Review

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Linking type 2 diabetes and gynecological cancer: an introductory overview

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Abstract: Type 2 diabetes (T2D) is a chronic disease with a growing prevalence and a leading cause of death in many countries. Several epidemiological studies observed an association between T2D and increased risk of many types of cancer, such as gynecologic neoplasms (endometrial, cervical, ovarian and vulvar cancer). Insulin resistance, chronic inflammation and high free ovarian steroid hormones are considered the possible mechanisms behind this complex relationship. A higher risk of endometrial cancer was observed in T2D, even though this association largely attenuated after adjusting for obesity. A clear relationship between the incidence of cervical cancer (CC) and T2D has still not be determined; however T2D might have an impact on prognosis in patients with CC. To date, studies on the association between T2D and ovarian cancer (OC) are limited. The effect of pre-existing diabetes on cancer-specific mortality has been evaluated in several studies, with less clear results. Other epidemiological and experimental studies focused on the potential role of diabetes medications, mainly metformin, in cancer development in women. The correct understanding of the link between T2D and gynecologic cancer risk and mortality is currently imperative to possibly modify screening and diagnostic-therapeutic protocols in the future.

Keywords: gynecological cancer; molecular mechanisms; type 2 diabetes.

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Introduction

Type 2 diabetes (T2D) is a chronic disease with an increasing global prevalence. Currently, 415 million adults are estimated to have T2D and 193 million people with diabetes are undiagnosed [1]. The global prevalence of T2D has nearly doubled since 1980, rising from 4.7% to 8.5% in adult populations, due to an increase in associated risk factors, such as overweight and obesity [2]. Diabetes and its complications, especially cardiovascular disease, are leading causes of death in many countries.

There is growing evidence of an association between T2D and increased cancer risk, although the accurate assessment of this risk in diabetes is complicated by the interference of several confounding factors, including obesity. In both men and women with T2D, most epidemiological studies observed an increased risk of cancer of the liver, pancreas, gallbladder, breast, endometrium, ovary, stomach, kidney, bladder, colon/rectum as well as leukemia, myeloma and lymphoma [3]. In this review, the main mechanisms of carcinogenesis behind the relationship between T2D and cancer in women (endometrial, cervical and epithelial ovarian cancer [EOC]) and the current epidemiological evidence are illustrated. Moreover, the potential role of diabetes medications in cancer development in women is discussed.

Biological links between T2D and gynecological cancers

A broad literature has demonstrated that there is a strong association between T2D and cancer development related to common pathogenetic features such as hyperglycemia, hyperinsulinemia and chronic inflammation [4, 5].

In females with T2D there is an important incidence and prevalence of gynecologic malignancies that share several common mechanisms with T2D, including increased insulin levels and IGF signaling, and a common dysregulation of ovarian steroid hormones [6].

Several studies have evaluated the effect of increased IGF [7]. IGF-I and -II are overexpressed in many cancers, which may lead to increased proliferation as well as stimulation of pathways involved in invasion and metastasis [8, 9].

The deleterious mitogenic effect of hyperinsulinemia is more marked in cancer cells that often overexpress the insulin receptor (IR): in response to insulin, cancer cells grow more than non-transformed cognate cells [10].

Insulin resistance with subsequent hyperinsulinemia is peculiar to T2D: when elevated, insulin can increase the hepatic expression of insulin growth factor-1 (IGF-1) and then activate the IGF-1 receptor, further stimulating cell growth [11, 12].

Moreover, it has been reported that elevated insulin levels also lead to a leptin overexpression: increased leptin plasma concentrations are believed to be associated with the occurrence and progression of endometrial and ovarian cancer [13–15]. Furthermore, leptin can also upregulate vascular endothelial growth factor (VEGF), a hallmark of malignant tumor development [16].

There is evidence that the rate of insulin secretion among individuals may influence the risk and progression of cancer: increased insulin levels are associated with increased risk of cancer and higher mortality in women with cancer, particularly endometrial and ovarian cancers [17, 18].

Hyperglycemia is the most prominent clinical sign of diabetes: a hyperglycemic environment contributes to tumor progression through multiple pathways leading to increased proliferative, anti-apoptotic and metastatic cancer activity [19–21].

In diabetes, hyperglycemia is responsible for the endothelial dysfunction and endothelial cell death and aberrant neoangiogenesis [22, 23].

Hyperglycemia-associated AGEs (advanced glycation end products) promote pathological activation of protein kinase C, which can lead to altered vascular proliferation. The interaction of AGEs with their receptors produces oxidative stress and inflammation, which promote cancer [24–26].

Additionally, hyperglycemia may favor angiogenesis in tumors by upregulating microRNA-467, a suppressor of the antiangiogenic protein thrombospondin-1: subsequently cancer neoangiogenesis will then favor malignant growth [22].

Furthermore, elevated glucose level interferes with epigenetic modulations of oncogenic pathways leading to "hyperglycemic memory", a condition that allows hyperglycemia-exposed cancer cells to permanently activate oncogenic pathways, even after normalization of glucose levels [27, 28].

This mechanism is probably caused by glucose-induced persistent expression of nuclear factor-κB (NF-κB) a well-established signal for cancer cell proliferation [29, 30].

Many studies concerning the association between inflammation and cancer in females suggest that the inflammatory pathways activated through NF-κB signaling play an important role in the development and progression of cancers such as endometrial, and epithelial ovarian cancers [31–33].

Ovarian steroid hormones, particularly estrogen, can activate NF-κB signaling, which induces the gene expression of inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor-α (TNF-α), and metalloproteinases (MMPs), thus facilitating inflammatory processes [34].

T2D and insulin resistance are associated with decreased serum sex hormone binding globulin, which can lead to elevated levels of free estrogen: the evidence for elevated estrogen as a carcinogen is well-established in EC and a recent murine models suggest that it may also play a role in ovarian cancer [35, 36].

Insulin resistance and hyperinsulinemia in T2D promote subclinical or low-grade chronic inflammation and females with T2D-increased bioavailable ovarian steroid hormones show even more enhanced inflammatory effects: a chronic inflammatory state in these patients may be the main mechanism associated with cancer development and progression.

Finally, adipose metabolic dysregulation is a hallmark of T2D and can lead to increased levels of inflammatory cytokines such as IL-6 and TNF-α: they can activate molecular pathways involved in cell proliferation, invasion and evasion of antitumor immunity [37, 38].

T2D and endometrial cancer

In developed countries, endometrial cancer (EC) is the fourth most common cancer in women. Every year, approximately 88.068 new cases are registered in the European Union and more than 90% of cases occur in women older than 50 years of age [39]. EC is strongly associated with endometrial hyperplasia and estrogen exposure, unopposed by progesterone [40].

It has been demonstrated that T2D is an important risk factor for EC and this association has been observed in most epidemiological studies [41–44].

A meta-analysis of 16 studies (13 case-control and three cohort studies) indicated a significantly increased risk of EC in T2D patients (RR 2.10, 95% CI: 1.75–2.53) and a meta-analysis of 21 prospective cohort studies, involving 12,195 incident cases of EC, showed that preexisting diabetes was associated with increased incidence of EC (RR 1.81, 95% CI: 1.38–2.37), compared with subjects without diabetes [45, 46].

A recent population-based and retrospective cohort study showed a strong association between T2D and EC, with an HR of 1.81 (95% CI: 1.37–2.41). However, more studies are needed to examine whether the association between T2D and EC is partly or largely dependent on obesity [43].

Many studies have suggested that T2D and EC share characteristics about the major modifiable determinates: mainly obesity and T2D are commonly observed in women with EC. Excessive adipose tissue leads to reduced concentration of progesterone and sex hormones binding globulin (SHBG). A decreased amount of SHBG results in an increased amount of bioavailable testosterone and estrogen, subsequently promoting carcinogenesis in the endometrium [47].

Even though there is consistent evidence based on various cohort studies and systematic reviews for an independent association between T2D and increased risk of incident EC, recently a large, prospective cohort study of 88,107 post-menopausal women aged 50–79 years found no significant association between T2D and EC after adjusting for BMI (HR: 1.16, 95% CI: 0.90–1.48). However, some modest independent elevated risk remained when considering a combination between diabetes diagnosed at baseline and during follow-up as time-dependent exposure (HR: 1.31, 95% CI: 1.08–1.59) [48].

Meta-analysis of the currently available clinical evidence supports the association between high serum adiponectin concentration and reduced risk of EC: women with EC were more likely to have low adiponectin levels than controls, even after adjusting for BMI [49, 50].

The independent and inverse association of adiponectin with EC suggested that insulin resistance is independently associated with EC [51].

The effect of T2D on the risk of death from EC is less clear [46, 52–55]. A prospective study reported a significantly increased age-adjusted risk of death (1.72, 95% CI: 1.40–2.12) [54]. An increased risk of all-cause death and death from EC was associated with T2D especially in women with BMI < 25 kg/m^2 [52]. Moreover, it has been observed that T2D is associated with poor survival after incident EC, independently from tumor stage or grade [55]. Conversely, in the previously cited meta-analysis of prospective cohort studies, EC mortality did not increase in T2D, in comparison with women without diabetes [46]. Thus, further studies are needed to draw consistent conclusions on this issue.

In vitro studies have shown that triggering insulin, IGF-1 and ovarian steroid hormone signaling pathways increased proliferation of EC cell lines [56]. This proliferation can be enhanced by PI3K signaling activated by an estrogen link with IGF-1R and also by Notch signaling activated thanks to the binding of androgen on the androgen receptor. Abnormal activation of the Notch pathway promotes proliferation in a variety of cancer cell types, including EC: *in vitro* studies have indeed suggested that androgen through the regulation of inflammatory and Notch signaling pathways could affect cell viability and proliferation [57, 58].

EC may also be connected to chronic inflammation typical of T2D: insulin resistance increases C-reactive protein, which is an inflammatory biomarker induced by IL-6, and is associated with augmented risk of developing EC among postmenopausal women [59].

EC has been prospectively associated with many inflammation markers including acute phase proteins, adipokines, pro- and anti-inflammatory cytokines, angiogenic factors. It has been observed that EC risk has an inverse association with anti-inflammatory markers (IL13, IL21), other inflammation markers/mediators (CCL3, IL1B, IL23), and a robust positive association with VEGFA: these associations were independent of BMI and estradiol, suggesting that there are other mechanisms influencing inflammation and EC development [60]. These concepts are summarized in Figure 1.

T2D and epithelial ovarian cancer

EOC is the fifth most common cancer and the fourth most common cause of cancer death in women. EOC is predominantly a disease of post-menopausal women with the majority (>80%) of cases being diagnosed in women over 50 years [61].

The exact cause of EOC is unknown, but many risk factors have been identified such as low parity, early menarche, late menopause and family history but also obesity, smoking, and diet with a high content of starch and/or fat [62].

Despite numerous studies have carefully screened the ovaries for precursor lesions, none have been found. This

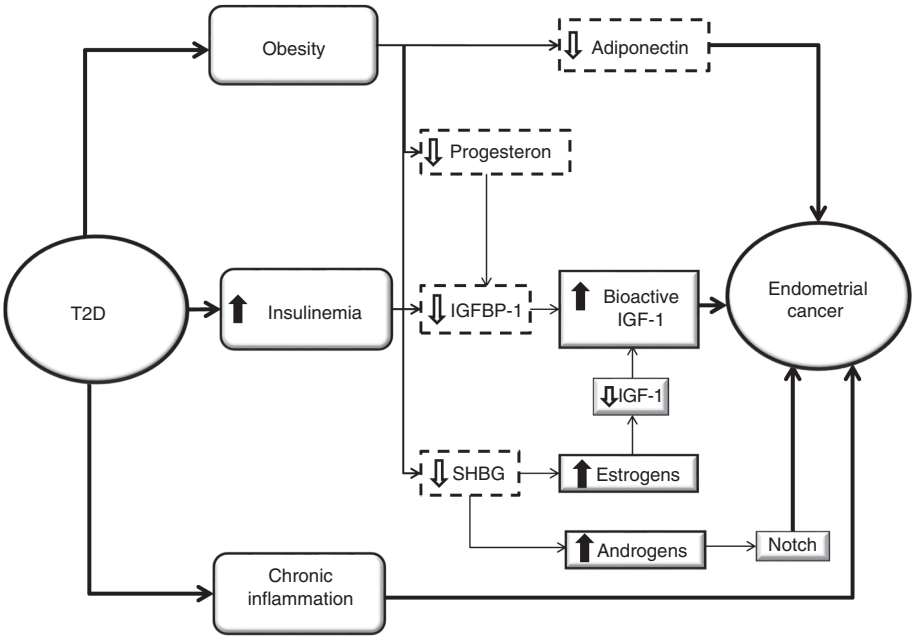

Figure 1: Molecular mechanisms linking type 2 diabetes and endometrial cancer.
T2D, type 2 diabetes; IGFBP-1, insulin-like growth factor binding protein 1; SHBG, sex hormone binding globulin; IGF-1, insulin-like growth factor-1.

has led to the assumption that ovarian cancer develops *de novo* [63]. It has been proposed that a proportion of ovarian carcinomas might develop as a result of implantation of malignant cells from a tubal carcinoma to the ovary [64, 65].

Fimbriae are exposed to the iron-induced oxidative stress generated from hemolysis of erythrocytes by pelvic macrophages during retrograde menstruation ('incessant menstruation' hypothesis): redox cycling of iron (Fe^{3+} – Fe^{2+}) is closely associated with the generation of reactive oxygen species that has a genotoxic effect [66, 67].

Studies dealing with the association between T2D and EOC are still limited and the impact of diabetes on EOC prognosis is not clear. In the Cancer Prevention Study-II Nutrition Cohort, a prospective study including 63,440 postmenopausal women, T2D status and duration were not significantly associated with EOC risk (T2D status RR = 1.05; 95% CI: 0.75–1.46; T2D duration <10 years RR = 1.04; 95% CI: 0.69–1.57; T2D duration >10 years RR = 1.06; 95% CI: 0.63–1.79) [68].

Conversely, a meta-analysis of 19 studies (7 case-control and 11 cohort studies) showed a significant increased risk of EOC in women with diabetes (RR = 1.17; 95% CI: 1.02–1.33) [69].

Many epidemiological studies showed an association between obesity and increased risk of EOC, mainly in post-menopausal women [70, 71]. Other studies indicated a possible relationship between obesity and higher mortality among patients with EOC [72, 73]. In a retrospective cohort study, patients with EOC and T2D had poorer survival compared to patients without diabetes and this association is independent from obesity [74].

An elevated risk of EOC among patients undergoing hospital treatment for T2D has also been observed and it has been noticed that the outcomes of patients with EOC in conjunction with comorbid T2D are poor: this could relate to the fact that these patients, because of diabetes-associated complications, could be submitted to a different treatment plan, and that T2D comorbidity may result in less dose-intense chemotherapeutic regimens such as platinum agents or paclitaxel [75–77].

It has recently been suggested in murine models that elevated estrogen levels, which are a typical feature of obesity, may play a role in EOC carcinogenesis [36]. Moreover some epidemiological studies have shown that increased androgen and decreased progesterone serum levels (hormonal changes which appear in diabetes) may be even more important for the risk of developing EOC: excess androgenic stimulation of ovarian epithelial cells might increase the risk and that it could, conversely, be decreased by factors related to greater progesterone stimulation [75]. This hormonal setting (increased serum androgen levels and decreased serum progesterone levels rather than altered serum estrogen levels) appear in diabetes and may be one reason for the increased risk of EOC in T2D.

Although there is no experimental evidence for the positive association between insulin and EOC, some studies have shown that the increased serum levels of IGF-1, IGF-1R and IGFBP-2 were associated with EOC tumorigenesis [18].

Additionally, it has been reported that the ovary displays insulin sensitivity and steroidogenesis induced by insulin and IGFs suggesting that T2D could be an important risk factor for ovarian cancer [78].

One study demonstrated that IGF-1 in human ovarian OVCAR-3 cells enhanced the expression of KCl cotransport (KCC). IGF-1 may promote cancer development and progression in part through its action on KCl cotransporter: IGF-1 binds to IGF-1 receptor on EOC cell activating PI3K and Erk1/2 MAPK whose signaling pathways are required for IGF-1 stimulating production of KCC isoforms. The KCC activity is necessary for IGF-1-dependent EOC invasiveness and proliferation *in vitro* [79].

Other studies have also shown that IGF-1 and IGFBP-2 in human EOC cell lines resulted in the induction of cellular proliferation and invasion through phosphorylation of AKT and ERK1/2 [80, 81].

Considering these findings, IGF-IR may be seen as a potential new molecular target in EOC: elevated IGF-I and IGF-II levels have indeed been associated with decreased survival in EOC. It has been evaluated the antineoplastic activity of an IGF-1R inhibitor in EOC and the impact of a combination therapy using IGF-1R inhibitor with a poly ADP-ribose polymerases (PARP) inhibitor: the results suggested that it might be an effective strategy to circumvent resistance to treatment in clinical settings [82–84].

It has been observed that the ovarian carcinogenesis inflammation is involved in the relationship between increased ovulation and ovarian cancer risk but is also related to the chronic inflammatory state typical of T2D: epidemiological evidence suggests that inflammation may be an underlying mechanism in the development of ovarian cancer and multiple inflammation markers, specifically PCR, IL-2, IL-4, IL-6, IL-12, and IL-13 may be associated with risk of EOC [85–87].

The role of androgen in stimulating the proliferation of EOC cells may also be associated with increased IL-6 and decreased transforming growth factor beta (TGF-β), which were included in the proinflammatory network of T2D [88].

The IL-6/STAT3 signaling pathway may mediate FSH-, LH- and estrogen-stimulated HOSE cell proliferation. Increased IL-6R alpha expression and constitutive STAT3 activation may be associated with ovarian cancer. Androgens may promote OC progression in part by decreasing TGF-β receptor levels, thus blocking the action of TGF-β, a potent inhibitor of ovarian epithelial cell growth in culture and ascites-derived ovarian cancer cells [89]. These concepts are summarized in Figure 2.

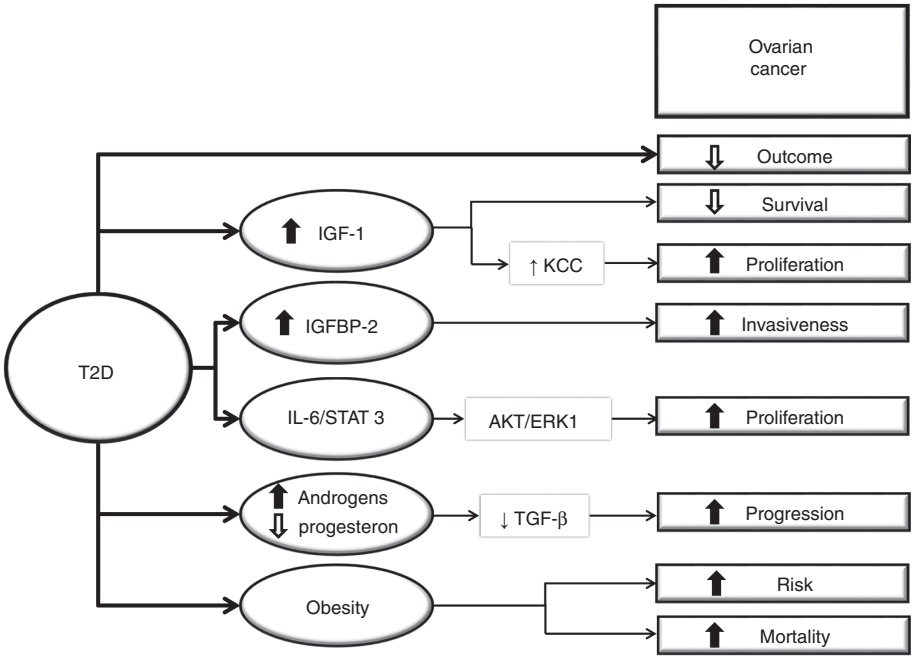

Figure 2: Biological connections between type 2 diabetes and epithelial ovarian cancer features.
T2D, type 2 diabetes; IGF-1, insulin-like growth factor-1; IGFBP2, insulin-like growth factor binding protein 2; IL-6, interleukin-6; KCC, KCl cotransporter; AKT/ERK1, AKT/extracellular-regulated kinase; TGF-β, transforming growth factor-β.

T2D and cervical cancer (CC)

Worldwide, cervical cancer (CC) is the fourth most frequent cancer in women with an estimated 530,000 new cases in 2012 representing 7.5% of all female cancer deaths. In 2012, approximately 270,000 women died from CC: more than 85% of these deaths occurred in low- and middle-income regions, as in developed countries screening programs make most pre-cancerous lesions identifiable at stages when they can easily be treated; early treatment prevents up to 80% of CCs in women from these countries [90].

A significant correlation between the incidence of CC and T2D, as well as the impact of T2D on prognosis for patients with CC, still has not been determined, but an association between the IGF-1 levels and CC has been reported [91].

Hyperglycemia and hyperinsulinemia in patients with T2D may reduce the hepatic production of IGF binding protein 1 and increase free IGF-1 levels: increased IGF-1 levels in T2D patients and overexpression of IGF-1R in CC cells activates the IGF axis and possibly results in poor prognosis [92].

Therefore, it has been hypothesized that CC cells' high-grade expression of IGF-1R could be seen as a predictor for high risk of death and disease recurrence in early stage CC [93].

Regarding the impact of T2D on patients who already have CC, it has been suggested that T2D may increase the risk of cancer recurrence and death for early stage CC patients, even after curative treatments. Thus, incorporating T2D screening should be considered as part of the continuum of care for early stage CC patients, and close surveillance during routine follow-up in this population should be recommended [94].

Early stage CC patients with type 2 DM have a poorer oncological outcome than patients without DM [95]. These concepts are summarized in Figure 3.

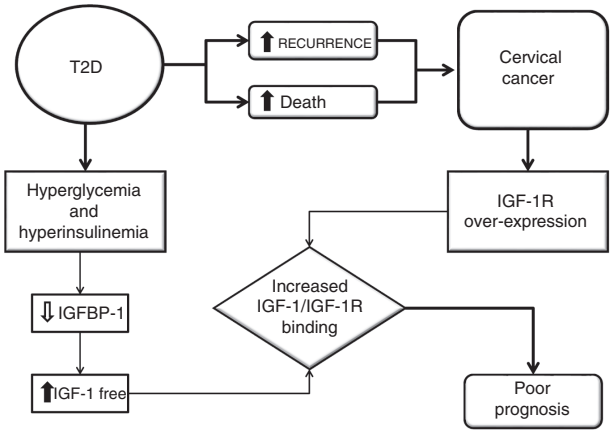

Figure 3: Possible links between type 2 diabetes and cervical cancer outcomes.
T2D, type 2 diabetes; IGF-1R, insulin-like growth factor-1 receptor; IGFBP-1, insulin-like growth factor binding protein 1; IGF-1, insulin-like growth factor-1.

T2D and vulvar cancer (VC)

Vulvar cancer (VC) is the fourth most common gynecologic cancer and accounts for 5% of all malignancies of the female genital tract (after uterine corpus, ovarian and cervical cancer).

Squamous cell carcinoma (SCC) accounts for approximately 95% of malignant tumors of the vulva [96]. Two causal pathways for vulvar SCC exist: HPV-related and non-HPV-related SCC. HPV related SCC arises in younger women (63 years) and accounts for 20% of invasive disease versus non-HPV-related SCC (70 years), which accounts for 80% of invasive disease [97]. Because of the rarity of VC, little is known about epidemiologic risk factors. T2D seems to correlate to the incidence of VC, but it does not appear to be responsible [98].

The association between major features of T2D and VC has been discussed in the literature. Several early clinical observations suggested that obesity had a distinctive role in the etiology of invasive SCC and might predispose to VC, but some epidemiologic studies have not confirmed significant relations. However, the Metabolic Syndrome and Cancer Cohort found that 1 standard deviation (SD) increase in BMI was associated with a 36% increased risk of VC, while the The Million Women Study found subjects with BMIs of ≥30 kg/m^2 to be at 70% higher risk than those with BMIs <25 kg/m^2. There is also a direct association of blood glucose with the risk of rare gynecological cancers overall and VC: T2D is often associated with vulvar dystrophies and chronic dermatitis and both are suspected risk factors for invasive VC. Hypertriglyceridemia which is a common feature in T2D, is associated with frequent infections and inflammation and was strongly associated with increased risk of VC [99]. Finally, we found that obesity, elevated concentrations of blood glucose and triglycerides, which were positively associated with risk of rare female cancers, all contribute to the development of hyperinsulinemia and the maintenance of low grade systemic inflammatory state that could underlie the association of these factors

and risk of VC even if the exact underlying molecular mechanism hasn't been clarified yet.

Moreover, it has been showed that diabetes is a risk factor for short and long-term complication after surgical treatment of VC but conversely, T2D does not seem to have a role in vulvar SCC prognosis, which is dependent most of all by inguinofemoral node status [100, 101].

Diabetes medications and gynecologic cancer

Several epidemiological and experimental studies focused on the potential role of diabetes medications in cancer development in women. In this section we discuss the relationship between women cancer risk and insulin and insulin analogs, metformin, thiazolidinediones (TZDs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Insulin and insulin analogs

As hyperinsulinemia and IGF-1 signaling seem to be involved in cancer promotion and progression, high circulating insulin levels in patients requiring insulin injection were suspected to increase cancer risk: elevated risk of cancer has been reported in patients on any use of insulin and in particular of long-acting insulin glargine [102–104].

In the literature the results are contrasting. The ORIGIN study (Outcome Reduction with Initial Glargine Intervention), a randomized, placebo-controlled, multi-country trial of 12,537 patients followed for a 6.2 years found no evidence of increased cancer risk (HR: 1.00; CI: 95%: 0.88–1.13) with insulin glargine [105]. This result was confirmed by the ORIGINALE (The ORIGIN and Legacy Effects) study, which measured post-trial effects on 4718 patients originally allocated to insulin glargine (2351) versus standard care (2367) during an additional 2.7 years: from randomization to the end of post-trial follow-up, no differences were found between glargine and standard care groups about any cancer (HR 0.99, CI: 95%: 0.88–1.12; p = 0.91) [106].

A tumor-promoting effect of glargine was found in *in vitro* studies on human endometrioid EC cells: glargine stimulated cell proliferation, displayed an anti-apoptotic effect, had a positive effect on cell cycle progression in endometrioid EC cell lines, and induced a dual activation of the IR and IGF1R [107].

Conversely, it is important to note that many studies found that glargine did not increase carcinogenic risk, and a neutral link between glargine and overall/cancer-specific outcomes was also suggested [108–110].

Metformin

Metformin is an insulin sensitizer which improves insulin sensitivity and reduces insulin circulating levels. It has additionally been identified to decrease carcinogenic risk and inhibit cancer cell growth [111].

The anticancer action of metformin involves the enhancement of phosphorylation of liver kinase B1, the inhibition of the mammalian target of rapamycin (mTOR) pathway through adenosine monophosphate-activated protein kinase (AMPK) activation [112].

Metformin is anticipated to exert antitumor effects in gynecological cancer, and its efficacy for the treatment of endometrial and ovarian cancer has been suggested in preclinical studies and clinical trials. Although the effect of metformin on CC remains to be examined in clinical trials, its antitumor effects have been reported in preclinical studies [113].

It has been demonstrated that an antidiabetic dose of metformin suppressed EC cell growth *in vivo* due to its effect on humoral factor(s) and among these, IGF-1 and leptin, but not insulin, were potentially responsible [114].

In vitro studies have demonstrated that metformin inhibits the growth of cancer cells in a dose-dependent way inducing cell cycle arrest and apoptosis and determining a decrease of EC cells migration and invasion [115].

Metformin was reported to inhibit the proliferation of EC cell lines by activating AMPK which negatively regulates aerobic glycolysis in cancer cells and suppresses tumor growth *in vivo* [116].

AMPK also negatively regulates mTOR, the mammalian target of rapamycin whose signaling is activated in many cancer types [117].

Endometrial cancer is characterized by genetic aberration including activation of mTOR and loss of PTEN, a tumor suppressor gene which regulates the cell cycle and survival through its signal transduction pathway and whose loss enhances stimulation of the mTOR pathway [118, 119].

A synergism between metformin and paclitaxel *in vitro* in animal models has also been demonstrated and it was found a synergistic action of metformin with medroxyprogesterone acetate and in downregulation of GloI expression, an important enzyme related to glycometabolism whose overexpression is related to progestin resistance in EC cells [120, 121].

The results of studies on EC survival and metformin use in diabetic women are still contrasting. Many *in vitro* studies reported that metformin was cytotoxic to the ovarian cancer cells activating the AMPK pathway in a time- and dose-dependent manner [122–124].

It has been shown that p53 is involved in mediating the energy-conserving response to AMPK activation and that loss of p53 heightens the metformin-induced energy stress on cancer cells, metformin may have increased efficacy in p53-deficient tumors, like ovarian cancer [125].

Two studies have also reported that metformin induces apoptosis in ovarian cancer cells and it has been shown that it inhibits ovarian cancer cell adhesion, invasion and migration [126–128].

Inhibition of angiogenesis was suggested and a recent report indicates that, in ovarian cancer, metformin inhibits adipocyte-induced proliferation and migration of cancer cells [129].

Preclinical reports, as well as *in vivo* and *in vitro* studies in ovarian cancer indicate that metformin increases the response to carboplatin and paclitaxel chemotherapy, and it has been widely demonstrated that metformin improves the response to cisplatin and that a combination of metformin and cisplatin inhibits the growth of ovarian cancer stem cells *in vitro* and in mouse models [130, 131].

Furthermore, it has been recently demonstrated that metformin may significantly reduce the risk of CC, especially when the cumulative duration is more than 2 years [132].

In T2D patients with CC metformin use has been associated with improved disease free survival (but not overall survival) and a lower cervical cancer-specific and overall mortality among older women with diabetes has been suggested in association with cumulative metformin use after CC diagnosis [133].

A suppression of CC cell growth with metformin treatment has been revealed in three studies using cell lines: in CC cells, metformin activates AMPK and cause mTOR underexpression, which has been associated with poor prognosis in CC [134–136].

Twenty percent of CCs have LKB1 mutations: metformin may augment LKB1 tumor suppressive effects, inhibit cell growth and decrease tumor cell viability via activation of LKB1AMPK signaling in CC [137].

Differently from other gynecological cancers, metformin in CC has an anti-proliferative effect by inducing apoptosis and autophagy rather than causing cell cycle arrest [138].

Lately *in vitro* studies on CC focused on Wnt/β-catenin signaling, inhibition of FOXM1 signaling, and inhibition of heme oxygenase-1 expression, which sensitizes CC cells to paclitaxel [139–141].

Other medications

Thiazolidinediones (TZDs)

TZDs are insulin-sensitizing drugs which reduce insulin-resistance: some authors found a decreased risk of carcinogenesis in TZD users [142, 143]. Particularly it has been observed that troglitazone decreased proliferation and inhibited the growth of ovarian cancer cells [144]. Conversely, another study presented an association between TZD and increased risk of cancer especially in T2D females [145].

Anyway the effects of these medications on cancer promotion and progression are inconsistent in *in vitro* and animal models [146]. Also epidemiological studies did not find a consistent association between TZDs and reduced risk of gynecologic cancer [147].

SGLT2 inhibitors

SGLT2 inhibitors are a new class of antidiabetic agents which lower blood glucose by reducing renal glucose reabsorption and increasing urinary glucose excretion.

Few papers have looked at SGLT expression in malignancies and only one published study has demonstrated functional glucose uptake through the SGLTs in tumors [148].

However, animal studies did not find an association between treatment with dapagliflozin and cancer risk. The relationship between SGLT2 inhibition and cancer is still inconclusive and studies with larger sample size and longer exposure are needed [149].

Conclusions

Currently, there is good evidence in epidemiological studies of a higher prevalence and incidence of female cancer in diabetes. T2D and gynecological cancers share common mechanisms, such as enhanced insulin and IGF signaling, and chronic inflammation. Ovarian steroid hormones have also been related to cancer initiation and progression and free steroid hormones seem to be increased in women with T2D.

The association between cancer in women and T2D is partly related to obesity. In particular, the link between EC and T2D regardless of obesity is less clear. Thus, future

research should focus on this aspect and more studies are needed to clarify the effect of other confounders, such as some diabetic medication. Accordingly, the American Association of Clinical Endocrinologists and the American College of Endocrinology affirmed the importance of further research on these issues in a joint consensus.

According to the literature, T2D women have an increased risk for developing gynecological cancers therefore we suggest planning surveillance programs for this population: they could include the dosage of biomarkers related to gynecological tumors as recent studies strongly demonstrated their capability to detect these malignances in the early stages, when more treatment options are available to improve patients survival [150, 151].

More studies should also investigate the real impact of diabetes on the prognosis of female neoplasms, in order to possibly better customize the diagnostic and therapeutic algorithms in patients with T2D and cancer and for improving the managing of specific cancers according to the personalized profile of each woman with T2D.

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