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Metformin use and gynecological cancers: A novel treatment option emerging from drug repositioning

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ABSTRACT

Metformin exerts antitumor effects mainly through AMP-activated protein kinase [AMPK] activation and phosphatidylinositol 3-kinase [PI3K]-Akt-mammalian target of rapamycin [mTOR] inhibition. This drug leads to activation of the cellular energy-sensing liver kinase B1 [LKB1]/AMPK pathway. LKB1 is implicated as a tumor suppressor gene in molecular pathogenesis of different malignancies. AMPK is a serine/threonine protein kinase that acts as an ultra-sensitive cellular energy sensor maintaining the energy balance within the cell. AMPK activation inhibits mRNA translation and proliferation in cancer cells *via* down-regulation of PI3K/Akt/mTOR pathway. Moreover, metformin decreases the production of insulin, insulin-like growth factor, inflammatory cytokines and vascular endothelial growth factor, and therefore it exerts anti-mitotic, anti-inflammatory and anti-angiogenetic effects. Recent *in vitro* and experimental data suggest that metformin electively targets cancer stem cells, and acts together with chemotherapy to block tumor growth in different cancers. Several epidemiological studies and meta-analysis have shown that metformin use is associated with decreased cancer risk and/or reduced cancer mortality for different malignancies. The present review analyzes the recent biological and clinical data suggesting a possible growth-static effect of metformin also in gynecological cancers. The large majority of available clinical data on the anti-cancer potential of metformin are based on observational studies. Therefore long-term phase II–III clinical trials are strongly warranted to further investigate metformin activity in gynecological cancers.

1. Introduction

According to the World Health Organization, 171 million people worldwide have type II diabetes and this number is expected to double by 2030 (Wild et al., 2004). Metformin is an oral biguanide which inhibits gluconeogenesis, reduces insulin resistance, and

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lowers insulin levels (Viollet et al., 2012). Several epidemiological studies and meta-analysis have shown that metformin use is associated with decreased cancer risk and/or reduced cancer mortality (Zhang et al., 2011a; Wang et al., 2014; Zhang et al., 2013a; Deng et al., 2015; Hwang et al., 2015; Decensi et al., 2010; Noto et al., 2012; Franciosi et al., 2013; Bowker et al., 2006; Evans et al., 2005; Bodmer et al., 2011; Romero et al., 2012). For instance, Decensi et al. (2010), who analyzed eleven observational studies or clinical trials reporting 4042 cancer events, found a 31% reduction in overall cancer relative risk [RR] (0.69; 95% confidence interval [CI] = 0.61–0.79) in patients taking metformin compared with those receiving other anti-diabetic drugs. The inverse association was significant for pancreatic and hepatocellular cancer, with a trend to a dose-response relationship. Noto et al. (2012) analyzed 11.117 (5.3%) cases of incident cancer at any site among 210.892 diabetic patients included in 10 studies. The pooled RRs among metformin users compared with non-metformin users were 0.67 (95%CI = 0.53–0.85) for all-cancer incidence, 0.68 (95%CI = 0.53–0.88) for colorectal cancer, 0.20 (95%CI = 0.07–0.59) for hepatocellular cancer, and 0.67 (95%CI = 0.45–0.99) for lung cancer. Franciosi et al. (2013), who reassessed forty-one observational studies including 1,029,389 patients, found a significant association between exposure to metformin and reduced risk of all malignancies (Odds ratio [OR] = 0.73, 95%CI = 0.61–0.88), hepatocellular cancer (OR = 0.34; 95%CI = 0.19–0.60), colorectal cancer (OR = 0.83, 95%CI = 0.74–0.92), pancreatic cancer (OR = 0.56, 95%CI = 0.36–0.86), gastric cancer (OR = 0.83, 95%CI = 0.76–0.91), and esophageal cancer (OR = 0.90, 95%CI = 0.83–0.98).

In a Canadian cohort of 10,309 people newly treated for type 2 diabetes and followed for about 5 years, a significant reduction in cancer mortality was noted among patients treated with metformin when compared with those treated with sulfonylureas or insulin (3.5% *versus* 4.9% *versus* 5.8%) (Bowker et al., 2006). At multivariate analysis, the sulfonylurea cohort had greater cancer-related mortality compared with the metformin cohort (hazard ratio [HR] = 1.3, 95%CI = 1.1–1.6; p = 0.012) and insulin use was associated with HR of 1.9 of cancer-related mortality (95%CI = 1.5–2.4; p < 0.0001).

Metformin has been also found to reduce the incidence and mortality of ovarian cancer (Bodmer et al., 2011; Romero et al., 2012; Kumar et al., 2013; Dilokthornsakul et al., 2013; Zhang and Li, 2014), endometrial cancer (Zhang and Li, 2014; Shafiee et al., 2014; Sivalingam et al., 2014; Ko et al., 2015; Tseng, 2015), and breast cancer (Zhang and Li, 2014; Bosco et al., 2011).

The aims of drug repositioning are to discover new pharmacological effects of a drug and to expand its therapeutic use to other diseases (Banno et al., 2015). Metformin, which reduces insulin and insulin-like growth factor-1 [IGF-1] levels and inhibits different intracellular signaling pathways, may represent an interesting agent for some gynecological cancers.

2. Antineoplastic activity of metformin

Metformin exerts antitumor effects mainly through AMP-activated protein kinase [AMPK] activation and phosphatidylinositol 3-kinase [PI3K]-Akt- mammalian target of rapamycin [mTOR] inhibition (Brown et al., 2013; Del Barco et al., 2011; Engelman and Cantley, 2010; Gallagher and LeRoith, 2011) (Fig. 1). This drug, which inhibits mitochondrial oxidative phosphorylation and ATP production, leads to activation of the cellular energy-sensing liver kinase B1 [LKB1]/AMPK pathway (Del Barco et al., 2011; Engelman and Cantley, 2010; Gallagher and LeRoith, 2011). LKB1 is implicated as a tumor suppressor gene in the molecular pathogenesis of different malignancies (Liu et al., 2012a; Richer et al., 2015; Dunlop, 2002). AMPK is a heterotrimeric serine/threonine protein kinase,composed of a catalytic subunit (α_1 and α_2) and regulatory

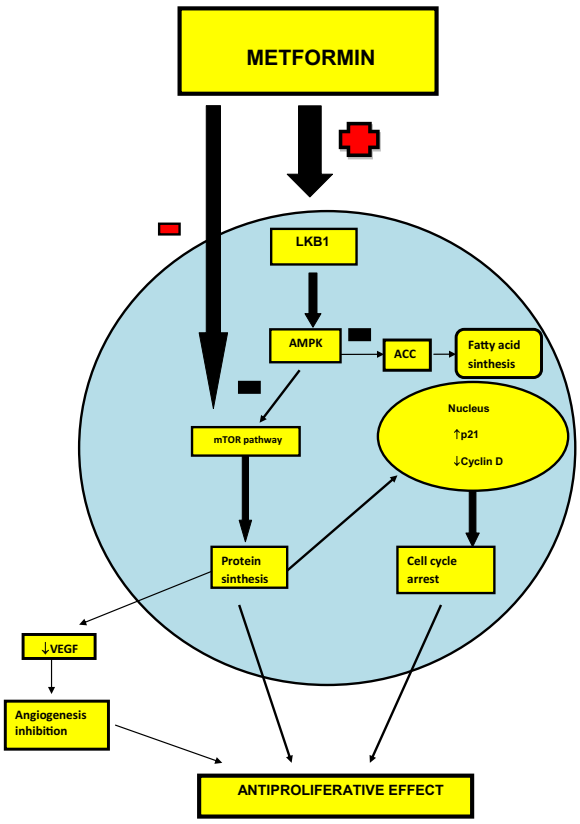

Fig. 1. Antitumoral effect of metformin. Metformin exerts antitumor effects mainly through AMP-activated protein kinase [AMPK] activation and phosphatidylinositol 3-kinase [PI3K]-Akt-mammalian target of rapamycin [mTOR] inhibition. Metformin exerts antitumor effects mainly through AMP-activated protein kinase [AMPK] activation and phosphatidylinositol 3-kinase [PI3K]-Akt-mammalian target of rapamycin [mTOR] inhibition (ACC,acetylcocarboxylase).

subunits (β_1, β_2, γ_1, γ_2 and γ_3), that acts as an ultra-sensitive cellular energy sensor maintaining the energy balance within the cell (Hardie, 2007, 2008). AMPK is activated in response to changes of AMP/ATP ratio under stress conditions and it is modulated by hormones, such as leptin and adiponectin (Hardie, 2008). mTOR controls protein synthesis by phosphorylation of the eukaryotic initiation factor 4E [eIF-4E]-binding protein-1 [4E-BP1] and of the S6 ribosomal protein kinase [p70S6K]. 4E-BP1 binds to eIF-4E, blocking the formation of the mRNA translation initiation complex and the synthesis of key proteins, such as c-myc, cyclin D1 and vascular endothelial growth factor [VEGF] (Wullschleger et al., 2006). When 4E-BP1 is phosphorylated, eIF-4E is released and the translation initiation complex is formed (Wullschleger et al., 2006). AMPK activation inhibits mRNA translation and proliferation in cancer cells *via* down-regulation of PI3K/Akt/mTOR pathway (Wullschleger et al., 2006; El-Mir et al., 2000). Another mechanism by which AMPK can exert anti-growth activity is the block of lipid biosynthesis *via* inhibition of the acetyl co-carboxylase [ACC], a rate limiting enzyme of the fatty acid synthesis (Hardie, 2008).

Rattan et al. (2011a) found that metformin inhibits proliferation of several chemo-responsive and -resistant ovarian cancer cell lines, leading to G1 phase growth arrest with concomitant inhibition of cyclin D1 and induction of p21 expression. These authors down-regulated AMPKα_1 expression in ovarian cancer cells using specific small interfering RNA [siRNA], and found that metformin was still able to block cell growth, although this inhibition was significantly less (~20%) compared with AMPK expressing parental cells. The anti-proliferative effects of metformin persisted in AMPK-silenced ovarian cancer cells, but not in LKB1-inactivated cells, thus

suggesting that LKB1 might have a pivotal role in antineoplastic action of the drug. Therefore the anti-growth activity of metformin seems to be LKB1-dependent, but can exert through both AMPK-dependent as well as AMPK-independent pathways.

Metformin decreases the production of inflammatory cytokines, such as tumor necrosis factor [TNF]-α and interleukin-6 [IL-6], and of VEGF through the inactivation of nuclear-factor kappa-B [NF-κB] and hypoxia-inducible factor [HIF]-1α, and therefore it exerts anti-inflammatory and anti-angiogenetic effects (Ersoy et al., 2008; Huang et al., 2009).

Recent *in vitro* and experimental data suggest that metformin electively targets cancer stem cells [CSC]s, and acts together with chemotherapy to block tumor growth in different cancers, such as breast cancer, prostate cancer, lung cancer, and ovarian cancer (Hirsch et al., 2009; Iliopoulos et al., 2011; Shank et al., 2012). The slow proliferation rate, the high expression of ATP-binding cassette [ABC] transporters serving as drug efflux pumps, the high expression of anti-apoptotic proteins, the ability to protect cells from DNA damage and efficient DNA repair mechanisms are responsible of chemo-resistance of CSCs (Kwon and Shin, 2013; Zhou et al., 2009). Aldehyde dehydrogenase [ALDH]s are a family of enzymes involved in detoxifying a wide variety of aldehydes, and ALDH activity has been used as a CSC marker in several tumors (Ma and Allan, 2011). The strategies attempted for eradication of CSCs include targeting the self-renewal controlling pathways (such as Wnt/β-catenin, Notch and Hedgehog), ALDH activity and ABC transporters, blocking epithelial–mesenchymal transition, and controlling CSC niches (Alison et al., 2012). Recent observations seem to suggest that metformin may function as anti-cancer agent also *via* targeting CSCs (Bao et al., 2014).

3. Metformin and ovarian cancer

3.1. Biological data

Metformin significantly restricts the growth of ovarian cancer cell lines *in vitro* and *in vivo* xenografts (Shank et al., 2012). Moreover, it is able to potentiate the anti-proliferative effect of cisplatin both *in vitro* and *in vivo* (Shank et al., 2012; Gotlieb et al., 2008; Rattan et al., 2011b). Rattan et al. (2011b) investigated the efficacy of metformin alone and in combination with cisplatin in nude mice intraperitoneally injected with A2780 ovarian cancer cells. Animals treated with metformin experienced a significant reduction of tumor growth, accompanied by inhibition of tumor cell proliferation assessed by immunohistochemical staining of Ki-67 and cyclin D1. Metformin-induced activation of AMPK correlated with decreased microvessel density and decreased VEGF expression. Moreover metformin inhibited the growth of lung metastases and significantly potentiated cisplatin-induced cytotoxicity. Erices et al. (2013) found that previous exposure and maintenance of micromolar concentrations of metformin in conjunction with carboplatin caused a synergistic enhancement in cytotoxicity of A2780 and SKOV3 ovarian cancer cell lines. Similarly micromolar metformin improved the response to carboplatin in 5 (44%) of the 11 ovarian cancer primary cultures derived from the ascites of patients with advanced disease. Lengyel et al. (2015) found that metformin decreases proliferation of ovarian cancer cell lines *in vitro* and induces cell cycle arrest but not apoptosis. Conversely, Yasmeen et al. (2011) observed that metformin is able to induce apoptosis in OVCAR-3 and OVCAR-4 ovarian cancer cell lines by up-regulating Bax and Bad, down-regulating Bcl-2 and Bcl-xl, and activating caspases-3 and -7. The induction of apoptosis by metformin was enhanced by cisplatin. In a prevention study performed by treating mice with intraperitoneal metformin or placebo for two weeks followed by intraperitoneal injection of the SKOV3ip1 human ovarian cancer cell line, Lengyel et al. (2015) detected that metformin- pretreated mice had significantly fewer tumor implants compared with controls. In a treatment study, mice who received intraperitoneal paclitaxel plus metformin had a 60% reduction in tumor weight compared with placebo-treated mice ($p < 0.005$), that was greater than that obtained with paclitaxel alone (40%) and metformin alone (42%). Therefore metformin appears to increase sensitivity to paclitaxel in mice models. Other experimental investigations revealed that metformin inhibits the ability of high-metastatic potential human ovarian cancer cell lines to adhere, invade and migrate *in vitro*, and it reduces hepatic, intestinal and lung metastases in a nude mouse model (Wu et al., 2012).

Metformin may exert an antineoplastic effect also *via* targeting the environmental milieu (Tebbe et al., 2014). Omental adipocytes can promote ovarian cancer growth by secretion of adipokines, cytokines and growth factors. Conditioned media obtained from differentiated mouse 3T3L1 preadipocites increased the proliferation and migration of the mouse ovarian surface epithelium cancer cell line ID8, and this promoting effect was attenuated by metformin.

3.2. Clinical data

A meta-analysis showed that patients with diabetes exhibit an increased risk of ovarian cancer (Lee et al., 2013). Moreover, diabetic women are more likely to have poorly differentiated tumor and to experience poor clinical outcome when compared with non-diabetic women, which could be due to the growth-promoting effect of elevated serum levels of insulin and IGF-1 (Bakhru et al., 2011; Jalving et al., 2010).

In a case-control study, long-term use of metformin, but not of sulfonylureas, showed a trend towards a reduced risk of ovarian cancer, whereas long-term use of insulin was associated with an increased risk of this malignancy (OR = 2.29, 95%CI = 1.13–4.65) (Bodmer et al., 2011) (Table 1a). A meta-analysis of 5 studies confirmed that metformin tended to decrease the occurrence of ovarian cancer among diabetic patients (Dilokthornsakul et al., 2013) (Table 1a). The meta-analysis of 28 studies performed by Zhang et al. (Zhang and Li, 2014) showed that metformin was associated with lower risk of all-cause mortality in cancer patients with diabetes, and especially for ovarian cancer (RR = 0.44, 95%CI = 0.30–0.64; $p < 0.001$).

In a cohort study including 341 ovarian cancer patients, Romero et al. (2012) found that both progression-free survival [PFS] and overall survival [OS] were significantly better for diabetic patients who used metformin compared with non-diabetic patients and diabetic patients who did not use metformin (Table 1b). At multivariate analysis metformin use remained an independent favorable prognostic factor for PFS (HR = 0.38; 95%CI = 0.16–0.90) but not for OS (HR = 0.43; 95%CI = 0.16–1.19). A case-control study confirmed a significantly better survival in ovarian cancer women who received metformin compared with ovarian cancer controls who did not (Kumar et al., 2013). Metformin remained an independent predictor for survival at multivariate analysis (HR = 2.2; 95%CI = 1.2–3.8; $p = 0.007$).

4. Metformin and endometrial cancer

4.1. Biological data

Metformin can inhibit cell proliferation and induce apoptosis in endometrial cancer cell lines and it can exert chemopreventive effects in endometrial carcinogenesis (Shafiee et al., 2014; Sivalingam et al., 2014; Ko et al., 2015; Cantrell et al., 2010).

Table 1
Metformin and ovarian cancer. (a) Metformin and ovarian cancer risk. (b) Metformin and prognosis of diabetic patients with ovarian cancer.

a

Authors	Study	Metformin users	Number	OC risk in metformin users OR (95%CI)
Bodmer et al. (2011)	Case-control 1611 OC cases (85 with diabetes) 9170controls (497 with diabetes)	Yes Not	1611 9170	0.61 (0.30–1.25)
Dilokthornsakul et al. (2013)	Meta-analysis of 5 studies (3 observational, 2 randomized)	Yes Not		0.57 (0.16–1.99)

b

Authors	Study	Patients	Number	5-year OS
Romero et al. (2012)	Cohort 341 OC patients	Diabetics who used metformin Diabetics who did not Use metformin Non diabetics	16 28 297	63% 37% 23% p = 0.03
Kumar et al. (2013)	Case-control 61 OC patients who used metformin 178 OC patients who did not use metformin	Metformin users Metformin non-users	61 178	67% 47% p = 0.007

OC, ovarian cancer; OR, odds ratio; 95% CI, 95% confidence interval; OS, overall survival.

Endometrioid-type endometrial cancer often shows alterations of the phosphatase and tensin homolog deleted on chromosome 10 [PTEN]/Akt/mTOR pathway, mainly due to PTEN inactivation or mutations, to amplification of the catalytic subunit-α of PI3K [PIK3CA], and more rarely to mTOR over-expression (Velasco et al., 2006; Oda et al., 2005; Gadducci et al., 2011). Metformin can: (i) activate LKB1-AMPK, which inhibits PTEN/Akt/mTOR pathway; (ii) inhibit PTEN/Akt/mTOR pathway directly, (iii) inhibit MAPK and cyclin D1 expression; (iv) induce progesterone receptor [PR] expression and recover progesterone sensitivity; (v) reduce VEGF expression and neoangiogenesis (Banno et al., 2015; Brown et al., 2013; Del Barco et al., 2011; Jalving et al., 2010; Ben Sahra et al., 2010; Viollet et al., 2012). Moreover *in vitro* studies on endometrial cancer cell lines showed that metformin down-regulates IGF-1 and IGF-1 receptor (IGF-1R) expression and up-regulates IGF-binding protein [IGF-BP] expression (Xie et al., 2014; Zhang et al., 2015).

A recent *in vitro* investigation revealed that metformin also induces apoptosis and inhibition of proliferation and migration of uterine papillary serous carcinoma cell lines (Sarfstein et al., 2013). K-Ras mutations occur in 10–30% of endometrioid-type endometrial carcinomas (Velasco et al., 2006; Gadducci et al., 2011). Metformin decreased tumor growth in xenograft mouse models of endometrial cancer, with the greatest responses observed in tumors harboring activating K-Ras mutations (Iglesias et al., 2013). Metformin displaces constitutively active K-Ras from the plasma membrane to the cytoplasm, causing K-Ras silencing and uncoupling of the MAPK signaling pathway. These observations provide a rationale for clinical trials using metformin in combination with PI3K-targeted agents for K-ras mutated endometrial cancers. In diabetic patients hyperglycemia may result in the increased production of a non-enzymatic glycation intermediate, termed methylglyoxal (Maessen et al., 2015). The reaction of methylglyoxal with amino acids causes protein degradation and cross-linkages to form irreversible advanced glycation end products [AGES], that are involved in the pathogenesis of diabetic complications and that may promote genetic mutations (Dong et al., 2012). Glyoxalase I [GloI] is the major enzyme that removes methylglyoxal, thus preventing AGES accumulation. However, an aberrant GloI over-expression seems to be involved in chemotherapy resistance in several malignancies (Sakamoto et al., 2000, 2001). GloI is over-expressed in endometrial cancer tissue and may induce progestin resistance (Zhang et al., 2011b). Metformin reverses progestin resistance and enhances the sensitivity of endometrial cancer cells to cisplatin and paclitaxel by down-regulating GloI expression (Dong et al., 2012). Telomerase activation is a fundamental step in cellular immortality and oncogenesis of several malignancies, including endometrial cancer, and human telomerase reverse transcriptase [hTERT] expression is the rate-limiting determinant of the enzymatic activity of human telomerase (Zheng et al., 1997). Metformin decreases hTERT mRNA expression, while paclitaxel alone had no effect on telomerase activity (Hanna et al., 2012).

Metformin could be especially useful as chemopreventive agent in women with polycystic ovary syndrome [PCOS], which have a 3-fold increased risk of endometrial cancer (Shafiee et al., 2014; Dumesic and Lobo, 2013; Shao et al., 2014). There is a progressive decrease in the expression of the endometrial insulin-dependent glucose transporter GLUT4 from healthy women to normo-insulinemic PCOS women to hyper-insulinemic PCOS women (Carvajal et al., 2013; Zhang and Liao, 2010). Metformin increases GLUT4 mRNA and protein expression in endometrial cells from women with PCOS, possibly through the activation of AMPK and its downstream targets such as myocyte enhancer factor (Carvajal et al., 2013; Zhai et al., 2012).

4.2. Clinical data

Type-2 diabetes is risk factor for endometrial cancer (Calle et al., 2003; Noto et al., 2011; Zhang et al., 2013c; Liao et al., 2014; Luo et al., 2014). A meta-analysis of 23 cohort studies showed that the summary RR of this malignancy among diabetics was 1.89 (95%CI = 1.46–2.45, p < 0.001) (Liao et al., 2014). Among the 88.107 postmenopausal women enrolled in the Women's Health Initiative [WHI] trial who had no hysterectomy at baseline, 1241 cases of endometrial cancers developed during a mean follow-up of 11 years (Luo et al., 2014). Women with self-reported diabetes and the subset of women with treated diabetes had significantly higher risk of endometrial cancer (HR = 1.44, 95%CI = 1.13–1.85 and HR = 1.57, 95%CI = 1.19–2.07, respectively), but these associations became non-significant after adjusting for body mass index (BMI). However an elevated risk was still observed after adjusting for BMI, when considering diabetes diagnosed at baseline and during follow-up as time-dependent exposure (HR = 1.31, 95%CI = 1.08–1.59). Type-2 diabetes is associated with increased serum levels of insulin and IGF-1 that are mitogenic factors (Markowska et al., 2013). In the normal endometrium, especially during the proliferative phase, estrogen binding to estrogen receptor [ER] acts as a transcription factor for local IGF-1 synthesis (Zhou et al., 1994). After binding to IGF-1R, signaling may occur through both PI3K/Akt/mTOR and MAPK pathways (Sachdev and Yee, 2007). Estrogen also increases endometrial IGF-1R synthesis (Kleinman

Table 2
Antiproliferative effects of preoperative treatment with metformin in EC tissues.

Authors	Metformine schedule	Patient number	Effect
Schuler et al. (2015)	850 mg d. for 4 wks	20	↓ cell proliferation ↓ pospho-Akt ↓ p70S6K ↓ pospho-4E-BP1 ↓ ER, unchanged PR
Mitsuhashi et al. (2014)	1500–2250 mg d. for 4–6 wks	31	↓ Ki-67 ↓topoisomerase II- α ↓ p70S6K ↓ ERK1/2 ↑ p27
Laskov et al. (2014)	1500 mg d. for a mean of 36.6 days	11	↓ Ki-67 ↓ p70S6 K

EC, endometrial cancer; d, day, wks, weeks.

et al., 1995), and over-expression of insulin receptor [IR] and IGF-1R can promote endometrial carcinogenesis (McCampbell et al., 2006; Wang et al., 2013). Moreover IGF-1 reduces PR expression in endometrial cancer cell lines (Xie et al., 2011). On the other hand, endometrial stromal cells produce IGF-BP, that negatively regulates the bioavailability of IGF-1 (Zhou et al., 1994; Gadducci and Genazzani, 1997). IGF-BP secretion is primarily stimulated by progesterone and inhibited by insulin (Lathi et al., 2005). Therefore in post-menopausal women with type-2 diabetes, the lack of local endometrial IGF-BP synthesis might translate into a higher binding of IGF-1 to IGF-1R and consequently in an unopposed stimulation of endometrial cells by IGF system (Sachdev and Yee, 2007; Gadducci and Genazzani, 1997). Forty-three women with abnormal uterine bleeding and histological diagnosis of disordered proliferative endometrium or simple endometrial hyperplasia were randomly allocated to receive metformin 500 mg twice daily or megestrol 40 mg daily for three months (Tabrizi et al., 2014). An endometrial atrophy at histological control was detected in 95.5% of the former *versus* 61.9% of the latter. Clinical studies have shown that the preoperative administration of metformin significantly reduces cell proliferation (Schuler et al., 2015) and decreases the expression of Ki-67 (Mitsuhashi et al., 2014; Laskov et al., 2014), topoisomerase II-α (Mitsuhashi et al., 2014), pospho-Akt (Schuler et al., 2015; Mitsuhashi et al., 2014), pospho-p70S6K (Schuler et al., 2015; Mitsuhashi et al., 2014; Laskov et al., 2014), popsho-4E-BP1 (Schuler et al., 2015), phospho-extracellular signal-regulated kinase 1/2 [ERK1/2] (Mitsuhashi et al., 2014), and ER (Markowska et al., 2013; Schuler et al., 2015) in endometrial cancer tissues, besides decreasing the serum levels of insulin, IGF-1, and leptin (Mitsuhashi et al., 2014; Laskov et al., 2014) (Table 2). Markowska et al. (2013), who assessed archived samples of endometrioid–type endometrial carcinoma from 81 postmenopausal women with type 2 diabetes, found a decreased ER expression in patients receiving metformin compared to those treated with insulin ($p = 0.004$). Conversely there was no significant difference in PR, IGF-1R, and β-catenin expression among women receiving metformin and those receiving other hypoglycemic treatment.

Metformin 1500–2250 mg daily plus medroxyprogesterone acetate [MPA] 400 mg daily were administered to patients with atypical endometrial hyperplasia or stage IA, well differentiated endometrioid-type endometrial carcinoma who wished to preserve fertility (Mitsuhashi et al., 2014). Combined therapy given for 6–9 months obtained a complete response in 91% of the women, that continued to take metformin following completion of MPA treatment. After a median follow-up of 26 months, the recurrence rate was only 5% compared with a recurrence rate ranging from 25% to 40% after progestin therapy alone according to literature data (Kalogera et al., 2014).

Metformin may be especially useful for prevention and treatment of endometrial cancer in women with PCOS and obesity (Shafiee et al., 2014; Sivalingam et al., 2014; Hawkes et al., 2014; Session et al., 2003; Shen et al., 2008; Johnson, 2014; Li et al., 2014; Zhang et al., 2013b; Umene et al., 2013; Stine and Bae-Jump, 2014). Two women with atypical endometrial hyperplasia not responsive to high-dose progestin had endometrial pathology reversed after 3 months of metformin and oral contraceptives (Shen et al., 2008). Combined treatment with Diane-35 and metformin for 6 months achieved an histologically documented complete response in 5 women with stage IA, low-grade endometrial carcinoma and insulin-resistance (Li et al., 2014).

In a retrospective US cohort analysis, Ko et al. (2015) assessed a large series of new users of metformin *versus* sulfonylureas who had no prior cancer (Table 3a). After a median follow-up of 1.2 years, 729 women developed endometrial cancer. Metformin use correlated with a lower risk of this malignancy at univariate analysis (HR = 0.81, 95%CI = 0.67–0.97). In a large cohort study including women with newly diagnosed type-2 diabetes, metformin ever users had a 32.5% risk reduction of endometrial cancer compared with metformin never users (Tseng, 2015). There was a dose-response relationship, with HRs of 1.089 (95%CI = 0.966–1.228), 0.707 (95%CI = 0.616–0.812) and 0.313 (95%CI = 0.262–0.374), respectively (p-trend < 0.0001), for the first, second, and third tertiles of cumulative duration of metformin use, and 1.062 (95%CI = 0.942–1.197), 0.620 (95%CI = 0.538–0.715) and 0.376 (95%CI = 0.317–0.447), respectively (p-trend < 0.0001), for the first, second, and third tertiles of cumulative dose of metformin. Conversely, Becker et al. (2013) found no difference in the incidence of endometrial cancer between metformin users and non users.

The meta-analysis of Zhang and Li (2014) showed that metformin use was associated with a significantly lower endometrial cancer mortality (RR = 0.49, 95%CI = 0.32–0.73; $p = 0.001$). A multicenter US cohort analysis on 1495 endometrial cancers diagnosed between 2005 and 2010, reported that 24% of patients were diabetic and 54% of them took metformin (Ko et al., 2014) (Table 3b). Non-metformin users had 1.8 times worse PFS ($p = 0.02$) and 2.3 times worse OS ($p = 0.005$), after adjusting for age, stage, grade, histology and adjuvant treatment. A single-institution cohort study of 985 endometrial cancer patients revealed that 12% had diabetes and were treated with metformin, 14% were diabetic but did not use metformin, and 74% were not diabetic (Nevadunsky et al., 2014) (Table 3b). OS was better in diabetics with non-endometrioid cancer who used metformin than in diabetics not using metformin and in not diabetics with non-endometrioid cancer ($p = 0.02$). This association remained significant after adjusting for covariates. Conversely, no association was observed between metformin use and OS in diabetics with endometrioid cancer (HR = 0.79, 95%CI = 0.31–2.00). These results appear to be parodoxical, although the risk factors for recurrence and survival may not be the same as for the initial development of the cancer.

Table 3
Metformin and endometrial cancer. (a) Metformin and endometrial cancer risk. (b) Metformin and prognosis of diabetic patients with endometrial cancer.

a

Authors	Study	Patients	Number	EC risk in metformin usersHR (95%CI)
Ko et al. (2015)	Cohort 541.128 diabetics	Metformin users Sulfonylureas users	456,838 84,290	0.81 (0.67–0.97)
Tseng (2015)	Cohort 478.921 diabetics	Metfromin ever users who developed EC Metformin never users who developed EC	728 2157	0.675 (0.614–0.742)
Becker et al. (2013)	Case–control 2554 EC cases (266 with diabetes) 15.324 controls (821 with diabetes)	Metformin users Metformin never users		OR (95% CI) 0.86 (0.63–1.18) ever users 0.79 (0.54–1.17) long-term users

b

Authors	Study	Metformin users	Number	Results
Ko et al. (2014)	Cohort 1495 EC patients (363 diabetics)	Yes Not	196 167	Metformin non-users: 1.8 times worse RFS (95%CI = 1.1–2.9, p = 0.02) 2.3 times worse OS (95%CI = 1.3–4.2 = 0.005)
Nevadunsky et al. (2014)	Cohort	Yes	114	Better OS in diabetics with NEC who used metformin *vs* diabetics not using metformin and not diabetics with NEC (p = 0.02).
	985 EC patients (250 diabetics)	Not	136	The association remained significant (HR = 0.54, 95%CI = 0.30–0.97, p < 0.04) after adjusting for age, stage, grade, chemotherapy, radiotherapy and hyperlipidemia

EC, endometrial cancer; HR, hazard ratio; 95% CI, 95% confidence interval; OR, Odds ratio; RFS, recurrence- free survival; OS, overall survival; EC, endometrial cancer; NEC, non-endometrioid cancer.

5. Metformin and breast cancer

5.1. Biological data

Metformin has chemo-preventive properties also in breast cancer through the effects of drug on insulin, IGF system and different intracellular signaling transduction pathways (Zhang and Li, 2014; Bosco et al., 2011). Moreover, metformin decreases the serum androgen and estrogen levels in non-diabetic women with breast cancer (Campagnoli et al., 2012, 2013).

Breast cancer is classified into five molecular subtypes: luminal A, luminal B, HER2-positive, breast-like and triple-negative (Cornejo et al., 2014; Lehmann et al., 2011). Luminal A subtype has the best prognosis, while HER2-positive and triple negative subtypes are associated with worst outcomes. Several preclinical investigations have assessed the effects of metformin in different subtypes. MCF-7 is a breast cancer cell line positive for ER and PR but without HER2 over-expression. Some *in vitro* studies have proved that metformin directly influences proliferation and apoptosis of MCF-7 cells through AMPK activation and PI3K/akt/mTOR inhibition (Zakikhani et al., 2006; Dowling et al., 2007). Alimova et al. (2009) have shown that metformin can inhibit PI3K/akt/mTOR in both ER positive and ER negative cells as well as in HER2-overexpressing and HER2-normal expressing cells. Some authors have found that metformin decreases cell proliferation and induces apoptosis also in triple-negative breast cancer cells (Liu et al., 2009; Williams et al., 2013; Deng et al., 2012; Zordoky et al., 2014).

Liu et al. (2012b) have demonstrated that the mTOR inhibitor everolimus and metformin sensitize breast cancer cells to cytotoxic effects of chemotherapeutic agents, such as carboplatin, paclitaxel and doxorubicin, *in vitro*. Moreover, Hirsch et al. (2009) have shown that the combination of metformin and doxorubicin kills both CSCs and non-CSCs in culture and that this combination reduces tumor mass and prevents recurrence more effectively than either drug alone in a xenograft mouse model.

Metformin has synergetic effects with tamoxifen on reducing tumor growth *in vitro* and *in vivo* in ER-positive breast cancer cells (Ma et al., 2014). Hyperthermia activates AMPK and inactivates PI3K/akt/mTOR and p70S6K, and markedly increases the effects of metformin against human breast cancer cells *in vitro* (Lee et al., 2014). Metformin resensitizes multidrug resistant breast cancer cells to 5-fluorouracil, doxorubicin and paclitaxel *via* activating AMPK (Qu et al., 2014), and overcomes the resistance to lapatinib in Her2-overexpressing breast cancer cells (Komurov et al., 2012).

Breast cancer associated gene 2 [BCA2] is a E3 ligase overexpressed in more than 50% of breast tumors, which acts as an endogenous inhibitor of AMPK (Buac et al., 2013). BCA2 siRNA increases the growth inhibitory effect of metformin in multiple breast cancer cell lines, thus suggesting that the combination of metformin and a BCA2 inhibitor can be more effective than metformin alone.

5.2. Clinical data

Diabetes is associated with increased breast cancer incidence and mortality (De Bruijn et al., 2013; Peairs et al., 2011; Hardefeldt et al., 2012; Boyle et al., 2012; Goodwin et al., 2002). The meta-analysis of forty studies has demonstrated a 20% increased risk of breast cancer in women with type 2 diabetes compared with non diabetics (Hardefeldt et al., 2012), probably due to increased serum levels of insulin and IGF-1 (Jalving et al., 2010).

An Italian randomized trial including women with stage I–II breast cancer candidates for elective surgery detected hat preoperative administration of metformin 1700 mg daily for 4 weeks significantly reduced Ki-67 expression in HER-2 positive ductal carcinoma in situ compared with placebo (DeCensi et al., 2015).

Metformin has shown promising results as chemopreventive agent against breast carcinogenesis in diabetic women (Bosco et al., 2011; Bodmer et al., 2010; Chlebowski et al., 2012) (Table 4). The longer is metformin use the greater the protective effect (Evans et al., 2005; Bodmer et al., 2010). In a UK case-control study long-term use of ≥40 prescriptions of metformin was associated with a 56% risk reduction, although this association was based on only 17 exposed patients (Bodmer et al., 2010). In a Danish case–control

Table 4
Metformin and breast cancer risk.

Authors	Study	Patients	Number	BC risk in metfomin users	
	Case-control	Metformin prescriptions		OR (95%CI)	p
Bodmer et al. (2010)	2.261 diabetics	None	140	1.00	
		1–9	64	1.20 (0.82–1.78)	0.35
		10–39	84	1.09 (0.76–1.55)	0.65
		≥40	17	0.44 (0.24–0.82)	0.01
Bosco et al. (2011)	Case-control	Metformin ≥ 1 year	96/393 BC patients	OR (95% CI)	
	4.323 diabetics aged ≥50 years	Metformin ≥ 1 year	1154/3930 controls	0.77 (0.61–0.99)	
Chlebowski et al. (2012)	Cohort	Metformin users	104	HR (95% CI)	p
	68.019 post-menopausal women(including 3.401 diabetics)	Metformin non-users	129	0.75 (0.57–0.99)	0.04
				1.16 (0.93–1.45)	ns
Soffer et al. (2015)	Cohort	Metformin only	143		HR (95% CI)
	66.778 diabetics of whom 1572 developed BC	Sulfonylureas only	55	Metfornin only *vs* combination	0.85 (0.69–1.04)
		Insulin only	125	Metformin only *vs* non-metformin 0.89	(0.79–1.09).
		Other non-metformin only	46		
		Metformin in combination	560		
		Non antidiabetic users	643		

OR, odds ratio; 95% CI, 95% confidence interval; BC, breast cancer; HR, hazard ratio.

Table 5
Metformin and prognosis of diabetic patients with breast cancer.

Authors	Study	Patients	Number	Results		
He et al. (2012)	Cohort	Metformin users	88		HR (95% CI)	p
	1983 patients with HER2+ BC (154 diabetics and 1829 non-diabetics)	Metformin nonusers	66	OS in metformin users	0.52 (0.28–0.979)	0.041
				BC-specific mortality in metformin users		
					0.47 (0.24–0.90)	0.023
Lega et al. (2013)	Cohort	Metformin users	1094		HR (95% CI)	
	2361 patients aged ≥ 66 years with diabetes and BC	Metformin nonusers	1267	BC specific mortality in metformin users		
					0.91 (0.81–1.03)	
Oppong et al. (2014)	Cohort141 patients with diabetes and BC who received chemotherapy	Metformin usersMetformin nonusers	76 65		HR (95% CI)	p
				RFS in metformin users	0.86 (0.38–1.90)	0.70
				OS in metformin users	0.80 (0.33–1.96)	0.63
Bayraktar et al. (2012)	Cohort	All patients	1448	5-year DMFS (95% CI)	5-year OS	(95% CI)
	1448 patients who received adiuvant chemotherapy for TNBC	Diabetics who used metformin	63	60% (58–63%)	66%	(64–69%)
		Diabetics who did not use metformin	67	73% (58–0.83%)	0.67%	(52–0.79%)
		Non- diabetics	1318	66% (0.52–0.77%)	0.69%	(55–0.79%)
				60% (0.57–0.62%)	66%	(63–69%)
				p = 0.23	p = 0.58	

HR, hazard ratio; 95% CI, 95% confidence interval; OS, overall survival, BC, breast cancer; RFS, recurrence-free survival; TNBC, triple negative breast cancer; DMFS, distant metastasis–free survival;

Table 6
Ongoing clinical trials on metformin as an anti-cancer treatment (was added).

Study	Type of study	Pts	Design of the study
NCT02122185	phase II trial[a]	stage III–IV EOC	random metformin + standard CT up to 6 cycles metformin maintenance for up to 2 years *vs* placebo + standard CT up to 6 cycles placebo maintenance for up to 2 years in absence of progression or toxicity
ANZGOG 1301	phase-II trial[b]	obese pts (BMI > 30 kg/m2) with early CAH or G1 endometrioid EC who wish to retain fertility or who are at risk of surgicalcomplications due to co-morbidities or obesity	random in a 3:3:5 ratio LNG-IUD : LNG-IUD + metformin : LNG-IUD + weight loss
NCT01101438	phase III trial[c]	early BC pts after definitive surgery and/or CT	random metformin up to 5 years *vs* placebo up to 5 years in absence of progression or toxicity
NCT01589367	phase II trial[d]	postmenopausal pts with ER+, Stage II–III BC	random Neoadiuvant metformin + letrozole for 24 weeks *vs* Neoadiuvant placebo + letrozole for 24 weeks

pts, patients; EC, EOC, epithelial ovarian cancer; CAH, complex atypical hyperplasia; EC, endometrial cancer; LNG-IUD, levonorgestrel.
[a] Aimed to assess if the addition of metformin to stardard adjuvant or neoadjuvant CT plus extended metformin beyond standard CT increases PFS when compared to 6 cycles of standard CT alone in nondiabetic pts with advanced EOC.
[b] Aimed to assess different conservative options for obese pts with early EC in terms of pathological complete response rate at six months from study treatment initiation.
[c] Aimed to compared DFS of pts with early BC treated with metformin *vs* placebo in addition to standard adjuvant therapy.
[d] Aimed to compare clinical response rate, pathological complete response rate, breast conserving rate, change in Ki 67 expression, breast density change, and toxicity profile in BC pts treated with letrozole + metformin *vs* letrozole + placebo in neoadjuvant setting.

study including type 2 diabetic women aged ≥50 years, metformin users had a 23% risk reduction of developing breast cancer than non users (Bosco et al., 2011). Similarly a large cohort study showed that diabetic women who were given metformin had a 25% risk reduction, whereas diabetic women receiving drugs other than metformin had a slightly higher incidence of breast cancer (Chlebowski et al., 2012). Nonetheless other authors failed to detect significant differences for breast cancer risk between metformin users and non-users (Currie et al., 2009; Soffer et al., 2015). These conflicting results may reflect differences in drug exposure, follow-up time and patient characteristics.

Retrospective clinical studies support the use of metformin as an anti-cancer treatment to improve survival rates in diabetic women with breast cancer (He et al., 2012; Kiderlen et al., 2013) (Table 5). He et al. (2012) have shown that metformin users with HER2-positive breast cancer had significantly improved OS and decreased specific mortality. In the study of Kiderlen et al. (2013), including 3124 elderly patients with non-metastasized breast cancer, relapse-free survival was better for women with diabetes compared with those without diabetes (HR = 0.77, 95%CI = 0.59–1.01), irrespective of other comorbidities and most evident in women aged ≥75 years (HR = 0.67, 95%CI = 0.45–0.98). A possible explanation might be the frequent use of metformin in diabetic patients. Nonetheless other observational investigations have proved no significant mortality reduction in diabetic women with breast cancer (Lega et al., 2013; Oppong et al., 2014; Bayraktar et al., 2012). Oppong et al. (2014), who assessed diabetic patients undergoing chemotherapy for breast cancer, found no significant differences in either 5-year recurrence-free survival or 5-year OS between metformin users and metformin non-users (90.4% *versus* 85.4%, and, respectively, 93.0% *versus* 89.7%). A retrospective US study on women receiving adjuvant chemotherapy for triple negative breast cancer, failed to detect significant differences in terms of distant metastasis-free survival and OS between diabetic patients treated with metformin, diabetic patients not treated with metformin, and non-diabetic patients (Bayraktar et al., 2012). The reasons for these conflicting results can include differences in tumor subtype, patient age, and comorbidities. Further clinical investigations on well stratified, larger series of patients are strongly warranted to better define whether metformin may have a role in breast cancer treatment.

6. Conclusions

Several *in vitro* and *in vivo* pre-clinical investigations have detected a growth-static effect of metformin also in gynecological malignancies, including ovarian cancer (Shank et al., 2012; Erices et al., 2013; Lengyel et al., 2015; Yasmeen et al., 2011; Wu et al., 2012; Tebbe et al., 2014; Lee et al., 2013; Bakhru et al., 2011; Jalving et al., 2010), endometrial cancer (Banno et al., 2015; Brown et al., 2013; Del Barco et al., 2011; Jalving et al., 2010; Gadducci et al., 2011; Ben Sahra et al., 2010; Viollet et al., 2012; Xie et al., 2014; Zhang et al., 2015; Sarfstein et al., 2013; Iglesias et al., 2013; Dong et al., 2012; Hanna et al., 2012; Shao et al., 2014; Xie et al., 2011) and breast cancer (Evans et al., 2005; Zhang and Li, 2014; Bosco et al., 2011; Hirsch et al., 2009; DeCensi et al., 2015; Bodmer et al., 2010; Soffer et al., 2015; He et al., 2012), mainly due to the effects of drug on the IGF system and different intracellular signaling transduction pathways.

Some epidemiological studies and meta-analysis have shown that metformin use is associated with decreased risk and/or reduced mortality of ovarian cancer (Bodmer et al., 2011; Romero et al., 2012; Kumar et al., 2013; Dilokthornsakul et al., 2013; Zhang and Li, 2014) endometrial cancer (Zhang and Li, 2014; Tseng, 2015; Becker et al., 2013; Ko et al., 2014) and breast cancer (Bosco et al., 2011; Bodmer et al., 2010; Chlebowski et al., 2012; He et al., 2012; Kiderlen et al., 2013). Metformin is especially useful for endometrial cancer prevention in women with PCOS and obesity (Shafiee et al., 2014; Sivalingam et al., 2014; Hawkes et al., 2014; Session et al., 2003; Shen et al., 2008; Johnson, 2014; Li et al., 2014; Zhang et al., 2013b; Umene et al., 2013) and can represent a novel interesting treatment option for atypical endometrial hyperplasia or early stage, well differentiated endometrioid-type endometrial carcinoma in young women who wish to preserve fertility (Mitsuhashi et al., 2014; Shen et al., 2008; Li et al., 2014). As far as breast cancer is concerned, the heterogeneity of tumor subtypes makes it difficult

to determine the actual benefits of metformin therapy (Hatoum and McGowan, 2015). To date, this is not approved for clinical use in breast cancer treatment by the Food and Drugs Administration (FDA) and it is still considered investigational.

The large majority of available clinical data on the anti-cancer potential of metformin are based on observational studies. Therefore phase II–III clinical trials designed to explore its efficacy in the prevention and treatment of gynecological cancers are strongly warranted to further investigate the activity of metformin in this clinical setting (Table 6).

Conflict of interest

The authors indicated no potential conflict of interest including any financial or personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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