therapeutic effects of metformin on the survival outcome of patients with ovarian cancer and in ovarian cancer prevention. However, this evidence was based on observational studies. Metformin has been shown to exert no statistically significant beneficial effect on cervical cancer incidence or mortality. By cancer site, the current limited insights highlight the need for clinical investigations and better-designed studies, along with evaluation of the effects of metformin on cancer at other sites.

Contents

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1. Introduction

Emerging evidence from observational studies and meta-analyses has suggested that diabetes mellitus may be associated with an increased risk of cancer. An increase in site-specific cancer incidence associated with diabetes mellitus has also been described in a number of systemic reviews and meta-analyses (1-6). Although the mechanisms underlying this association are yet to be investigated, the most frequently proposed hypothesis is the effect of insulin resistance with secondary hyperinsulinemia, since insulin may exert mitogenic effects via the insulin-like growth factor-1 (IGF1) receptor (7-11). Furthermore, hyperglycemia itself may enhance carcinogenesis via the induction of oxidative stress (12-14).

Metformin, a biguanide frequently used in the treatment of type 2 diabetes, has been demonstrated to exert marked chemopreventative and antiproliferative effects against various types of cancer (1,2,15-20). Metformin is able to inhibit cell growth via insulin and non-insulin dependent mechanisms (1,2,15-17), while enhancing insulin receptor sensitivity, increasing insulin uptake and therefore reducing systemic insulin levels. Metformin is also able to inhibit cell proliferation via activation of the growth inhibitory adenosine monophosphate-activated protein kinase (AMPK). AMPK blocks signaling via the phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) pathways, downstream of the insulin and IGF1 receptors (2,15,16).

The results of *in vitro* and *in vivo* studies (see Table I), have indicated that metformin may be able to inhibit cancer cell growth and reduce the cancer risk of certain solid tumors. The present review aimed to systematically evaluate available evidence regarding the association between metformin exposure and the risk of various types of cancer and cancer mortality, in the field of gynecologic oncology (Table I).

2. Metformin mechanism of action

Metformin suppresses hepatic gluconeogenesis, which results in decreased serum levels of glucose and insulin. AMPK is a cellular energy sensor located within the cytoplasm, which is involved in the regulation of metabolism within cells (2,21-23). Metformin reduces adenosine triphosphate (ATP) production, resulting in an increased AMP:ATP ratio, which leads to activation of the liver kinase B1 (LKB1)-AMPK signaling pathway (2,21-23). LKB1 protein is the product of the LBK1

Table I. Results of clinical and preclinical studies of metformin targeting gynecological cancer.

First author (year; ref no.)	Cancer subtype	Clinical trials	*In vitro* studies
Franciosi (2013; 33)	Ovarian cancer	Potential therapeutic effects	
Home (2010; 34)			
Baur (2010; 35)			
Dilokthornsakul (2013; 36)			
Erices (2013; 37)		No effect	
Rattan (2011; 38)			Proliferation inhibition effects
Yasmeen (2011; 39)			
Kim (2014; 40)			
Xiao (2012; 41)	Cervical cancer	No report	Proliferation inhibition effects
Owen (2000; 23)	Endometrial cancer	Potential therapeutic effects	Proliferation inhibition effects
Nevadunsky (2014; 42)		Potential therapeutic effects	
Currie (2012; 47)		Potential therapeutic effects	
Ko (2014; 48)		Potential therapeutic effects	
Becker (2013; 49)		No effect	
Cantrell (2010; 50)		Potential therapeutic effects	Proliferation inhibition effects
Tan (2012; 51)			Proliferation inhibition effects
Hanna (2012;52)			Proliferation inhibition effects
Shao et al (2014; 55)			Proliferation inhibition effects
Takahashi (2014; 56)			Proliferation inhibition effects
Sarfstein (2013; 57)			Proliferation inhibition effects
Stevens (2012; 61)		Proliferation inhibition effects	
Zhang (2014; 62)		Proliferation inhibition effects	
Costello (2007; 64)		Proliferation inhibition effects	

tumor suppressor gene. LKB1 has been demonstrated to induce AMPK phosphorylation and AMPK-mediated signal transduction, while metformin inhibits hepatic gluconeogenesis in an LKB1- and AMPK-independent manner, by decreasing hepatic energy status (2,24-26). Additional studies have suggested that metformin may inhibit carcinogenesis and/or cancer cell growth via diverse pathways (15,27-29). Phosphorylation of the AMPK catalytic subunit occurs in the presence of LKB1, and is facilitated by AMP. Increasing intracellular levels of AMP therefore activates AMPK, which results in the inhibition of mammalian target of rapamycin (mTOR) signaling, downregulating liver gluconeogenesis.

Metformin exerts indirect (insulin-dependent) and direct (insulin-independent) effects at the cellular level. The direct effect of metformin is mediated by AMPK activation and reduction of the mTOR signaling pathway, which leads to inhibition of gluconeogenesis in the liver, protein synthesis and proliferation of cancer cells (25,30-32). The indirect effects of metformin are mediated through its blood glucose lowering capabilities and subsequent reduction in circulating insulin levels.

Fig. 1 outlines the potential anticancerogenic effects of metformin. Metformin activates AMPK in the liver and skeletal muscles, thereby reducing gluconeogenesis in the liver and enhancing glucose uptake by the peripheral tissues, resulting in lower blood glucose and insulin levels (2,15,16). Insulin has been found to exert mitogenic activity and thus may, theoretically, have a promotional effect on the growth of tumor cells.

Although various anticancer effects of metformin have previously been described (1,2,15-20,24,25), the suppression of LKB1-mediated mTOR signaling is hypothesized to be the fundamental mechanism underlying these effects. Metformin has been demonstrated to be associated with reduced risk and enhanced overall survival rates of several obesity-associated types of cancer, although variable results have been obtained between studies.

3. Metformin and ovarian cancer

Three studies, comprising two randomized controlled trials (33,34) and one observational study (35), examined the association between the use of metformin and ovarian cancer. The results of these studies revealed potentially beneficial effects of metformin on the survival outcomes of ovarian cancer and in the prevention of ovarian cancer. However, the majority of this evidence is based on the results of observational studies. Further, well-conducted, controlled clinical trials are therefore required to verify the beneficial effects of metformin on ovarian cancer survival and prevention (36).

In vitro studies have revealed that metformin is able to enhance the effects of various chemotherapeutic treatment strategies by improving drug efficacy, and circumventing chemoresistance in epithelial ovarian cancer (30,37-39). Erices *et al* (37) demonstrated that no significant decrease in viability or alteration in the cell cycle was observed in ovarian cancer cell lines treated with micromolar concentrations

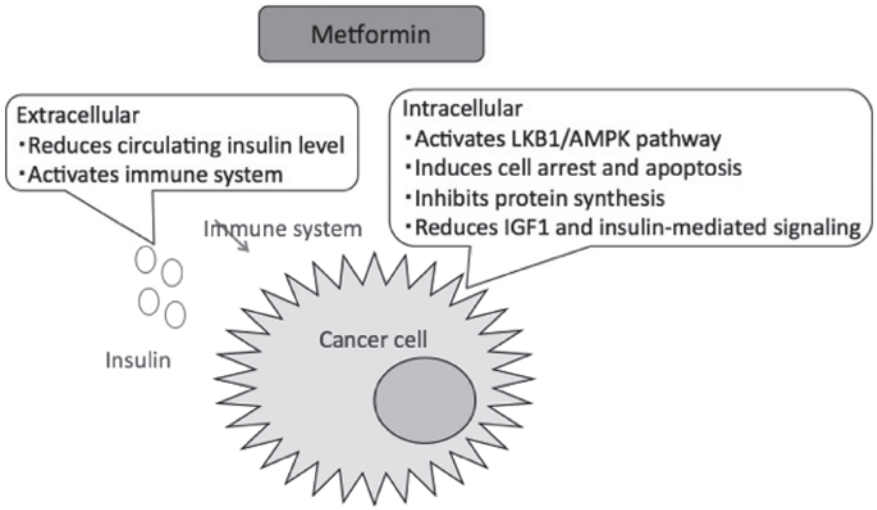

Figure 1. Proposed antitumor effects of metformin. AMPK, adenosine monophosphate kinase; LKB1, liver kinase B1; IGF1, insulin-like growth factor 1.

of metformin alone; however, significant cytotoxicity was observed following treatment with micromolar metformin in combination with chemotherapy, at concentrations where chemotherapy alone induced no loss of cell viability. The specific mechanism underlying the synergistic effect of metformin and chemotherapy remains to be fully elucidated. One potential explanation is that metformin may be selectively toxic to the ovarian cancer stem cell, which is considered to be the cause of chemoresistance (40).

4. Metformin and cervical cancer

To date, there have been few studies or clinical trials investigating the potential use of metformin for the treatment of cervical cancer. Due to the mechanisms by which metformin is suggested to induce tumor suppression, it is likely able to attenuate the growth of cancer in multiple systems, including cervical cancer. One study, using an *in vivo* cell culture system, demonstrated that metformin inhibited the growth of certain cervical cancer cells by stimulating apoptosis and autophagy (41). The metformin-sensitive cells expressed LKB1 at normal levels and exerted an AMPK-mTOR signaling response following metformin application. Therefore, metformin may augment LKB1 tumor suppressive effects, inhibit cell growth and decrease tumor cell viability via activation of LKB1-AMPK signaling in cervical cancer.

5. Metformin and endometrial cancer

Obesity is a major risk factor for endometrial cancer; therefore, the incidence of endometrial cancer has been predicted to increase as a consequence of the obesity epidemic, which may also worsen endometrial cancer outcomes (42,43). However, the association between endometrial cancer and obesity varies according to disease histology. Obesity exhibits a greater association with the risk of endometrioid (type 1) endometrial cancer, than non-endometrioid (type 2) endometrial cancer (44). Data from multiple studies has indicated that the obesity-endometrial cancer association occurs as a result of the higher average circulating insulin and estradiol levels detected in obese females, and that this effect is specific to endometrioid tumors (42,45,46).

There are a number of clinical studies regarding the effect of metformin on endometrial cancer outcomes. In one population-based study, diabetic women diagnosed with ovarian or endometrial cancer who were being treated with metformin at the time of diagnosis exhibited half the risk of mortality (of any cause) than that of the non metformin-treated patients [hazard ratio, 0.48; 95% confidence interval (CI), 0.28-0.81] (47). However, these results do not consider cancer pathology, stage or treatment strategy, which are significant factors, given the biological heterogeneity of endometrial cancer subtypes. Another retrospective study reported improved overall survival rates among diabetic patients on metformin with non-endometrioid type cancer, compared with that of non-metformin users and non-diabetic patients; however, cancer specific recurrence or progression were not reported (42). In a multi-institutional retrospective cohort analysis, the effects of metformin use on treatment-associated outcomes of endometrial cancer were evaluated using univariate and multivariate modeling (48). Metformin use was associated with improved recurrence-free survival (RFS) and overall survival (OS) but not time to recurrence (TTR). The role of metformin in the modification of cancer recurrence remains elusive.

A case-control analysis study investigated the association between the use of various antidiabetic drugs, including metformin, and the risk of endometrial cancer, using the United Kingdom-based General Practice Research Database (49). In total, 2,554 cases exhibiting endometrial cancer and 15,324 matched controls were identified. The risk of endometrial cancer was not found to differ between patients what had ever used metformin and those who had never used metformin [adjusted (adj.) odds ration (OR), 0.86; 95% CI, 0.63-1.18)]. Following stratification by duration of exposure, long-term (≥25 prescriptions) use of metformin (adj. OR, 0.79; 95% CI, 0.54-1.17), sulfonylureas (adj. OR, 0.96; 95% CI, 0.65-1.44), thiazolidinediones (≥15 prescriptions; adj. OR, 1.22; 95% CI, 0.67-2.21) or insulin (adj. OR, 1.05; 95% CI, 0.79-1.82) were not found to be significantly associated with the risk of endometrial cancer.

In vitro cell system analyses have demonstrated that metformin: i) inhibits the growth of various endometrial cancer cell lines; ii) attenuates the invasion and metastasis of endometrial cancer cell lines by modifying the nuclear factor-κB, matrix metalloproteinase-2/9/Akt and $Erk_{1/2}$ pathways; and iii) enhances endometrial cancer cell chemosensitivity to cisplatin and paclitaxel by reducing glyoxalase I expression and regulating the mTOR signaling pathway (23,50-52). At the molecular level, the fundamental activity of metformin inhibits mitochondrial oxidative phosphorylation, and may exert energy-associated stress on neoplastic cells (23). This inhibition of oxidative phosphorylation reduces the production of ATP, activating the cellular energy regulator AMPK and its downstream effectors, including mTOR (53). At the whole-organism level, the antiproliferative effects of metformin may be attributed to the decrease in circulating insulin levels induced by the reduced hepatic gluconeogenesis characteristic of insulin-responsive tumors (54). Metformin potently inhibits growth in a dose-dependent manner in endometrial cancer cell lines. Metformin resulted in G1 phase cell cycle arrest, induction of apoptosis and decreased human telomerase reverse transcriptase expression in endometrial cancer cells (50,55). Treatment with metformin attenuates the estrogen-dependent proliferative expression of c-myc and c-fos in the obese rat endometrium, an effect which was accompanied by inhibition of the phosphorylation of insulin and IGF1 receptors, as well as $Erk_{1/2}$ (17,55). *In vitro* studies have indicated that metformin inhibits rat endometrial cell line proliferation and suppresses endometrial cancer cell growth via cell cycle arrest and concomitant autophagy and apoptosis (55,56).

Regarding non-endometrioid endometrial cancer, diabetic endometrial cancer patients with non-endometrioid tumors who were taking metformin were demonstrated to have a lower risk of mortality than that of patients with endometrial cancer who did not use metformin (42). Metformin may therefore function as an adjuvant therapy for the treatment of non-endometrioid endometrial cancer. Investigating uterine serous carcinoma, an aggressive subtype of endometrial cancer, Sarfstein *et al* (57) demonstrated that metformin interacted with the IGF pathway, inducing apoptosis and inhibition of proliferation and migration of uterine serous carcinoma cell lines with wild-type or mutant p53.

6. Conclusion

The anticancer effects of metformin discussed in the present review indicate the possibility that certain diabetes-associated types of cancer may be circumvented. AMPK-dependent and -independent pathways have been suggested to underlie the anticancer effects of metformin treatment. The results of *in vitro* and *in vivo* studies have indicated that metformin may perturb cancer cell growth and reduce the cancer risk of certain solid tumors. Numerous clinical trials have suggested positive effects of metformin on pathological complete responses to neoadjuvant chemotherapy in diabetic patients with endometrial cancer, which suggest that metformin may augment the efficacy of chemotherapeutic treatment of endometrial cancer.

Metformin is a safe, low-cost drug, and therefore remains one of the most commonly prescribed drugs worldwide (6). In the majority of observational studies, the beneficial effect of metformin in the reduction of cancer risk was evident when the drug was used for >5 years (15,58-61). However, existing evidence is not sufficient to support the anticancer effect of metformin on malignancies other than endometrial cancer. Long-term randomized clinical trials specifically designed to determine the effects of metformin on cancer risk are required in order to evaluate the hypothesis that metformin has an anticancer effect.

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