Molecular Aspects of Medicine 108 (2026) 101459

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

# Impact of type 2 diabetes on malignancies of the female reproductive system

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ARTICLE INFO

*Keywords:*
Type 2 diabetes
Gynecological cancer
Endometrial cancer
Ovarian cancer
Breast cancer
Insulin resistance
Inflammation
Hormonal dysregulation
PI3K/AKT pathway
Metabolic reprogramming
Metformin
Estrogen

ABSTRACT

Type 2 diabetes mellitus (T2DM) contributes significantly to the development and progression of cancers of the female reproductive tissues, particularly endometrial, ovarian, and breast. Hallmarks of T2DM, such as hyperinsulinemia, insulin resistance, and chronic low-grade inflammation, disrupt endocrine and metabolic homeostasis, promoting carcinogenesis through enhanced mitogenic signaling, hormonal dysregulation, and immune activation. T2DM can alter ovarian, endometrial, and mammary physiology by affecting estrogen/progesterone receptor activity, stromal remodeling, and specialized cell function. Furthermore, give the fluctuations in a woman's hormonal levels and reproductive status, the presence of excess weight and T2DM may have altering risks depending on the lifecycle. These effects are exacerbated by adipose-derived cytokines and leptin resistance, further amplifying estrogens' bioavailability and pro-inflammatory signaling. Endometrial cancer risk is nearly doubled in diabetic women, independent of body mass index, with hyperglycemia inducing PI3K/AKT/mTOR and NF-κB pathway activation, reduced sex hormone-binding globulin (SHBG) levels, and upregulation of estrogen receptor signaling. Ovarian cancer in diabetic patients is associated with more aggressive histological subtypes, advanced-stage presentation, and poorer survival, likely driven by Insulin-like growth factor 1 (IGF-1) signaling, oxidative stress, and impaired treatment response. Similarly, T2DM increases the risk and worsens outcomes in breast cancer via enhanced expression, AGE-RAGE interactions, and estrogen-independent ERα activation. Herein, we synthesize current epidemiological evidence and mechanistic insights to delineate the multifaceted relationship between T2DM and these cancers. Despite increased risk, diabetic women often face underdiagnosis due to suboptimal screening practices. As T2DM prevalence rises globally, tailored cancer prevention and treatment strategies for diabetic populations are urgently needed. Metformin has shown robust benefits in reducing T2DM-related complications and potential in the antineoplastic setting. This review underscores the endocrine and inflammatory mechanisms linking T2DM to cancers of the female reproductive system and advocates for integrated clinical protocols that include early screening and individualized management in diabetic women.

## 1. Introduction

Approximately 588 million individuals worldwide were living with T2DM in 2024. Projections indicate that by 2050, the global prevalence of T2DM will rise to nearly to over 852 million, with African, middle eastern, and southeast Asian populations expected to register the highest rates of increase (Duncan et al., 2025). A prospect study from the UK Biobank gathering information from nearly half a million participants clearly demonstrated that T2DM is associated with a higher risk for all-cause mortality (Muilwijk et al., 2019). There is increased recognition of many secondary complications associated with diabetes such as cardiovascular disease, liver disease, cognitive decline, and cancer (Duncan et al., 2025; Muilwijk et al., 2019). Furthermore, preclinical obesity, obesity and insulin resistance (IR), which frequently accompany

This article is part of a special issue entitled: Cancer and diabetes published in Molecular Aspects of Medicine.

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https://doi.org/10.1016/j.mam.2026.101459
Received 23 September 2025; Received in revised form 4 February 2026; Accepted 6 February 2026
Available online 11 February 2026

T2DM, have been implicated in increasing the risk of menstrual disturbances, infertility, and in the onset of Polycystic Ovary Syndrome (PCOS) in affected women (Mohammed et al., 2025; Thong et al., 2020). Data gathered from the UK Biobank (459,342 participants) with 11 years of follow-up reported 47,060 incident cancer cases of which preclinical obesity was positively associated with 11 cancer types across multiple organ types, including cancers of the reproductive tract. Particularly postmenopausal breast cancer (BC) and metabolically driven malignancies such as endometrial cancer (EC) were reported (Leitzmann et al., 2025). In accordance, there are established links between triglyceride-glucose related indicators and postmenopausal BC incidence (Z. Li et al., 2025). Collectively, these findings underscore the growing recognition of T2DM as a significant risk factor for cancer development, particularly hormone-related and metabolically driven malignancies.

Cancer is a major global health concern and represents the second leading cause of mortality worldwide (Sung et al., 2021). The Global Burden of Disease Study reported that between 1990 and 2021, varying rates of increase in the global burden of female-specific cancers occurred (T. Li et al., 2025). In 2021, BC was diagnosed 2.08 million times, with 660,000 deaths. In comparison, 300,000 ovarian cancer (OC) cases and 470,000 ECs were reported in the same timeframe. This study describes a worrying trend towards an increase in female cancer rates, with breast and OC increasing the most (T. Li et al., 2025). On the other hand, T2DM is characterized by a combination of insulin resistance, progressive β-cell dysfunction, and chronic hyperglycemia, leading to widespread alterations in carbohydrate, lipid, and protein metabolism (Galicia-Garcia et al., 2020). These metabolic disturbances are accompanied by low-grade inflammation, dysregulated adipokine secretion, and hormonal imbalances that affect multiple tissues (Dilworth et al., 2021; Hameed et al., 2015). Such systemic changes create a metabolic and inflammatory environment that can profoundly influence cancer biology, affecting cell proliferation, survival pathways, and tumor–host interactions.

Epidemiological evidence indicates that diabetes mellitus, particularly T2DM, is associated with an increased risk of several malignancies, including the increase in gynecological cancers reported above (Giovannucci et al., 2010). Proposed pathophysiological mechanisms underlying this association include hyperinsulinemia, chronic low-grade inflammation, and increased circulating estrogen levels secondary to insulin resistance (Gunter and Leitzmann, 2006). Notably, women with T2DM exhibit nearly a two-fold increased risk of developing EC compared to non-diabetic individuals, a relationship that persists independently of body mass index (BMI) (Friberg et al., 2007), and an increased risk of both breast (Hardefeldt et al., 2012) and OC (Lees and Leath, 2015). Elevated BMI is also a risk factor for both endometrial and OC (Dikaiou et al., 2024; T. Li et al., 2025; Guo et al., 2022). In fact, high BMI is speculated to contribute to 0.34% and 0.09% of uterine and OC deaths respectfully (W.-Z. Tang et al., 2025).

Metformin, a biguanide widely used as first-line therapy for T2DM, exerts pleiotropic effects on glucose metabolism and insulin sensitivity through both AMP-activated protein kinase (AMPK)-dependent and -independent mechanisms. Metformin inhibits hepatic gluconeogenesis, leading to increased AMP:ATP ratios, activating AMPK which in turn enhances insulin sensitivity and suppresses glucose production (LaMoia and Shulman, 2021). Additional mechanisms include gut–liver axis modulation, increased glucagon-like peptide-1 secretion, and intestinal microbiota alterations, suggesting a significant gastrointestinal contribution to its glucose-lowering effect (Rena et al., 2017). Clinically, metformin has demonstrated robust benefits in reducing diabetes-related complications and improving survival in patients with T2DM (Turner et al., 1998). More recently, interest has grown in its potential antineoplastic properties since impaired glucose metabolism is a risk factor for cancer development and progression (Vona-Davis and Rose, 2012).

Epidemiological and clinical findings, coupled with the shared metabolic and hormonal disruptions observed in both conditions, underscore the need for a deeper understanding of the biological links between diabetes, gynecological cancers and their treatment regimens. Thus, this review aims to examine the pathophysiological relationship between T2DM on breast and gynecological cancers, focusing on the underlying biological mechanisms, epidemiological and clinical evidence supporting their association.

## 2. Ovarian physiology and T2DM

T2DM induces profound alterations in ovarian physiology through multiple interconnected mechanisms (Fig. 1). Women with T2DM often exhibit lower levels of Anti-Müllerian Hormone (AMH), suggesting a reduced ovarian reserve and impaired follicular development (Isik et al., 2012; Thong et al., 2020). As insulin resistance progresses, compensatory hyperinsulinemia arises, directly affecting ovarian steroidogenesis while preserving ovarian insulin sensitivity, a paradox that drives hyperandrogenism despite systemic insulin resistance (García-Romero and Escobar-Morreale, 2006). This hormonal imbalance impairs folliculogenesis by preventing the recruitment of dominant follicles, leading to anovulatory states and menstrual disturbances (Thong et al., 2020). Concurrently, hyperglycemia triggers oxidative stress and mitochondrial dysfunction in granulosa cells, which are essential for oocyte development and steroid hormone production (X. Qin et al., 2023). This altered metabolic microenvironment accelerates granulosa cell pyroptosis (an inflammatory, programmed form of cell death) and disrupts connexin expression, further compromising oocyte–granulosa communication, oocyte competence, and pregnancy outcomes (X. Qin et al., 2023; Thong et al., 2020). The accumulation of small antral follicles without dominant follicle selection frequently results in polycystic ovary syndrome (PCOS), a condition closely linked to hyperinsulinemia and T2DM (Purwar and Nagpure, 2022; Thong et al., 2020). Notably, insulin resistance and PCOS, common in women with T2DM, have been identified as predisposing factors for spontaneous abortion. Evidence from a large cross-sectional analysis within the UK Biobank cohort, which included 170,599 women, demonstrated that both T2DM and gestational diabetes are significantly associated with increased odds of spontaneous abortion (Hanna et al., 2010; S. Liu et al., 2025; Song et al., 2025). This association may be explained by shared pathophysiological factors between T2DM and miscarriage, including chronic low-grade inflammation, represented by elevated levels interferon-γ and Tumor Necrosis Factor-α (TNF-α) (Giakoumelou et al., 2016), along with hormonal imbalances, immune dysregulation, and endothelial dysfunction—hallmarks of both conditions. Collectively, these mechanisms highlight how T2DM contributes to a complex endocrine and cellular disruption that impairs ovarian function at multiple levels.

## 3. Mammary gland physiology and T2DM

T2DM induces significant changes in mammary gland physiology beyond its carcinogenic potential. A distinctive manifestation is diabetic mastopathy, an uncommon but significant proliferation of fibrous tissue in the breast parenchyma (J. Kim et al., 2016). Although benign, diabetic mastopathy illustrates how sustained metabolic dysregulation, particularly chronic hyperglycemia, can lead to structural and functional alterations in breast tissue. The hyperinsulinemic state characteristic of T2DM affects mammary tissue development and function through direct effects on mammary epithelial cells, which express both insulin and Insulin-Like Growth Factor-1 (IGF-1) receptors (Wolf et al., 2005). Insulin and IGF-1 can enhance the activity of the aromatase enzyme found in adipose tissue that converts androgens to estrogens which, in part, explain the overproduction of estrone and estradiol in obese T2DM subjects (Lueprasitsakul et al., 1990; Miller, 2006). This mechanism is particularly relevant in postmenopausal women, where adipose tissue becomes a primary source of estrogen. Indeed, increased aromatase activity has been reported in postmenopausal women,

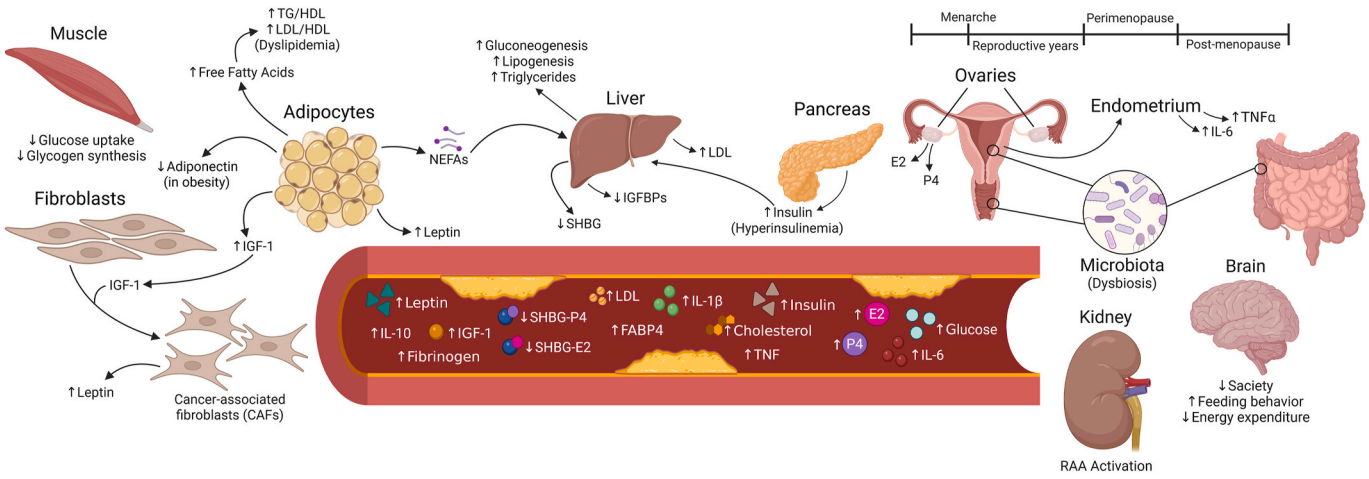


**Fig. 1.** Systemic alterations in response to T2DM and their potential impact of signaling of the female reproductive organs. Yellow squares represent O-GlcNac modification and red circles represent phosphorylation (Created in https://BioRender.com).
CITA: Veas-Torres, J., Miranda D. I. (2025) https://BioRender.com/2c71qo7.

especially among those with elevated BMI (Brown et al., 2017). Chronic hyperglycemia leads to changes in the tissular microenvironment, promoting inflammation and oxidative stress (Giri et al., 2018) that can modify breast tissue architecture. Additionally, diabetes-induced changes in the extracellular matrix composition and collagen organization within the breast tissue can alter tissue mechanical properties and cellular behavior (Lega and Lipscombe, 2020). The condition also impacts wound healing and tissue repair processes in the mammary gland, potentially affecting recovery from various post-operative complications (X.-B. Zhao and Ren, 2016). Furthermore, the presence of each type of diabetes can complicate breast imaging interpretation due to increased tissue density and fibrosis, potentially affecting screening accuracy and leading to delayed diagnoses, highlighting the awareness of diabetes status in breast health management and screening protocols (Wolf et al., 2005).

## 4. The endometrium and T2DM

Diabetes significantly impacts normal endometrial physiology (Fig. 1). The hyperglycemic environment leads to structural and functional changes in the endometrial tissue, affecting its normal cyclical responses to hormonal stimulation (Jackuliak et al., 2025). T2DM-associated metabolic disturbances significantly impact the hormonal milieu, particularly the regulation of endogenous sex hormones. Hyperinsulinemia has been shown to decrease the hepatic production of Sex Hormone-Binding Globulin (SHBG), resulting in elevated concentrations of free, biologically active estrogens and androgens (Fig. 1) (Ferroni et al., 2015; Wolf et al., 2005). The chronic low-grade inflammation and oxidative stress characteristic of T2DM also contribute to a pro-tumorigenic microenvironment, further fostering cancer initiation and progression (Ferroni et al., 2015; X.-B. Zhao and Ren, 2016). Insulin resistance reduces SHBG causing hormonal imbalances that disrupt normal endometrial proliferation and differentiation (Joung et al., 2015). Diabetes-induced inflammation disrupts normal tissue homeostasis and, along with hormonal imbalances, impairs endometrial receptivity and decidualization, creating altered angiogenesis and reduced blood flow, contributing to infertility and recurrent miscarriage (potentially due to a lack of endometrial implantation) in diabetic women (J. Chen et al., 2021; Jackuliak et al., 2025; Joung et al., 2015; Y. Chen et al., 2017).

The complex relationship between endometriosis and T2DM represents an emerging area of clinical investigation (Alhallak et al., 2023). T2DM is not directly involved in endometriosis development (Vaduva et al., 2023), large prospective cohort studies have found no overall significant association between laparoscopically confirmed endometriosis and risk of developing T2DM (Farland et al., 2021). Nonetheless, endometriosis generates a pro-inflammatory environment at both local and systemic levels, which may further impair insulin sensitivity (Alhallak et al., 2023; Farland et al., 2021). T2DM increases estrogen receptors and decreases progesterone levels in endometriosis lesions, both of which are markers of disease progression (Chantalat et al., 2020). However, more studies are needed to confirm whether T2DM directly drives these receptor alterations or if they reflect overlapping pathological mechanisms.

While endometriosis is typically considered benign in its initial stage, a history of ovarian/tubal endometriosis is an independent risk factor for clear-cell and endometrioid OC subtypes (Alhallak et al., 2023). Recent findings have demonstrated that endometriotic lesions contain cancer-associated somatic mutations including KRAS, ARID1, and PIK3CA, suggesting potential for malignant transformation given appropriate signals and context (Anglesio et al., 2017).

In summary, T2DM disrupts hormonal and metabolic homeostasis in female reproductive tissues. Hyperinsulinemia reduces SHBG levels, increasing bioavailable estrogens and androgens linked to hormone-dependent cancers. Insulin and IGF-1 signaling drive abnormal epithelial proliferation and matrix remodeling, while chronic inflammation and insulin resistance impair vascularization, hormonal signaling, and cell adhesion. Together, these alterations highlight the role of T2DM in increasing cancer susceptibility, as discussed in the following sections.

## 5. Malignacy of the female reproductive tract and T2DM: A pathophysiological nexus

The escalating global prevalence of T2DM extends its impact beyond metabolic dysregulation to influence the risk and progression of various malignancies, among which are breast and gynecological cancers (Cosmin Stan and Paul, 2024). As mentioned above, chronic hyperinsulinemia and insulin resistance may promote carcinogenesis through increased levels of circulating estrogens and IGFs, which stimulate cell proliferation and inhibit apoptosis (Gallagher and LeRoith, 2010). Epidemiological studies have demonstrated that women with hyperglycemia are at a higher risk of developing EC (Byrne et al., 2020). Furthermore, emerging evidence indicates a moderate but consistent association between T2DM and an increased risk of ovarian (L. Wang et al., 2020) and BC (Eketunde, 2020). These findings support a biologically plausible link between metabolic dysregulation in T2DM and the development of breast and gynecological cancers (Fig. 1). The underlying pathophysiological mechanisms contributing to this association

will be explored in the following sections. T2DM offers poor clinical prognosis across all cancers studied. For instance, within three months of starting chemotherapy, diabetic patients had a significantly higher occurrence of grade 3 or 4 adverse effects G3/4 compared to those with no form of diabetes (Mailliez et al., 2023). In a cohort of 70,781 people, of whom 14,414 (20.36%) were diagnosed with a diabetes type, in patients who received chemotherapy the presence of diabetics increased hospitalization incidence, any chemotherapy toxicity (Odds Ratio (OR), 1.38), infection or fever (OR, 1.43), neutropenia (OR, 1.22), and anemia incidence (OR, 1.24). Overall, patients with diabetes had a higher all-cause mortality (hazard ratio [HR], 1.35) (Srokowski et al., 2009).

### 5.1. Clinical association of T2DM and BC

Epidemiological studies have consistently highlighted a significant overlap between T2DM and BC. It is reported that up to 16% of patients with BC also have diabetes, with T2DM potentially conferring a 10–20% excess relative risk for developing BC ((Ferroni et al., 2015; Wolf et al., 2005). This connection is further compounded by shared risk factors such as advanced age and obesity, both of which are independently associated with an increased incidence of T2DM and postmenopausal BC (Wolf et al., 2005). While obesity is a critical confounding variable, several studies, after adjusting for BMI, have found that a statistically significant positive association between T2DM and BC risk persists, suggesting that T2DM may influence BC development through mechanisms independent of obesity (Xue and Michels, 2007). However, to date, there is a lack of studies specifically examining this association in women with normal BMI, leaving unanswered the question whether T2DM alone in absent the confounding effect of adiposity contributes to BC risk.

Central to the mechanistic link between T2DM and BC is the state of chronic hyperinsulinemia. Elevated circulating insulin levels can exert direct mitogenic and anti-apoptotic effects on mammary epithelial cells, thereby promoting carcinogenesis (Ferroni et al., 2015; Lega and Lipscombe, 2020). Insulin receptors are not downregulated in the setting of hyperinsulinemia in breast tumors, as opposed to metabolic signaling through the insulin receptor (IR) pathway (Lega and Lipscombe, 2020). In fact, BC cells often overexpress the IR, particularly, the IR-A isoform, which preferentially mediates mitogenic signaling in response to insulin binding (Lega and Lipscombe, 2020; Wolf et al., 2005). Furthermore, hyperinsulinemia indirectly promotes cell proliferation by increasing the bioavailability of IGF-1. Insulin can reduce the hepatic synthesis of IGF-binding proteins (IGFBPs), leading to higher levels of free, biologically active IGF-1 (Lega and Lipscombe, 2020). The IGF-1 pathway, which shares structural and functional homology with the insulin pathway, is a potent stimulator of cell growth, differentiation, and survival, and its activation is implicated in BC development (Wolf et al., 2005; Xue and Michels, 2007).

The coexistence of T2DM and BC significantly worsens patient prognosis and complicates treatment. Several studies and meta-analyses have identified pre-existing T2DM as an independent predictor of poorer overall survival (OS) and disease-free survival (DFS) in women with BC (Coughlin et al., 2004; X.-B. Zhao and Ren, 2016; Wolf et al., 2005). In accordance, a meta-analysis reported a 23% increased risk for BC in patients with T2DM and a 38% higher cancer-specific mortality among those with both conditions (Ferroni et al., 2015). As a result, diabetic patients often requiring dose reductions or modifications that can compromise treatment outcomes (X.-B. Zhao and Ren, 2016). Surgical outcomes are also affected, with increased wound infection rates and long-term upper limb dysfunction observed in diabetic women post-mastectomy (Wolf et al., 2005). Radiation therapy poses a greater risk for both early and late complications in this population, though evidence in BC patients remain limited. Moreover, high-dose glucocorticoids used as antiemetics may trigger severe hyperglycemia, necessitating close glycemic monitoring. Additionally, due to comorbidity concerns, clinicians may opt for less aggressive therapies, thereby compromising cancer outcomes. Further strengthening the association, Mendelian randomization studies have provided evidence suggesting a potential causal role for genetically predicted fasting insulin levels in the development of BC (Pearson-Stuttard et al., 2021). It is also noteworthy that the impact of T2DM may vary across different BC subtypes (e.g., estrogen receptor-positive/negative, HER2-positive), although this area requires more detailed investigation (Xiong et al., 2024). Collectively, these factors contribute to substantially reduced survival, with some studies reporting a 51% shorter OS rate in BC patients with T2DM compared to their non-diabetic counterparts (X.-B. Zhao and Ren, 2016).

### 5.2. Clinical association of T2DM and EC

T2DM is strongly associated with an increased risk of EC, with large-scale studies reporting a relative risk of up to 1.72 compared to non-diabetic women (Saed et al., 2019). Moreover, T2DM is linked to more aggressive tumor behavior, reduced survival, and higher recurrence rates (McVicker et al., 2022). Data from the Women's Health Initiative, involving 88,107 postmenopausal women, indicate that the elevated risk is largely mediated by obesity, a factor whose influence may originate as early as the premenopausal period (Lachance et al., 2006; Luo et al., 2014).

EC is most often diagnosed at an early stage, particularly in women of reproductive-age, with up to 90% presenting in Stage I (Lachance et al., 2006). In the general population, Stage I accounts for 68.2% of cases, although the proportion of Stage IV diagnoses has increased from 5.2% between 2005 and 2008 to 7.1% in the period 2017–2020 (Adekanmbi et al., 2024). In diabetic women, this cancer is often diagnosed at an early stage, with 59% presenting with stage I disease (Agarwal et al., 2023). Tumors tend to be of moderate to high grade, with 39.5% grades 2 and 16.5% grade 3 lesions (Agarwal et al., 2023). Five-year survival is significantly lower, with a pooled hazard ratio of 1.76 (Barone et al., 2008), and cancer-specific mortality is increased two-fold in diabetic individuals, particularly among those with multiple comorbidities, such as obesity (Agarwal et al., 2023; Njoku et al., 2022). The endometrium becomes particularly susceptible to neoplastic transformation due to diabetes-induced changes at molecular, cellular, and tissue levels (La Vecchia et al., 1994). In the diabetic state, hyperglycemia leads to enhanced glucose availability in endometrial cells, promoting aerobic glycolysis and providing abundant energy for cellular proliferation (Joung et al., 2015; Onitilo et al., 2012). The endometrial tissue of diabetic patients shows upregulation of glucose transporters and increased expression of IRs, particularly the IR-A isoform, which has greater mitogenic potential (Joung et al., 2015).

Molecular pathway dysregulation in diabetic endometrium involves complex interactions between insulin/IGF signaling and downstream effectors. The PI3K/AKT pathway becomes hyperactivated in endometrial cells exposed to elevated insulin levels, leading to increased cellular survival and proliferation. Simultaneously, the Ras/MAPK pathway amplification in diabetic endometrium enhances cellular growth signals and reduces apoptotic responses (Joung et al., 2015; La Vecchia et al., 1994). These molecular alterations may create a pro-survival environment that facilitates neoplastic transformation (Onitilo et al., 2012).

Hormonal disruption in T2DM represents a critical mechanism for cancer development. Diabetes-induced insulin resistance leads to decreased production of SHBG, resulting in increased bioavailable estrogen in blood (Joung et al., 2015). The endometrial tissue shows enhanced expression of estrogen receptor alpha (ERα) and increased local production of estrogen through aromatase upregulation (Joung et al., 2015). This hormonal dysregulation is particularly significant as it creates a state of unopposed estrogen stimulation, a well-established risk factor for both endometriosis and EC (Beral et al., 2005; Braun et al., 2016).

The inflammatory milieu of diabetic endometrium contributes significantly to carcinogenesis. Chronic inflammation in diabetic patients results in the increased local production within the endometrial

tissue of pro-inflammatory cytokines, particularly IL-6 and TNF-α (Joung et al., 2015). These inflammatory mediators activate NF-κB signaling pathways in endometrial cells, promoting the expression of genes involved in cell survival, angiogenesis, and invasion. The inflammatory environment also enhances local production of reactive oxygen species, leading to DNA damage and genomic instability in endometrial cells (Onitilo et al., 2012). Hyperglycemia promotes the acquisition of mesenchymal and introduces changes in integrins and cadherins, and cell-matrix interactions (Rahn et al., 2018). In the endometrium, these modifications in the architecture facilitate tissue remodeling and potential invasion of transformed cells (Y. Chen et al., 2017; Joung et al., 2015). The metabolic reprogramming of endometrial cells in T2DM extends beyond glucose metabolism. Insulin resistance can lead to altered lipid metabolism and increased local inflammation, creating a tissue environment that favors cancer development (Joung et al., 2015). The endometrial tissue shows enhanced expression of genes involved in fatty acid synthesis and cholesterol metabolism, contributing to the overall metabolic dysregulation (Onitilo et al., 2012). The persistent inflammatory state and metabolic alterations continue to support tumor growth and progression even after cancer development (Y. Chen et al., 2017).

This comprehensive clinical association pattern underscores the need for specialized care protocols for diabetic women with EC. The complex interplay between T2DM and EC requires a multidisciplinary approach to optimize outcomes.

### 5.3. Clinical association of T2DM and OC

Both Type 1 and type 2 diabetes have been associated with increased risk and progression of OC (Alhallak et al., 2023). Diabetic patients with OC tend to be present with distinct characteristics. Patients are diagnosed at a more advanced age (65.35 ± 10.13 years vs 61.30 ± 8.87 years) compared to non-diabetic patients (Akhavan et al., 2018), and demonstrate more aggressive disease patterns, with higher grade tumors and more advanced stages at diagnosis (J.-Y Lee et al., 2013; Shah et al., 2014). There is a higher proportion of stage III-IV disease in diabetic patients, suggesting either a more aggressive tumor biology or a delayed diagnosis (Slavchev et al., 2021). Although awaiting confirmation in larger cohorts, T2DM seems to be associated more with non-serous than serous histologic subtypes (Gapstur et al., 2012).

T2DM exerts a significant negative impact on clinical outcomes in patients with OC. OS is markedly reduced in diabetic individuals compared to their non-diabetic counterparts (27.97 months vs. 41.01 months), with studies also reporting a significantly shorter progression-free survival (PFS) (14.10 months vs. 28.83 months) in diabetic patients. Notably, the hazard ratio for disease progression remains elevated in this group (HR 2.73, 95% CI: 1.18–6.95), even after adjustment for demographic and pathological variables (Akhavan et al., 2018). Potential contributors to this increased risk include poorer tolerance and altered pharmacokinetics of chemotherapy in diabetic patients (Slavchev et al., 2021), as well as a higher incidence of surgical complications, often associated with comorbidities such as obesity (Shah et al., 2014). Correspondingly, based on patient diabetes status, glycemic control and surgical management modification is recommended.

Several interconnected molecular pathways link T2DM to increased OC risk and progression. Hyperinsulinemia and elevated IGF-1 play central roles by activating cell cycle progression, with studies showing higher concentrations of IGF-1 receptors in OC cell lines compared to normal ovarian tissue (J.-Y Lee et al., 2013). The hyperglycemic state in T2DM triggers the production of inflammatory cytokines, including TNF-α, interleukin-1β (IL-1β), and IL-6, which create a tumor-favorable microenvironment and promote immune hyperactivation (L. Wang et al., 2020). This chronic inflammation influences tumor growth, invasion, and metastasis (Z. Zhao et al., 2024). At the molecular level, diabetes affects tumor development through multiple mechanisms: elevated insulin and IGF-1 levels stimulate increased free estrogen levels (via decreased SHBG), increased and cancer cell proliferation, while adipose metabolic dysregulation promotes inflammatory pathways (Shah et al., 2014). Additionally, high glucose levels increase the expression of vascular endothelial growth factor, a potent proangiogenic factor associated with tumor development (L. Wang et al., 2020). The pathophysiology is further complicated by insulin resistance and chronic hyperinsulinemia, which cause menstrual irregularity and chronic anovulation, potentially affecting OC development through hormonal mechanisms.

## 6. Potential mechanisms crosslinking T2DM and cancers of the female reproductive system

T2DM creates significant alterations that promote carcinogenesis and further cancer progression through multiple interconnected pathways across each cancer presentation. Each reproductive tissue has its own response to estrogen, progesterone, testosterone, gonadotrophins, insulin, somatotrophins and the interplay of other factors, which can sometimes be paradoxical and thus will have specific impacts on cancer incidence and risk.

As described in detail by Samuel and colleagues, the development of T2DM and the metabolic re-programming upon insulin resistance may have three consequences which may eventually result in carcinogenesis in the diabetic patient (Samuel et al., 2018). Firstly, hyperlipidemia (dyslipidemia, i.e. high levels of cholesterol and triglycerides), followed by hyperinsulinemia and then hyperglycemia leading to the promotion of inflammatory disease (Ghareghomi et al., 2024; Sun and Kashyap, 2011). These consequently lead to lipotoxicity, glucotoxicity, oxidative stress, and endoplasmic reticulum stress leading to an unfolded protein response (UPR) (Fig. 2), with the eventual cancer initiating results of cellular and DNA damage (Berry et al., 2018; A. Li et al., 2019; Samuel et al., 2018). In the following section we first give a brief out of how these three abovementioned steps trigger signaling pathways that promote cancer, then we will examine the specific pathway modifications observed in breast, endometrial, and ovarian tissues when T2DM coexists with malignancy.

T2DM is associated with hyperlipidemia, which contributes to cancer progression through multiple interconnected pathways (Y.-Y. Zhang et al., 2024). Hyperlipidemia manifests primarily in two ways. Firstly, elevated cholesterol levels favor steroid synthesis, particularly estrogens, which play a key role in the development of estrogen-responsive cancers such as breast, ovarian, and EC (J. Hu et al., 2010). Increased cholesterol may also contribute to the formation of lipid rafts, thereby altering membrane signaling, potentially either enhancing signal potency or interfering with inactivation within cells under diabetic control (Mollinedo and Gajate, 2020). Additionally, elevated cholesterol may support increased membrane synthesis, promoting cellular proliferation. Cholesterol can also be metabolized into derivatives that activate the ER, initiating downstream signaling cascades. Simultaneously, hyperlipidemia increases levels of non-esterified fatty acids (NEFAs), which can activate the atypical protein kinase C isoform (e.g. PKC θ) signaling (Schmitz-Peiffer et al., 1997). These NEFAs promote β-oxidation, generation of signaling lipids, and membrane lipid synthesis, including the production of glycosylated ceramides, lipid species implicated in enhanced proliferation and also tumorigenesis (in particular, those involved in the sphingosine-1-phosphate pathway) (C. Huang and Freter, 2015). Thus, both NEFA interplay and feedback are crucial in cancer biology and therapy resistance. As T2DM progresses to insulin resistance and hyperinsulinemia, signaling via the IR maybe intensified. Central to these processes is the AKT signaling pathway (discussed in more detail below), which can be activated via ER signaling or through PKC-mediated mechanisms. AKT signaling diverges into the mTOR pathway, driving increased protein synthesis, or the GSK3β pathway, which releases β-catenin to translocate into the nucleus and drives transcription of oncogenic genes (Fig. 2) (Glaviano et al., 2023; Hermida et al., 2017). An increase in estrogen (via aforementioned increased

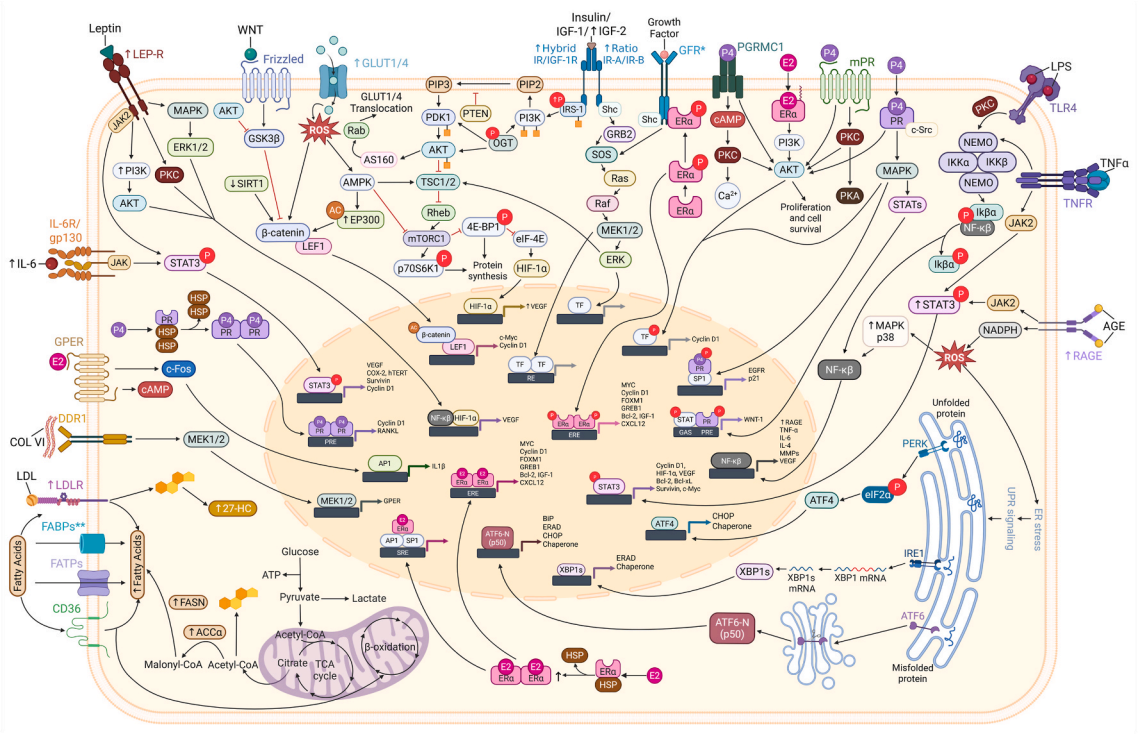


**Fig. 2.** Signaling pathways altered by T2DM in the normal and cancerous cells of the female reproductive organs (Created in https://BioRender.com). https://BioRender.com/n3qk9db.

peripheral synthesis in adipose tissue and reduced levels of SHBG) working together with AKT signaling, promotes the translocation of glucose transporters (GLUTs) to the cell membrane, enhancing glucose uptake (Fig. 2) (Garrido et al., 2013). The resulting hyperglycemia fuels glycolysis and alternative glucose metabolic pathways such as the Warburg effect (Iacobini et al., 2021). Downstream, this metabolic shift activates the AGE–RAGE axis and sustains activation of the PI3K–AKT pathway. This promotes the accumulation of reactive oxygen species (ROS), which in turn cause oxidative DNA damage (Stefano et al., 2016). These genotoxic events may drive oncogenic mutations, furthering tissue dysregulation and oncogenesis.

### 6.1. *Insulin receptor isoforms and the PI3K/AKT/mTOR pathway dysregulation*

The IR has two isoforms: A and B. Isoform B is mostly metabotropic and leads to the canonical pathway where GLUT-4 translocates to the cell membrane (Belfiore et al., 2017). As T2DM progresses, there is an upregulation of IR isoforms (particularly isoform A, lacking 12 amino acids) and related receptors, such as the IGF-1 receptor (IGF-1R), which further activates the PI3K/AKT/mTOR axis and promotes cancer progression (Fig. 2). Isoform A, signals more to cell growth and its presence is also related to ovarian and BC (Kalli et al., 2002; Massimino et al., 2021; Vella et al., 2019). An excellent review of this topic has been published elsewhere (Escribano et al., 2017). Nonetheless, direct evidence of insulin resistance leading to a shift in the IR isoform, which in turn leads to gynecological cancer, is lacking. IGF-2 is a growth factor often secreted by cancer cells that have high affinity for IR-A. There is a direct connection between an increase in the IR-A/IR-B ratio in insulin resistance and pro-malignant signaling of IGF-2 to solid tumors (Fig. 2) (Frasca et al., 1999; Scalia et al., 2020). Additionally, insulin and related signaling can stimulate the MAPK pathway, which synergizes at the transcriptional level with the AKT–mTOR axis to reinforce proliferative signaling (Roux and Topisirovic, 2018). As obesity, inflammation, hyperglycemia, and insulin resistance are common features of T2DM that can independently stimulate the PI3K pathway, the PI3K/AKT/mTOR signaling cascade may represent a central hub for metabolic and proliferative signals that becomes significantly dysregulated in diabetes-associated breast and gynecological cancers (Fontana et al., 2024; Glaviano et al., 2023; Varma et al., 2005).The binding of insulin and IGF-1 to their receptors, initiates a phosphorylation cascade that activates phosphoinositide 3-kinase (PI3K), resulting in the increased intake and utilization of glucose, and activation of mTOR that stimulates transcription and translation which then drives malignant transformation (Hopkins et al., 2020). IGF-1, a peptide with mitogenic and anti-apoptotic properties, can promote the proliferation of breast epithelial cells. However, a positive relation between circulating IGF-1 concentration and risk of BC was found only among premenopausal but not postmenopausal women (De Marco et al., 2015). Interestingly, there is only a strong relationship between BMI and breast cancer incidence in post-menopausal women (Y Chen et al., 2017). In diabetic conditions, chronic hyperinsulinemia leads to overactivation of IRs and IGF1R, both highly expressed in BC cells (Wolf et al., 2005). This hyperactivation results in enhanced phosphorylation of insulin receptor substrate-1 (IRS-1) and subsequent PI3K activation (Fig. 2) (Samuel et al., 2018; Wolf et al., 2005). T2DM is a major risk factor for the development of vascular complications. Furthermore, hyperglycemia can impair PI3K/AKT mediated signaling, promoting endothelial cell dysfunction in diabetes (Varma et al., 2005). As will be discussed in a section below, chronic PI3K activation in the presence of T2DM may lead to increased glucose uptake and utilization (aerobic glycolysis or Warburg effect), supporting the high energy and biosynthetic needs of cancer cells (Fontana et al., 2024).

Obesity is linked with increased IGF1 bioavailability. IGF1/IGF1R signaling may stimulate collagen VI-dependent DDR1 activation, followed by ERK-mediated GPER and increase in c-Fos resulting in the production of and autocrine secretion of IL-1β (Fig. 2) (Scordamaglia et al., 2025). IL-1β may then stimulate the differentiation of normal fibroblasts into cancer-associated fibroblast-like cells, which may promote the proliferative and motility of triple-negative BC cells (TNBC).

Thus, IL-1β has been speculated as a therapeutic target in obese TNBC patients presenting with high IGF-1 bioavailability (Scordamaglia et al., 2025).

Albeit in cerebral tissue, the AKT and GSK3 signaling pathways are regulated *in vivo* in the mouse in response to both physiological and pathological changes in insulin and glucose levels (Clodfelder-Miller et al., 2005). This suggests that T2DM associated with hyperglycemia can upregulate pathways downstream of these activators. In EC, the PI3K/AKT pathway becomes particularly important due to frequent loss of PTEN tumor suppressor function, which normally counteracts PI3K signaling (Kanamori et al., 2001). T2DM -associated hyperinsulinemia further amplifies this pathway through direct IR activation and IGF-1 mediated cross-activation (Y. Wang et al., 2022). The resulting enhanced mTOR complex 1 (mTORC1) activity promotes protein synthesis through phosphorylation of S6K1 and 4E-BP1, supporting rapid cell growth and division (Fig. 2) (Panwar et al., 2023). The IR and IGF-1R can also activate the Ras/Raf/MEK/ERK transduction cascade, also central to the progression of many cancer tissues (Ahmad et al., 2004), and dual activation of the PI3K and Ras/Raf/MEK/ERK signaling pathways promotes cellular proliferation and invasion (Saltiel et al., 2021). In a human ovarian cell line, IGF-1 was shown to increase expression of the potassium chloride cotransporter (KCC). The authors suggested that IGF-1 may promote cancer progression in part via its action on this cotransporter which promotes the activation of the PI3K and Ras/Raf/MEK/ERK signaling pathways (Fig. 2) (Shen et al., 2004).

Insulin and IGF-I receptors share structural homology and have been reported to form hybrid heterodimers. Little is known about the Hybrid IR/IGF-IRs to date, however, they are present in neurons, corneal epithelial cells and endothelial cells and may preferentially signal via IGF-I (Chisalita and Arnqvist, 2004; Martinez-Rachadell et al., 2019; Titone et al., 2018). Interestingly, in endothelial cells, hybrid receptor expression was reported to be higher in diabetic patients than those without this condition (Fig. 2) (Myers et al., 2024). To date, hybrid receptor presence in reproductive tissue or its vasculature is unknown, however this may be an interestingly avenue of research in the coming years.

In summary, chronic activation of the PI3K pathway in diabetes, driven by high insulin and metabolic disturbances, creates conditions that favor cancer initiation, growth, and resistance to treatment. Insulin resistance may lead to compensatory hyperinsulinemia, which further activates PI3K signaling and creates a feedback loop that exacerbates both metabolic dysfunction and cancer risk (Glaviano et al., 2023). This highlights the importance of targeting the PI3K pathway in managing cancer risk among diabetic patients.

### 6.2. *Wnt/β-catenin and Sirtuin 1 (SIRT1) signaling*

Wnt signaling is a conserved developmental pathway that becomes aberrantly activated in many breast and gynecological tumors, driving proliferation, metastasis, stemness, immune microenvironment evasion, and therapy resistance. Across these cancers, both canonical (β-catenin–dependent) and the non-canonical branches can participate (Xu et al., 2020; McMellen et al., 2020). High glucose levels have been reported to promote cisplatin resistance in triple negative breast cancer cell lines via the Wnt/β-catenin pathway (Viedma-Rodríguez et al., 2025). Wnt related pathways undergo significant modifications in diabetes-associated breast and gynecological cancers, with hyperglycemia directly enhancing pathway activity through metabolic mechanisms (Ghareghomi et al., 2024; García-Jiménez et al., 2014; Fatima et al., 2021; Arend et al., 2013; McMellen et al., 2020; Xu et al., 2020; Viedma-Rodríguez et al., 2025). Correspondingly, Wnt related pathways are also reported to be linked to sex steroid hormone signaling (Fatima et al., 2021). Nuclear β-catenin accumulation correlates with advanced disease stage and poor prognosis in EC (Markowska et al., 2013). Relating both prognosis and frequency of cancer with diabetes, the high glucose-dependent acetylation of β-catenin/LEF1 transcription factors may facilitate nuclear complex formation and pro-cancerous Wnt target gene expression (Chocarro-Calvo et al., 2013) (Fig. 2).

Sirtuin 1 (SIRT1) is an $NAD^+$-dependent deacetylase acting on histones and non-histone proteins (p53, NF-κB, others), influencing metabolism, DNA repair, apoptosis and cell cycle (J Chen et al., 2021). SIRT1 is a key metabolic sensor and regulator of energy homeostasis, with reduced activity heavily implicated in the development of insulin resistance and T2DM. It functions as a protective agent against diabetic complications by modulating oxidative stress, inflammation, and mitochondrial function. SIRT1 may act as a tumor suppressor by inhibiting β-catenin and NF-κB signaling (Y Zhang et al., 2025). (Fig. 2). Despite being either oncogenic or tumor-suppressive depending on context, in breast, cervical, endometrial, ovarian cancers there is now solid evidence correlating SIRT1 dysregulation associates with tumor growth, metastasis, and treatment resistance (Moore et al., 2012; J Chen et al., 2021). Significantly higher SIRT1 expression is present in both BR, EC and cervical cancer cells compared with normal counterparts indicating that this protein's signaling pathways may contribute to these malignancies (Asaka et al., 2015; Moore et al., 2012; Elangovan et al., 2011). Mechanically, estrogenic pathways may promote SIRT1 expression, and in turn SIRT1 is reported to alter estrogen secretion and ERα expression resulting in the development and maintenance of estrogen-dependent cancers (Elangovan et al., 2011). A similar role is also observed in gynecological cancers where SIRT1 promotes estrogen-dependent proliferation and p53-FOXO1 inhibition in type I endometrial cancer, while potentially supporting genomic stability in high-grade type II tumors (reviewed in J Ding et al., 2025). From a therapeutic standpoint, SIRT1 is reported to counteract the therapeutic effect of PARP inhibitors (J Chen et al., 2021). While SIRT1 may serve as a marker of poor patient prognosis, this observation raises the possibility that SIRT1 inhibitors may act synergistically with PARP inhibitors in gynecologic oncology treatment.

An emerging new field of cancer research that may have implications for breast and gynecological cancers and T2DM-based in the observation that the formation of breast cancer is promoted by a loss of a maintained circadian rhythm (Maiese, 2017). The body's circadian clock appears to rely upon the regulation of the critical pathways of autophagy, the mechanistic target of rapamycin (mTOR), AMP activated protein kinase (AMPK), and SIRT1 as well as proliferative mechanisms of the Wnt/β-catenin pathway to favor tumor growth (Maiese, 2017). Current publications linking mechanistically the participation of SIRT1 and Wnt/β-catenin pathways to the initiation, progression and therapy resistance of cancers is predominantly well defined only in gastrointestinal tumors and thus remain an insufficiently explored area in malignancies of female reproductive organs.

### 6.3. *Glucose transporter (GLUT) upregulation*

GLUT family member expression is significantly enhanced in cancer, facilitating increased glucose uptake and metabolic reprogramming (Medina and Owen, 2002; Medina et al., 2004; Nualart et al., 2009). A fundamental characteristic of all cancer cells is metabolic reprogramming (the Warburg effect), which switches energy production through glycolysis rather than mitochondrial oxidative phosphorylation (reviewed in Shin and Koo, 2021). In EC, enhanced GLUT expression correlates with increased glucose uptake and supports rapid cell proliferation through provision of metabolic substrates for biosynthetic pathways (Byrne et al., 2020). The high glucose environment also promotes O-linked β-N-acetylglucosamine (O-GlcNAc) modifications of proteins, affecting oncogene function and metabolic enzyme activity (Byrne et al., 2020). Hyperinsulinemia, a characteristic of T2DM, was shown to contribute BC-promoting pathways by a PI3K and mTOR-dependent mechanisms which involved increased GLUT1-mediated glucose uptake (Silva et al., 2022). BC cells demonstrate particularly robust GLUT4 upregulation in response to insulin and IGF-1 signaling, with enhanced translocation to the plasma membrane

supporting increased glucose utilization. This metabolic reprogramming supports the energetic demands of rapid proliferation and provides substrates for nucleotide and lipid synthesis (Samuel et al., 2018). Interestingly, IGF-2 activation of IR-A may increase GLUT1 and offer an additional or alternative mechanism to GLUT4 in T2DM and cancer (Scalia et al., 2020). The GLUT family of glucose transporters is a large family which is still awaiting closer investigation. Identified in breast and prostate cancers, GLUT12 is also upregulated in many solid tumors and is responsive to insulin and high glucose, suggesting a role in cancer cell glucose uptake, particularly relevant in hyperglycemic or insulin-resistant states such as T2DM (Burgos et al., 2025; White et al., 2018). GLUT12 is also expressed in reproductive tissues and thus future investigation may bring to light its role as a second insulin-responsive transporter.

### 6.4. Estrogen and progesterone

Sex-hormones control normal breast development, growth and function; however, they also impinge on both cancer development and disease progression (Fig. 1). Estrogen receptors (ER) occur as two homologues (separate genes), ERα and ERβ, which belong to the nuclear receptor family of transcription factors, while Progesterone Receptors (PRs) occur as two isoforms, with forms A and B arising through differential start sites (Owen and Zelent, 2000). The GPR30/G-protein estrogen receptor (GPER) also signals in response to estrogen in normal breast and reproductive tissue (De Marco et al., 2015). These receptors are often present sex-hormone associated cancers such as breast, ovarian, and endometrial (Beral et al., 2005; Z. Fu et al., 2025; Joung et al., 2015; Lai et al., 2004; Groshong et al., 1997). The direct and indirect effects and their action on different receptors and on reproductive cell types makes sex-hormone signaling roles difficult to decipher. Estrogen's proliferative effects on the endometrium are counteracted by progesterone, reducing the risk of hyperplasia and EC (Kim et al., 2013). However, combined estrogen and progesterone exposure can increase breast cell proliferation (Hilton et al., 2018). In addition to the classical nuclear receptors ERα and ERβ and the progesterone receptor isoforms PR-A and PR-B, sex hormones also act through non-classical pathways. Estrogen signals via the membrane-bound G protein–coupled estrogen receptor (GPER) (Clusan et al., 2023), while progesterone engages membrane-associated receptors such as the mPR family and PGRMC1 (Pedroza et al., 2020). Together, these receptor systems coordinate genomic and rapid non-genomic signaling through pathways like PI3K/AKT and MAPK, reinforcing their role in tumor proliferation, survival, and therapy resistance (Fig. 2).

In childhood, estrogen and progesterone levels are low. At puberty, rising levels drive breast development, menstruation, and fertility. During a woman's fertile years, cyclical hormonal fluctuations regulate ovulation, pregnancy, and menstrual cycles. With perimenopause, then menopause, both hormones decline sharply, ending fertility and causing symptoms like hot flashes and bone loss (Fig. 1). Demonstrating the impingement of excess body weight on the hormonal system, between the ages of 7 to 15, obesity (>30 BMI) is associated with decreased fecundability (the probability of achieving a pregnancy within one menstrual cycle) and a lower number of children. A BMI >25 during 11-15 years of age is associated with a higher risk of childlessness (even after excluding women with PCOS). Equally, demonstrating that nutrition is closely linked to reproductive outcome, being underweight between ages 11-15 is also associated with an increased risk for future infertility treatment (Laru et al., 2021). How the exposure of the burgeoning reproductive tract to excess body weight modifies future cancer risk is still a matter of ongoing investigation.

The story of T2DM and female reproductive health is not a simple one of impingement on the action of reproductive hormones. Cancer generally comes later in life, and more often than not, after menopause (Fig. 1). The perimenopause, followed by the menopause, marks the transition in a woman's life characterized by declining estrogen levels that trigger susceptibility to age-related degenerative diseases. Metabolic adaptations in menopausal women are related to insulin resistance, increased total body fat mass, and abdominal fat accumulation, all of which predispose women to the development of T2DM. Metabolic syndrome has a high prevalence in postmenopausal women, indicating the loss of estrogen protection on metabolic and cardiovascular health. Metabolic syndrome, common in postmenopausal women, is also associated with hypertension, insulin resistance and cortisol production that may potentially impinge on diabetic and oncogenic development (Baudrand et al., 2014). Moreover, earlier age at menopause has been related to increased risk of T2DM. Accordingly, hormone replacement therapy (HRT) may reduce T2DM incidence and improve glycemic control in women with existing T2DM (Paschou et al., 2024). An analysis of 8219 postmenopausal women demonstrated that early menopause, which results in a shorter lifetime exposure to endogenous estrogen, is associated with a higher risk of certain gynecologic cancers, including cervical, ovarian, and uterine cancers, even after controlling for confounding factors such as age, lifestyle and BMI (Abulajiang et al., 2025). Confirming that endometriosis is not a risk marker of T2DM, the French E3N prospective cohort of 98,995 women reported that surgically-confirmed endometriosis was not associated with T2DM (Vaduva et al., 2023). A still not fully unexplained observation is that obesity is more a risk factor for BC in postmenopausal women than during the fertile years (Korzets et al., 2021). While pre-menopausal women have high circulating hormone levels than may mask the increased synthesis of estrogens in the adipose tissue, there are several other factors which may be responsible. Interestingly, the hormone estrone plays a dominant role after menopause. In contrast to anti-inflammatory actions of 17β-estradiol, estrone has been reported to be pro-inflammatory. In menopausal women, the role in BC development of estrogens and progestogens in replacement therapy is still a matter of discussion. In human mammary adipocytes, cytokine expression increases with obesity, menopause, and cancer. An adipocyte and BC cell interaction is suggested to promote estrone-dependent pro-inflammatory cytokine upregulation and estrone drives more rapid ER + BC growth *in vivo* than estradiol (Qureshi et al., 2020). Interestingly, metformin (discussed below) has been reported to have more favorable actions in women who have not yet experienced menopause, potentially due to the contribution to weight loss and reduced inflammation (Lim et al., 2025).

The Million Women Study (Beral and Million Women Study Collaborators, 2003) and the Women's Health Initiative trials reported that the use of combined hormone therapies increased the risk of BC, however the French E3N cohort study (Fournier et al., 2008) did not report this increase with estrogen-progestagen combinations (however, elevated relative increase was detected in women receiving estrogen-dydrogesterone, and other progestogens). Therefore, the role of estrogens combined with different progestogens in the development of BC in menopausal women is not determined and, as it was not a specific parameter of investigation in these cohort studies, less is known about the role of T2DM and cancer incidence at this stage of life (Y. Deng and Jin, 2021). The participation of progesterone in female cancer is equally unclear. Combination pills are thought to be more hazardous than estrogen alone for BC incidence. However, consistent with a potential protective effect when progesterone is added to estrogen formulations, in the Million Women's Study the odds ratio of OC fell in combination arms. In EC, fertile women taking oral contraceptives are protected after menopause from malignancy, while after menopause progesterone is generally added to reduce estrogen-mediated carcinogenesis (Narod, 2007).

Due to enhanced thromboembolic risk, HRT now has a tendency not to be recommended for initiation in women over 60 years old or after 10 years since menopause onset (Paschou et al., 2024). In T2DM postmenopausal women, HRT is well tolerated if the regime has been properly selected according to their metabolic, cardiovascular, and osteopathic risk. Given the beneficial effects of estrogen (oral

17β-estradiol) on glucose metabolism, this hormone is often preferred in women with T2DM, especially in the presence of low cardiovascular risk. However, progesterone, (e.g. micronized dydrogesterone a synthetic form of progesterone or transdermal norethisterone, a progestin) is also often preferred in postmenopausal women with T2DM to add protection to an intact uterus. Thus, HRT may reduce T2DM incidence and improve glycemic control in women with existing T2DM (Paschou et al., 2024).

T2DM significantly modulates steroid hormone signaling. In breast and gynecological cancers, through multiple mechanisms affecting both hormone levels and receptor function, hyperinsulinemia suppresses hepatic production of SHBG, resulting in increased bioavailable estrogen and androgen promoting cellular proliferation through enhanced receptor activation (Samuel et al., 2018; Vrachnis et al., 2016). The GPER also signals in response to estrogen in malignant cells, and also in cancer-associated fibroblasts (CAFs) (Fig. 1) (De Marco et al., 2015). There is consensus that estrogens are drivers of ER + breast, ovarian and ECs, and the ER is a principal target for cancer therapy (Agnoletto and Brisken, 2025; Beral et al., 2005). In BC, insulin resistance leads to increased aromatase activity in adipose tissue, elevating local estrogen production (Vrachnis et al., 2016). Additionally, insulin and IGF-1 directly phosphorylate ERα, enhancing its transcriptional activity independent of ligand binding (Vrachnis et al., 2016). This mechanism operates across all gynecological cancer and ER positive breast types and represents a key link between metabolic dysfunction and hormone-dependent malignancies (Bradley et al., 2008; Samuel et al., 2018; Vrachnis et al., 2016). The insulin/IGF1 system and estrogens are interconnected and act synergistically as potent stimulators of growth in normal breast as well as in breast tumor cells (Bradley et al., 2008). Functional crosstalk between estrogenic GPER transduction and the insulin/IGF1 pathways is a factor in reproductive tissue malignancy progression (De Marco et al., 2015). EC demonstrates particularly strong associations with altered estrogen/progesterone ratios in diabetic patients (Anastasi et al., 2018). Chronic anovulation associated with insulin resistance leads to unopposed estrogen stimulation and reduced progesterone levels, creating a hormonal environment that promotes endometrial hyperplasia and malignant transformation (Vrachnis et al., 2016). Estrogen treatment is shown to increase IR-B and IRS-1 phosphorylation (Fig. 2), whereas insulin induced ERα phosphorylation (Tian et al., 2019). Combining insulin and estradiol increased both expression and phosphorylation of AKT and MAPK pathways and increased growth in an *in vivo* xenograft of EC. This suggests that insulin and estrogen have a synergistic role in EC carcinogenesis and progression (Tian et al., 2019). Interestingly, within the general MAPK pathway, the silencing of the ERK5 impaired NF-kB pathway in EC cells (and xenografts) with alterations in the MEK5-ERK5 pathway being observed in 48% of EC patients (Diéguez-Martínez et al., 2022).

It is clear that, given the numerous ways in which sex steroid hormones can signal, the wide variety of tissues responsive to them, and the notable changes across a woman's reproductive lifespan, understanding the roles of estrogen and progesterone remains complex—particularly how they may be modified by weight gain and diabetes. In the future, to decipher this mosaic of hormone activity, clinical and observational studies should integrate multiple parameters, including body weight, leptin levels, hormone profiles, and the life stage of each participating woman.

### *6.5. Diabetes, hyperlipidemia, and cancer progression via lipid metabolism pathways*

Metabolic reprogramming associated with T2DM may create a permissive environment for cancer cell growth while providing the necessary substrates for rapid proliferation and survival under metabolic stress conditions (Martin and McGee, 2018). Diabetes-associated hyperlipidemia contributes to cancer progression through multiple interconnected mechanisms, notably involving altered lipid uptake and transport. As a result of dyslipidemia, cholesterol may increase in cell membranes and thus impact upon membrane fluidity and subsequent signaling. Cholesterol is also the precursor of estrogens and other sex-steroid hormones. The relationship between cholesterol and reproductive tissue cancer risk is complex and inconsistent. Some studies suggest elevated cholesterol may increase risk, while others find no association or even an inverse relationship, particularly for total and HDL cholesterol (Murdock et al., 2023). However, this does not exclude the possibility that increased circulatory cholesterol in combination with other circulating factors (hormones, glucose, leptins, etc.) or comorbidities may play a significant role in cancer incidence and progression. Tumors arising in adipocyte-rich tissues, such as BC, show enhanced assimilation of extracellular fatty acids (FAs), which supports tumor growth and metastasis (Balaban et al., 2018; Corn et al., 2020; Dana et al., 2023). Fatty acid synthase (FASN) is elevated in 30% of HER2-overexpressing BCs (J. S. Lee et al., 2013). FASN and acetyl-CoA carboxylase (ACCα) support membrane synthesis and may lead to cellular proliferation (Fig. 2) (Y. Fu et al., 2021). Interestingly, the pharmacological inhibition of FASN has been shown to reduce levels of HER2 protein in BC cell lines (J. S. Lee et al., 2013). Assimilation of extracellular FAs is mediated by membrane-associated transporters including CD36, fatty acid transport proteins (FATPs), and fatty acid binding proteins (FABPs) (Fig. 2) (L. Deng et al., 2023; Y. Fu et al., 2021). FABPs, especially FABP4 and FABP5, regulate lipid homeostasis are implicated in tumor-promoting interactions among cancer cells, adipocytes, and tumor-associated macrophages (Amiri et al., 2018; Başarır Sivri and Çiftçi, 2024; D. Chen et al., 2023; Hancke et al., 2010; D. Yang et al., 2018; Zeng et al., 2020). *In vivo* models have shown that deletion of FABP4 or FABP5 reduces tumor progression and metastasis, particularly in obesity-associated BC (D. Chen et al., 2023). Elevated circulating FABP4 and FABP5 levels have also been observed in BC patients, with FABP4 emerging as a potential independent biomarker (Guaita-Esteruelas et al., 2017). Obese women with BC show especially high FABP4 levels, correlating with larger tumors and worse prognosis (Hao et al., 2018). In parallel, cholesterol metabolism is dysregulated in cancer. Cancer cells commonly overexpress the low-density lipoprotein receptor (LDLR) to enhance LDL-cholesterol uptake, which supports cellular proliferation and motility (Loos et al., 1988; Modi et al., 2022; Pires et al., 2012; Torres et al., 2011; H.-X. Yang et al., 2020);. Overexpression of LDLR is linked with tumor aggressiveness, chemoresistance, and poor clinical outcomes in BC (Loos et al., 1988; Modi et al., 2022). In hyperlipidemic conditions, reducing LDLR expression in triple-negative and HER2-positive BC cells impairs tumor growth and increases apoptosis (Gallagher et al., 2017). Furthermore, a crucial enzyme in cholesterol metabolism is the NAD/NADP dependent steroid dehydrogenase-like (NSDHL) has been identified as a potential metastatic driver in triple negative BC (M. Chen et al., 2021). These findings underscore how lipid transport and signaling alterations driven by diabetes-induced hyperlipidemia can promote tumor development and progression through distinct but converging pathways. Accordingly, there is now interest in developing inhibitors of the fatty acid pathway as therapeutic agents for malignancies overexpressing the HER2 protein.

## 7. Inflammation and adipose tissue dysfunction

Chronic low-grade inflammation in T2DM activates the IL-6–JAK2–STAT3 axis, which promotes tissue damage and creates a favorable microenvironment for the bourgeoning cancer cell. In breast and gynecological tissues this pathway links metabolic disease to carcinogenesis, metastasis and chemoresistance. Chronic inflammation in T2DM is linked to elevated IL-6 and TNF-α, and IL-6 can activate the IL-6R/JAK2/STAT3 pathway in diabetic tissues. BMI has also been significantly positively correlated with the TNF-α and IL-6, concentrations (Mohammad et al., 2024). Meta-analysis indicates that T2DM risk as whole was strongly associated with elevated levels of inflammatory cytokines (IL-1β, IL-6, IL-18, CRP), TNF-α and low levels of adiponectin

(Liu et al., 2016).

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a central inflammatory transcription factor implicated in both metabolic disease and tumor biology. Playing a major role in all the pathogenesis related to inflammation, the activation of proinflammatory transcription factor NFκB is a commonly observed phenomenon in breast cancer (W. Wang et al., 2015). In diabetes, chronic low-grade inflammation drives NF-κB–dependent insulin resistance and β-cell stress, while in BC and EC, NF-κB supports tumor growth. Hyperglycemia-induced oxidative stress is known to activate protein kinase C (PKC) isoforms, which phosphorylate IκB kinase and lead to NF-κB nuclear translocation (Fig. 2) (Samuel et al., 2018). In EC, NF-κB activation promotes expression of inflammatory genes and supports angiogenesis (Anastasi et al., 2018). The pathway becomes further activated through TNF-α–mediated signaling (Fig. 1), creating a chronic inflammatory microenvironment that supports malignant transformation. BC tissues demonstrate enhanced NF-κB activation through multiple diabetes-related mechanisms, including advanced glycation end product formation (discussed below) and the abovementioned inflammatory cytokine stimulation.

Adipose tissue dysfunction through cytokine signaling is shared in both T2DM and BC, with adipokine signaling directly associated with BMI (Wintrob et al., 2017*)*. T2DM or related obesity can disrupt the dynamic role of the adipocyte in energy homeostasis, resulting in alteration of adipokine (for example, leptin and adiponectin) and inflammation signaling. Leptin, an adipokine elevated in obesity, activates the JAK2/STAT3 signaling pathway, leading to increased expression of genes involved in cancer progression and survival. Leptin binds to the ObR receptor, triggering JAK2 activation and subsequent phosphorylation of STAT3 (Fig. 2). Activated STAT3 translocates to the nucleus, where it upregulates genes such as cyclin D1, COX-2, VEGF, survivin, and hTERT (Fig. 2) (Mullen and Gonzalez-Perez, 2016). Also activating STAT3 and creating a positive feedback loop for inflammatory signaling are the Advanced Glycation End products (AGEs) formed in hyperglycemic conditions interact with their receptor RAGE (Fig. 2).

The growth of ER + cancers is under estrogen influence, and these hormone levels increase in overweight and obese postmenopausal women due to the aromatization of androstenedione and androgens to estrogens in adipose tissue (Goodwin et al., 2012; J.-J. Hu et al., 2025; Khandekar et al., 2011). In fact, obesity-related variables such as BMI, body weight, and leptin family members all have prognostic associations in BC patients in multivariable analyses (Goodwin et al., 2012). Plasma leptin levels may correlate with total body aromatization in cancer patients and with plasma levels of estradiol and estrone sulfate in both BC patients and healthy postmenopausal women (Geisler et al., 2007). These findings suggest that leptin may influence aromatase activity *in vivo*, providing a potential link between obesity, associated conditions such as diabetes, and plasma estrogen levels in relation to female estrogen-dependent cancer risk. The leptin receptor is overexpressed in BC tissues, particularly in patients with concurrent T2DM (Garofalo et al., 2006). As leptin and related adipokines undergo significant alterations in diabetes-associated gynecological cancers, they may contribute to tumor growth (Fernandez et al., 2021). Furthermore, diabetes-associated obesity leads to leptin resistance and compensatory hyperleptinemia, which promotes cancer cell proliferation and angiogenesis (Vrachnis et al., 2016). In BC, elevated leptin levels enhance vascular endothelial growth factor (VEGF) expression, which via HIF-1a stabilization supports tumor angiogenesis (Anastasi et al., 2018) (Fig. 2). Leptin and adiponectin are both adipokines (hormones secreted primarily by adipose tissue) but they have almost opposite roles in energy balance and metabolism. In general, adiponectin levels are significantly reduced in diabetes-associated gynecological cancers, removing protective anti-inflammatory and anti-proliferative effects. Low adiponectin levels are inversely associated with EC risk and correlate with increased insulin resistance, independently of other metabolic factors (Li et al., 2016). The leptin-to-adiponectin ratio is a recognized biomarker of insulin resistance and has been positively associated with an increased risk of EC in postmenopausal women exhibiting elevated leptin/adiponectin ratios (Ashizawa et al., 2010; Vrachnis et al., 2016). In the latter study, the leptin-to-adiponectin ratio association with EC risk remained after adjusting for BMI, hypertension, and T2DM presence (Ashizawa et al., 2010). Molecular modulation of the leptin/Ob-R complex may make a novel target for prevention and treatment of breast and gynecological cancers, particularly in the context of obesity and T2DM (Guo et al., 2012).

### *7.1. Glycosylation on proteins and lipids, and the disruption in diabetes*

Glycolipids are lipids with attached carbohydrates, crucial for cell membrane structure and cell recognition, particularly in the immune response. Through modification of glycolipid metabolism, abnormal cell function and adipokine imbalance, obesity could promote BC incidence and propagation (J.-J. Hu et al., 2025). The dysregulation of glycolipid metabolism (the biochemical processes of synthesis, modification, and breakdown of glycolipids) caused by T2DM or obesity upon the cancer cell, may favor the increase and/or subcellular localization of cholesterol and fatty acids. The formation of cancer-associated adipocytes or lipid-associated macrophages during obesity, the secretion of inflammatory factors, together with adipokine imbalance cancer may trigger multiple cellular abnormalities promoting an immunosuppressive tumor microenvironment (J.-J. Hu et al., 2025).

Glycosylation, the enzymatic process of adding sugar chains (glycans) to proteins and lipids, is frequently disrupted in T2DM due to persistent hyperglycemia. This disruption can contribute to cancer development by altering cell signaling, immune responses, and the tumor microenvironment. In T2DM, hyperglycemia leads to abnormal glycosylation patterns, particularly through the enhanced activity of the hexosamine biosynthetic pathway, resulting in the aberrant glycan expression on proteins and cells (Fig. 2) (Vasconcelos-Dos-Santos et al., 2017). Glycosylation is a complex post-translational modification involving two principal types of glycans: N-linked glycans (attached to asparagine residues) and O-linked glycans (attached to serine or threonine residues). Carcinogenesis is frequently associated with dysregulation in glycosylation machinery, resulting in the expression of tumor-associated glycans. These glycans often arise from incomplete glycosylation processes, producing novel or truncated glycan structures (Dusoswa et al., 2020). Altered glycosylation affects several cancer-relevant pathways. For example, changes in the glycosylation of integrins and cadherins can impair cell-cell adhesion and promote motility. Similarly, glycosylation-dependent signaling in tumor-infiltrating immune cells can suppress anti-tumor immunity and support immune evasion. Modifications of vascular endothelial growth factor receptors and other receptor tyrosine kinases can enhance pro-angiogenic signaling and contribute to drug resistance (Chandler et al., 2019). Additionally, glycosylation of membrane transporters and signaling receptors can modulate proper folding, stability, and routing to the plasma membrane (Schinkel et al., 1993).

In the context of diabetes, components of the insulin signaling pathway are modified by O-linked N-acetylglucosamine (O-GlcNAc). The interplay between O-GlcNAcylation and phosphorylation is critical to diabetic signaling. For instance, phosphorylation-mediated insulin signaling can be antagonized by O-GlcNAcylation. During prolonged insulin stimulation, O-GlcNAc promotes the translocation of O-GlcNAc transferase (OGT) to the plasma membrane, which in turn reduces AKT activity and its downstream signaling targets (Fig. 2) (Morales and Pratt, 2024). These glycosylation changes are not confined to a single cancer type (Dusoswa et al., 2020). Notably, O-linked glycosylation alterations have been particularly associated with cancer progression in patients with T2DM (Vasconcelos-Dos-Santos et al., 2017). One example is the O-glycosylation of CD44, which facilitates its interaction with hyaluronic acid, enhancing CD44 signaling and potentially supporting a cancer stem cell phenotype in BC (Walker et al., 2022). This latter

signaling pathway is extremely interesting as high molecular weight hyaluronic acid may contribute to stronger extracellular matrix and prevent tumor growth and metastasis, while low molecular weight forms may have the opposite effect and/or be proinflammatory (Seluanov et al., 2018). The CD44 receptor expression or over-expression in cancer cells is also associated with increased metastatic potential and poorer OS (Gostomczyk et al., 2025).

Glycosylated hemoglobin (HbA1c) forms when glucose binds non-enzymatically to hemoglobin in red blood cells. HbA1c is routinely measured to evaluate long-term glycemic control, reflecting average blood glucose concentrations over the preceding 8 to 12 weeks. It serves as a key biomarker for T2DM diagnosis, monitoring, and risk assessment (Nathan et al., 1984). In a large East Asian cohort, elevated HbA1c levels were associated with an increased risk of developing T2DM but paradoxically with a decreased risk of BC (Han et al., 2025). Conversely, in a Spanish cohort, women with both T2DM and pre-diagnosed BC exhibited an increased prevalence of elevated fasting blood glucose (≥126 mg/dL) and HbA1c (≥48 mmol/mol or 6.5%) (Fernández-Arce et al., 2024).

Alterations in glycosylation patterns of circulating proteins may also offer new diagnostic opportunities in oncology (Ruma et al., 2025). The glycosylated protein CA125 is widely used as a biomarker for OC, particularly in monitoring tumor burden following treatment. However, T2DM appears to negatively influence the diagnostic performance of CA125. One study found that women with both T2DM and hypertension had significantly lower CA125 levels (Ahmed and Abdou, 2019), while another reported that serum CA125 levels in T2DM patients were significantly higher than those in healthy controls (Cai et al., 2022). Notably, the role of glycosylation in modulating CA125 levels was not directly addressed in these studies. In the future, panels of glycoproteins, independent of CA125, may have superior diagnostic accuracy for distinguishing benign conditions from OC, offering potential improvements over traditional markers.

The presence of chronic inflammation and insulin resistance not only increases cancer risk but also exacerbates treatment resistance, and thus weight-loss drugs such as metformin may improve the efficacy of obesity-related cancer treatment. Intervention strategies targeting adipose tissue remodeling, lipid metabolism and leptin regulation also show potential clinical value, however further research is needed to clarify their safety and efficacy.

### 7.2. Advanced Glycation End products (AGE) and RAGE signaling

Linked to the etiology of cancer, glycation (*not to be confused with glycosylation*) is a non-enzymatic process that produces advanced glycation end products (AGEs). The AGE–RAGE (receptors for AGE) axis links chronic hyperglycemia, inflammation and cancer biology. In diabetes, excess AGEs and upregulated RAGE create a pro-tumor environment that appears relevant for several gynecologic malignancies, especially BC and EC (Khan et al., 2024). AGE-RAGE can chronically drive signaling pathways such as NFκB, MAPK/ERK, JNK, TGF-β and PI3K/AKT and is strongly associated with T2DM progression (Khalid et al., 2022). Chronic hyperglycemia promotes AGE formation through non-enzymatic glycation of proteins and lipids. AGE-RAGE activation can upregulate genes such as HIF-1α, VEGF, Survivin, Bcl-xL, Bcl-2, Cyclin D1, MMPs, as well as pro-inflammatory cytokines such as TNF-α and IL-6 (Fig. 2) (Muthyalaiah et al., 2021). In BC, AGE-RAGE interactions activate multiple downstream signaling pathways including NF-κB, and oxidative stress pathways (Fig. 2). Once activated within the nucleus, NF-κB initiates an inflammatory response that drives the secretion of TNF-α, IL-4, IL-6, VEGF and matrix metalloproteinases (MMPs) (Fig. 2), thereby facilitating tumor progression (Dariya and Nagaraju, 2020). OC demonstrates particularly strong AGE-RAGE signaling activation, with enhanced expression of p70S6K1, STAT3, and MAPK p38 (Fig. 2) (Samuel et al., 2018). The AGE-RAGE axis is reported to promote EC progression by upregulating choline kinase-α (CHKA), and activating PI3K/AKT, enhancing malignant behaviors (Shu et al., 2025). This axis also facilitates the generation of reactive oxygen species (ROS) through both free radical formation and auto-oxidation reactions, thus disrupting redox homeostasis resulting in elevated oxidative stress (Dariya and Nagaraju, 2020).To elucidate a molecular link between T2DM and EC a proteomic approach investigated the role of T2DM in clinical ECs samples (Mujammami et al., 2022). In this study, within the diabetic arm, a total of 53 proteins significantly increased and clustered around dysregulation of ERK1/2 and F-actin signaling pathways. Related to metabolism, peroxiredoxin-1 (an antioxidant), was upregulated while superoxide dismutase (protecting cells from damage caused by superoxide radicals) was downregulated. However, further studies in larger cohorts are needed to determine the significance of these findings (Mujammami et al., 2022). Inhibition the AGE pathway, potentially via a CHKA inhibitor, could be a novel targeted therapy for gynecological cancers (Shu et al., 2025)

### 7.3. The genetics of T2DM, obesity and cancer

The accumulation of mutations is a requirement for carcinogenesis. Despite only a few genetic alterations being drivers of cancer, many passenger mutations, even Single Nucleotide Polymorphisms (SNPs) maybe contribute to changes in regulatory pathways and thus affect cancer development, type and outcome. A causal genetic association is suggested between endometriosis and OC (Rueda-Martínez et al., 2021). To date no T2DM-risk SNPs have been robustly linked to OC. Albeit in cancer of the male reproductive system, three Hepatocyte Nuclear Factor 1B (HNF1B) SNPS (rs11649743, rs4430796, and rs7501939) are associated with lower prostate cancer risk and are also associated with an increased risk of diabetes. However, authors of this latter publication speculate that while the HNF1B variants are directly associated with both T2DM and cancer, T2DM does not appear to mediate gene variant-prostate cancer relationships, and the relationship between these diseases is not mediated via these gene variants (Stevens et al., 2010). It will be interesting to see if these SNPs also have an association with estrogen dependent cancers of the female reproductive tract.

The association between 143 SNPs near 29 genes of established diabetic risk revealed twelve SNPs with an association with BC risk. Interestingly, on the multiplicative interaction scale, diabetic status modified the associations between rs4876369 (*SLC30A8)* and rs2241745 and BC incidence (Parada et al., 2019). In a separate study, three genetic variants (rs9939609 (FTO), rs7903146 (TCF7L2) and rs8042680 (PRC1)) were associated with the risk of both T2DM and BC (Z. Zhao et al., 2016). However, in a separate study, the rs7903146 intron variant of *TCF7L2* (transcription factor 7 like 2) showed no association with either BC risk or mortality (Parada et al., 2019). A further study reported that three T2DM risk alleles (rs5945326-G, rs12518099-C), rs7578597-T) were positively associated with BC risk, whereas two T2DM risk alleles (rs1111875-C, rs10923931-T) were inversely associated with BC risk (albeit varying between women of Caucasian or African) (Hou et al., 2012). Demonstrating both the study population and the statistical power of the cohort, other studies did not show these effects (Parada et al., 2019).

T2DM often comes associated with increased BMI and an association with the presence of SNPs and cancer has been identified. While appearing only in abstract form to date, significant SNPs changes associated with BMI in *RBFOX1 (*rs17804012) and LINC00317 *(*rs2014791) have been reported, although no correlation was found with BC risk and independent assessment by other studies is still lacking (J.-J. Hu et al., 2025). Interestingly, the same study reported gene correlation with cancer risk, in particular, a *thyroid hormone receptor (THR) B* gene polymorphism in premenopausal women with a BMI >23.2. Incorporating *this gene* in a BMI-related gene set, pathway analysis varied with menopausal status and/or BMI level and associated to BC risk (J.-J. Hu et al., 2025). THRB resistance has also been associated with metabolic traits, and interestingly gene variants in the THRA are shown to increase

the risk of developing obesity and show gene-diet interactions. Suggesting that SNPs in the THRA gene are associated with obesity development, the THRA rs1568400 is strongly associated with fasting triglyceride levels (Fernández-Real et al., 2013). T2DM is associated with a fat-rich diet and the of SNPs in the peroxisome proliferator-activated receptor-γ (PPARγ) are known to modulate BMI and T2DM risk, albeit in a population dependent manner (Lamri et al., 2012; Pozio et al., 1989; Syed et al., 2020).

Studies have shown that common variants near melanocortin 4 receptor gene (*MC4R)* influence fat mass, weight and obesity risk (R. J. F. Loos et al., 2008). In European populations, the combined effects of polymorphisms in MC4R and Obesity Associated gene (*FTO)* are predictive of obesity and T2DM (Cauchi et al., 2009). While being independent of BMI, the interaction between *FTO* and *MC4R* polymorphisms is associated with BC, with the allele combination of C/T/C (*FTO rs1121980/FTO rs9939609/MC4R rs17782313*) giving a 4.59-fold higher cancer risk. MC4R rs17782313 alone showed an independent increased BC risk (da Cunha et al., 2013). Furthermore, in regard to BMI, SNP rs1861868 in the *FTO* gene showed significant protective associations (Al Asoom et al., 2020). A protective effect to BMI was also observed with the SNP rs7975232 of *the vitamin D receptor* (VDR) gene. VDR gene polymorphisms have been associated with gestational diabetes mellitus and lipid metabolic disorders (Sekar et al., 2025). As previously mentioned, PCOS is a known risk factor for EC incidence, and furthermore, an association exists between genetic variations and a predisposition of PCOS (Almotairi et al., 2025). Demonstrating that this signaling involved between *FTO* and *MC4R* may be detrimental to other gynecological tissues, an interaction between common variants of these genes is also associated with risk of PCOS (Al Asoom et al., 2020). Monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 (PAI-1) are biomarkers of inflammation and endothelial dysfunction involved in cancer progression and are elevated in PCOS patients. In a cohort of Kashmiri women, polymorphisms in PAI-(1675 4G/5G) and MCP-1 (2518A/G) were associated with predisposition to PCOS (Yousuf et al., 2022).

Estrogen exposure is the principal indicator of reproductive health and ERa positive cancer risk in women. Using 10 specific SNPs, Yuk and colleagues (2025) demonstrated an association between SNPs, cancer risk and lifetime estrogen exposure (Yuk et al., 2025). Randomization studies have implicated a causal genetic association between age at menopause with BC, OC, and T2DM (Louwers and Visser, 2021). Furthermore, further Mendelian randomization analysis proposed a causal inverse association, independent of BMI, between puberty timing and risks for breast and ECs (Day et al., 2017).

While to date T2DM associated SNP or genetic risk scores have not been predictive of cancer risk overall, the future investigation of shared genetic mechanisms between T2DM and female cancers in terms of incidence and proliferation of a specific cancer type and response to treatment may show further reasons why diabetic patients have a greater incidence of cancer and have a poorer prognosis. Furthermore, introducing hormonal variables such as menopause nulliparity and menopause may influence these statistical outcomes.

### 7.4. The immune response and the tumor microenvironment

Obesity and T2DM can significantly alter immune infiltration in the tumor microenvironment, often promoting immunosuppression and impacting anti-tumor immunity. It's speculated that reduced infiltration and impaired function of cytotoxic $CD8^+$ and $CD4^+$ T cells, with increased expression of exhaustion markers like PD-1, result in a weakened anti-tumor response (Bader et al., 2024; Fang et al., 2023; Ringel et al., 2020). In obese or overweight patients presenting with ER + BC, a paracrine interaction between macrophages and preadipocytes, has been proposed to cause elevated levels of aromatase (enzyme converting androgens to estrogen) and the secretion of pro-inflammatory cytokines and adipokines which have a direct impact on the immune-tumor microenvironment (Savva et al., 2023). Furthermore, an enhanced recruitment and polarization of immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs), M2-like tumor-associated macrophages (TAMs), and regulatory T cells (Tregs), have been speculated to further suppress the body's immune surveillance (Y. Liu et al., 2023; H. Zhang et al., 2023).

In OC preliminary studies have suggested a link between obesity and metastasis in a mouse model of diet-induced obesity. The investigators in this study observed an enhanced tumor burden with an accompanying decrease in M1/M2 tumor-associated macrophage ratio (Y. Liu et al., 2023). An enhancement of tumor fibrosis was also observed in this model. The treatment with paclitaxel/carboplatin chemotherapy (standard of care for OC) resulted in significantly lowered response in HFD mice relative to low fat diet controls. The authors concluded that obesity impacts OC patient survival by altering M1/M2 tumor-associated macrophage ratio in the tumor microenvironment and through enhanced fibrosis on chemosensitivity (Y. Liu et al., 2023). Further studies have shown that metabolic reprogramming such as altered fatty acid and glucose metabolism in both tumor and immune cells can impair immune cell infiltration and function (Bader et al., 2024; Ringel et al., 2020). As previously mentioned, obesity-driven upregulation of FASN promotes fatty acid synthesis. This enhanced fatty acid synthesis can contribute to immunosuppression by altering CD8 T-cell and natural killer cell populations. Moreover, increased fatty acid synthesis may impair DNA repair mechanisms, thereby facilitating cancer progression, and it may also play a potential role in the development of drug resistance (J.-J. Hu et al., 2025; Lawrence et al., 1987). Reprogramming of glucose metabolism via G protein-coupled receptor 81 (GPR81) in BC has been associated with remodeling of the immune landscape in the tumor microenvironment. Resultant alterations in glycolytic capacity, dependent on the Hippo-YAP signaling pathway, caused lower lymphocytes $CD8^+$ T cells infiltration and an increase in the percentage of $FOXP3^+$ T cells (X. Li et al., 2023).

Lifestyle changes and diet control are an important part of T2DM therapy. In fact, short-term fasting protects tumor-bearing mice against the toxic effects of chemotherapy while enhancing therapeutic efficacy (de Groot et al., 2020). In a randomized clinical study, 131 patients HER2-negative stage II/III BC without T2DM received either a fasting mimicking diet or their standard diet for 3 days prior to and during neoadjuvant chemotherapy. Encouraging, certain aspects of pathological response were significantly improved in fasting mimicking diet arm and moreover less chemotherapy-induced T-lymphocyte DNA damage was observed. Further clinical studies will explore the potential benefits of fasting in cancer therapy (de Groot et al., 2020).

### 7.5. Microbiota, T2DM and hormonal fluctuations

Both type 1 and type 2 diabetes are closely linked to changes in the microbiome (Fig. 1). This dysbiosis may unfavorably alter both metabolic and signaling pathways within the body (Sharma and Tripathi, 2019). Microbiome mediated breaching of the intestinal barrier and/or tight junctions may relate to insulin resistance (Sharma and Tripathi, 2019). The metabolites derived from microbes may interact with receptors upon cardiac, hepatic and epithelial cells changing host physiology (Sharma and Tripathi, 2019). Obesity and low-grade inflammation are closely related to the gut microbiota and are relevant in cardiovascular disease (G. Yang et al., 2021). Patients with T2DM often manifest reduced diversity in gut microbiome, with a decrease in beneficial butyrate-producing bacteria such as *Faecalibacterium prausnitzii* and *Clostridium*, and an increasing balance towards harmful bacteria such as *Dorea, Sutterella*, and *Streptococcus* (Arora et al., 2021). Microbial metabolites, such as short-chain fatty acids, play a role in regulating insulin sensitivity and inflammation. A lower production of short-chain fatty acids is common in diabetes types and is linked to worse metabolic outcomes (Arora et al., 2021; Lin et al., 2025). Elevated levels of Proteobacteria in the gut microbiota are generally considered a

marker of imbalance (dysbiosis) in the microbial community associated with various health disorders. The Proteobacteria which may include many Gram-negative bacteria such as *Escherichia*, *Salmonella*, *Klebsiella*, and *Helicobacter*, which possess the endotoxin lipopolysaccharide (LPS) in their outer membranes, and this can activate TLR4 (Toll-like receptor 4), leading to systemic and local inflammation (Fig. 2). An elevation in Proteobacteria is reported independently in T2DM and in post-menopausal women (Arora et al., 2021; Lin et al., 2025). This may suggest an added effect of T2DM and hormone levels in inflammatory disease which is a risk factor for cancer incidence and progression. In a Danish study, five bacterial genera were differentially abundant between adult individuals with prediabetes, overweight, insulin resistance, dyslipidemia compared to age- and sex-matched individuals possessing normal glucose regulation (Allin et al., 2018). Further studies in the Danish and Indian populations confirmed inflammation signatures and a trans-ethnic microbiome associated with prediabetes (Pinna et al., 2021).

The diversity and abundance of specific microbial species determined by hormonal pathways or other mechanisms can influence the reproductive system ultimately affecting fertility, pregnancy outcomes and reproductive cancers. Both menstrual and lifetime sex-hormone fluctuations alter the microbial balance of both the reproductive tract and the body. Estrogen fluctuations have been reported to alter the microbial balance in the oral cavity, intestine, urethra and vagina. The transition from perimenopause to menopause is associated with health issues that go beyond the well reported osteoporosis and increased cardiovascular risk (which is influenced by gut microbiota and dietary patterns). These may include reproductive system disorders (e.g., uterine fibroid incidence), metabolic syndromes (obesity, T2DM), increased risk of urinary and reproductive tract infections, and changes in mental health (Adebamowo et al., 2023; Lin et al., 2025; Mehta and Manson, 2024). Dysbiosis in the GI-tract and reproductive tract have been associated with conditions such as PCOS, pre-eclampsia, endometriosis, reproductive cancers and gestational diabetes (B. Li et al., 2025). Demonstrating a role for changes in hormonal balance, several studies have examined the influence of oral contraception and the menstrual cycle on taxonomic composition of the gut microbiome (Terrazas et al., 2025). One study showed no differences in overall gut microbial diversity with hormonal contraceptive use when measuring at day 2 of the menstrual cycle yet observed changes in microbial richness but not composition during the luteal phase (day 21) (Terrazas et al., 2025). Compared to non-hormonal methods, the use of either combined oral contraceptive or levonorgestrel intrauterine devices did not demonstrate a difference in microbial diversity. Recent research is now suggesting that the composition and diversity of the vaginal microbiome is influenced by T2DM, raising implications for infection risk, mucosal immunity, and general reproductive health which may extrapolate to cancer risk (Kim et al., 2025). However, during menses a vaginal microbiome diversity was observed, followed by a subsequent expansion of *Lactobacillus* species correlating with serum estrogen levels during the follicular and luteal phases (Krog et al., 2022). Interestingly, the presence of *Lactobacillus* within the endometrial microbiota has been associated with favorable live births in fertility treated patients (Moreno et al., 2022). Suggesting a further hormonal influence, higher luteinizing hormone levels are associated with lower levels *Pseudomonas* (T. Yang et al., 2024). Further analysis of the gut microbiota in PCOS patients with dyslipidemia showed that *Faecalibacterium* and *Holdemanella* were negatively correlated with the lipid profiles (T. Yang et al., 2024). Early studies on the microbiome speculated that in hormonal-based changes might be related to the abundance of short-chain fatty acid-producing taxa (Brito et al., 2025).

Modification of the microbiota, both the intestine and the female reproductive tract, may be a therapeutic target for T2DM or targeted treatment of its consequences (G. Yang et al., 2021). The understanding of the role of the microbiome in the incidence, natural history and treatment of T2DM is still in its infancy. Long-term, continuous sampling studies will help us fully understand the relationship, not only on metabolic syndrome, but also the female reproductive cycle, cancer incidence, progression and treatment. Women undergoing HRT have been reported to experience a rise in the relative prevalence of beneficial gut bacteria (Leite et al., 2022). An intestinal microbiome-based therapeutic strategy outside specific benefits of fecal transfer, probiotics and lifestyle changes (Hsieh et al., 2018; G. Yang et al., 2021). An interesting study would be to understand better if the changes in microbiome associated with Metformin use may play a role in these drugs beneficial effects on both T2DM control and cancer incidence. However, the identified microbiome associations may be offering potential early indicators for individuals at risk of dysglycemia, T2DM and cancer (G. Yang et al., 2021).

## 8. Metformin in gynecological cancers: Potential mechanisms and clinical evidence

The principal drug-based diabetic treatment, Metformin, exerts pleiotropic effects on glucose metabolism and insulin sensitivity through the inhibition of hepatic gluconeogenesis and enhancement of insulin sensitivity (LaMoia and Shulman, 2021). Current interest centers on this drug's potential to both offer and enhance antineoplastic effects. (Vona-Davis and Rose, 2012).

### 8.1. Potential cellular mechanisms of metformin in cancer

Elevated insulin and glucose levels are well-recognized promoters of tumorigenesis as are increased circulating levels of IGF-1 (Calle and Kaaks, 2004; Hua et al., 2020). Metformin improves insulin sensitivity, resulting in lower blood glucose and insulin levels while IGF-1 concentrations in adults generally remain unchanged (LaMoia and Shulman, 2021; X. Yang et al., 2020). By reducing circulating insulin, metformin indirectly decreases the activation of both insulin and IGF receptor, potentially attenuating growth-promoting signaling pathways (Insin and Prueksaritanond, 2018; Rodriguez-Monterrosas et al., 2018). In addition to its metabolic effects, metformin modulates sex hormone homeostasis by lowering circulating estrogen levels and increasing SHBG concentrations (Barba et al., 2009; Campagnoli et al., 2013). At least in part, these effects appear to be mediated, by the inhibition of aromatase, an enzyme whose activity is paradoxically stimulated by insulin (Rice et al., 2009). The clinical relevance of SHBG is underscored by evidence showing that low circulating SHBG is a strong predictor of T2DM risk in women (Ding et al., 2009). Additionally, metformin has been reported to downregulate ERα expression in endometrial and BC cells, with some studies also suggesting a concomitant upregulation of progesterone receptor expression in both endometrial and BC (Berstein et al., 2011; Davies et al., 2017; J. Kim et al., 2016; Markowska et al., 2013; Y. Xie et al., 2011). Together, these effects shift the hormonal milieu toward a less proliferative state (J. Zhang et al., 2017).

Metformin has been shown to inhibit epithelial to mesenchymal transition (EMT), a key driver of cancer stemness, invasion, and metastasis (Veloso et al., 2022). This effect appears to be mediated by upregulation of epithelial markers such as E-cadherin and concomitant downregulation of mesenchymal markers and EMT-inducing transcription factors. Translational studies in EC tissue corroborate these findings, demonstrating EMT suppression and increased E-cadherin expression (Laskov et al., 2016). Furthermore, metformin exerts anti-inflammatory and antioxidant effects (Arbab et al., 2021), counteracting two hallmarks of tumor-promoting microenvironments (Sorriento, 2024).

The antitumor effects of metformin also extend to epigenetic regulation, including DNA methylation and microRNA (miRNA) biogenesis. Metformin induces genome-wide DNA methylation changes by decreasing intracellular levels of S-adenosylhomocysteine, an endogenous inhibitor of S-adenosylmethionine–dependent DNA methyltransferases, ultimately leading to enhanced DNA methylation (Cuyàs

et al., 2018). These epigenetic modifications have been associated with antitumor activity in ovarian endometrial, and BC cells (G. Tang et al., 2018; Zhong et al., 2017). In addition, metformin modulates the miRNA processing machinery by increasing the protein levels of the endoribonuclease DICER1 in both murine models and humans (Noren Hooten et al., 2016). DICER1 is a critical enzyme in miRNA biogenesis, and its reduced expression has been consistently associated with poor clinical outcomes in ovarian breast), and ECs (Khoshnaw et al., 2012; Merritt et al., 2008; Zighelboim et al., 2011).

Beyond its metabolic, anti-proliferative and epigenetic effects, metformin has also been reported to enhance antitumor immunosurveillance. It inhibits the suppressive activity of myeloid-derived suppressor cells (MDSCs) by downregulating CD39 and CD73 expression and ectoenzymatic activity thereby boosting $CD8^+$ T-cell cytotoxic function and strengthening antitumor immune responses (L. Li et al., 2018; G. Qin et al., 2018). Moreover, metformin suppresses programmed death-ligand 1 (PD-L1) expression in cancer cell lines (Park et al., 2024), potentially augmenting the efficacy of immune checkpoint blockade.

Metformin also exerts chemosensitizing effects. In OC, it has been reported to partially reverse platinum resistance and enhance paclitaxel sensitivity (Lengyel et al., 2015; Romero et al., 2012; Tossetta, 2022). In EC, clinical evidence is less consistent, though preclinical data and biological plausibility support a potential benefit (Ezewuiro et al., 2016; T. Y. Lee et al., 2018). Metformin directly interferes with oncogenic signaling by inhibiting STAT3 activation and downregulating HER2 expression and tyrosine kinase activity (Bashraheel et al., 2023; W. Zhang et al., 2023)). Given that HER2-positive BC represents one of the most aggressive subtypes these effects are particularly noteworthy (Swain et al., 2023). Consistently, metformin has been shown to reduce tumor growth and metastasis in HER2-positive BC cell lines and murine cancer models (Bashraheel et al., 2023).

### 8.2. Metformin in EC

Initial evidence suggested a favorable effect of metformin on EC outcomes in diabetic patients. A recent meta-analysis of observational studies reported reduced all-cause mortality and longer PFS among diabetic EC patients taking metformin (H. Xie et al., 2024), but several cohort/propensity-matched analyses found no clear survival benefit after adjustment for confounders (Al Hilli et al., 2016; Drevinskaite et al., 2024). However, improved OS and PFS was observed in diabetics patients with non-endometrioid EC who used metformin (Nevadunsky et al., 2014). In a further study of stage III-IV or recurrent EC patients, the median OS was 45.6 months for diabetic patients who used metformin compared to 12.5 months for diabetic patients who did not (Ezewuiro et al., 2016). These abovementioned positive results open the door to potential beneficial outcomes of Metformin in non-diabetic EC patients.

In an *in vivo* mouse model, metformin treatment did not change serum IGF-1 levels nor decrease tumor weight of the grafted Ishikawa endometrial cell line (Santos Fortes Dos Reis et al., 2025). In accordance, a randomized phase II/III study of with or without metformin together with standard of care (paclitaxel/carboplatin), reported that the hazard ratios for PFS and OS endpoints was not sufficiently decreased in the presence of metformin to justify continuing the trial (Bae-Jump et al., 2025). The PREMIUM (PRE-surgical Metformin In Uterine Malignancy) controlled Phase III Trial reported that standard diabetic doses of metformin did not reduce tumor proliferation in endometrioid EC awaiting hysterectomy. This study further casts doubt on the potential of Metformin in the primary and adjuvant treatment settings (Kitson et al., 2019).

### 8.3. Metformin in BC

In BC, the evidence is more heterogeneous. Some observational studies have shown that the use of metformin in diabetic patients with BC is associated with a significant reduction in overall mortality (G. H. Tang et al., 2018; Xu et al., 2015), while others suggest that this association requires a specific cancer setting (A. Y. Kim et al., 2015) and others do not report a benefit (Oppong et al., 2014). In contrast, some studies failed to demonstrate superiority with metformin treatment on BC mortality (Hosio et al., 2020). Interestingly, supporting the role of maintained metformin use during BC treatment, an increased risk of both overall and BC-specific mortality was observed in the 12 months after metformin discontinuation (Peeters et al., 2013). Neoadjuvant studies have reported higher pathologic complete response rates (24%) in metformin users compared with diabetic non-users (8%) (Jiralerspong et al., 2009)

However, the use of metformin outside the setting of T2DM is less positive. An ongoing phase II randomized clinical trial (METTEN) of neoadjuvant metformin in combination with trastuzumab and chemotherapy in women with early HER2-positive BC will be of great interest to determine whether the suggested correlation between metformin use and survival benefit in patients is truly causal (Martin-Castillo et al., 2018). However, a large (2533 patients analyzed) who were randomized in the adjuvant trial (MA.32) in non-diabetic steroid receptor positive patients were reported to have no benefit for adding metformin to improve invasive disease-free survival (Goodwin et al., 2022).

### 8.4. Metformin in OC

Encouragingly, a statistically significant protective effect with metformin use has been observed when restricting the analysis to the diabetic cohort. After adjusting for confounders, metformin use has been reported to be associated with a lower risk for disease relapse and disease-related death among OC patients (stage I to IV epithelial ovarian, fallopian, or peritoneal cancer) with T2DM (S.-B. Wang et al., 2017). A further study of the 341 OC patients reported that the PFS at 5 years was 51% for diabetic patients using metformin compared 8% for the T2DM patients who did not use metformin ($P = 0.03$). Interestingly, the OS at 5 years was 63%, 37%, and 23% for diabetic patients with metformin, nondiabetic patients, and the diabetic patients who did not use metformin, respectively (Romero et al., 2012). Also, when restricting to the diabetic cohort, there was statistically significant protective effect reported with metformin use in a population-based study in British Columbia, Canada (Kaur et al., 2024). I these numerous studies confined to diabetic patients the requirement of continuous metformin during standard of care OC has been a reoccurring observation (S.-B. Wang et al., 2017).

However, despite optimism in diabetic patients, just as observed in breast and ECs there is little evidence to convince the practicing oncologist that metformin should be used in non-diabetic patients (Micha et al., 2023; Romero et al., 2025).

As is becoming clear in the cancer community, all cancers are unique and thus Metformin (or other drugs) could be tailored to meet the individual needs of the ovarian (and other) cancer patient. *In vitro* studies have demonstrated that metformin may help overcome carboplatin resistance and reduce the pro-cancerous effects of platelets on cancer growth (Erices et al., 2013, 2017). In a mouse model of OC, Metformin significantly reduced tumor burden and immune infiltration into the tumor microenvironment (elevated $CD8^+$ T cell, Granzyme B and IFN-γ expression). Furthermore, metformin lowered PD-L1 levels and combined with PD-L1 inhibitors to further increase $CD8^+$ T cell activity (Q. Zhang et al., 2025).

## 9. Conclusion

This comprehensive analysis demonstrates that T2DM creates a complex molecular environment that promotes gynecological cancer development and progression through multiple interconnected signaling pathways. Understanding these mechanisms provides important insights

for developing targeted therapeutic approaches and identifying potential biomarkers for early detection and monitoring of disease progression in diabetic patients with breast and gynecological malignancies. In essence, the interplay of sex hormones, gonadotrophins and insulin signaling pathway and their effects on reproductive tissues is complex and context-dependent, leading to situations where the same hormone can have opposing effects in different tissues or even within the same tissue type. While it appears that overall genetic predisposition to T2DM does not strongly predict cancer risk, further investigation into whether T2DM alone in the absence of other confounding effects such as adiposity contributes to cancer risk should be targeted specifically in future clinical studies. For example, thrombocytosis is associated with increased likelihood of recurrence and increased risk of death in OC patients, while the coagulation system is reported to favor metastasis in several tumor types (Arce et al., 2019; Pergialiotis et al., 2024). A poorly explored area of clinical research is the association between the coagulation system in cancer progression, especially in the presence of diabetes. The complication of T2DM might worsen cancer outcome. Interestingly, while overall, no increased risk of cancer was found in women with type 1 diabetes, a reduced risk of BC has been observed together with an increased incidence and mortality of OC (Pliszka and Szablewski, 2024). Since these findings vary and are sometimes controversial, further studies are required to clarify the association, and moreover what common factors may be present between type 1 and 2 diabetes in causing this reproductive cancer incidence.

The presence of chronic inflammation and insulin resistance not only increases cancer risk but also exacerbates treatment resistance. Potentially drugs leading to weight-loss such as metformin could improve the efficacy of obesity-related cancer treatment to some extent. Intervention strategies targeting adipose tissue remodeling, lipid metabolism and leptin regulation also show potential clinical value, however more research is needed to clarify safety and efficacy. It will be interesting to observe how GLP-1 receptor agonists, currently in use used for T2DM and obesity, associate with risk and outcome of obesity-related cancers. This review agrees with the narrative that diabetes, especially T2DM is a driver of cancer incidence and progression. A repurposing of metformin and other existing antidiabetic drugs may help patient quality of life by both reducing cancer incidence and treating diabetic patients with diagnosed cancer. However, to date, clinical evidence is pointing to a beneficial effect of metformin use during treatment for breast, endometrial and OC patients only in the presence of existing diabetes. All cancers are unique, all cancer types have subtypes, and each subtype may have a different treatment. Moreover, all discussed female reproductive cancer so extremely sensitive to hormones that fluctuate throughout a women's lifetime. This observation may underline why promising *in vitro* data of metformin has not converted into improved PFS or OS for patients with reproductive tissue cancers (or cancer in general, with any therapy). Another aspect that is important to request in clinical practice and correlate with clinical outcome is the adherence of the patient to the medication. Furthermore, unfortunately, most clinical trials often do not present results by phenotype of the cancer under study cancer, nor the patients' stage of life.

Looking at T2DM and cancer from the other side of the coin, a study investigated the association between anti-estrogen therapy for BC and resulting T2DM incidence. This cohort of 2246 BC survivors saw 324 patients develop T2DM over a mean follow-up of just under six years (Hamood et al., 2018). The hazard ratio for T2DM incidence for tamoxifen (competitive anti-estrogen) use (HR, 2.25) was less pronounced than the use of aromatase (enzyme converting androgens to estrogens) inhibitors (HR, 4.27). The authors conclude that while active hormone therapy in BC is a significant risk factor for increased T2DM, cessation of treatment is not recommended because the survival benefits of hormone therapy outweigh the risks (Hamood et al., 2018). These studies further highlight the complex relationship between T2DM and cancer. Potentially, lifestyle modifications, such as diet modification exercise may minimize this increased risk in BC survivors. It would be interesting to see if early markers of T2DM could be screened in cancer patients and Metformin introduced to treatment regimens. Preliminary *in vitro* studies suggest that this might be an option (Mahmoudi et al., 2024).Certainly, there is consensus that women using metformin before cancer diagnosis can continue during subsequent treatment.

These studies bring to the fore both critical gaps and opportunities in future clinical trial design. Continuing with this line of thinking, as we move towards personalized treatment and prevention of obesity-diabetes-cancer progression we need better clinical studies designed from multiple perspectives. This review highlights a bias towards BC research, more than that of other reproductive tissues. As sex steroid hormones have often opposed actions between the breast, ovary and endometrium (among other reproductive tissues), this limits our true understanding and maybe interpretation of the best way to treat patients.

Further analysis of the underlying mechanisms of chronic inflammation, leptins and adipokines, metabolic reprogramming and changes of these processes throughout the lifespan of the women from adolescence-fertility-infertility will better present future therapeutic strategies. Hopefully, future mechanistic understanding and clinical trials will establish a more robust foundation for the intersection of T2DM and cancer. The medical community is already suggesting that cancer should be screened as part of routine T2DM assessment, and T2DM patients should undergo recommended age-appropriate cancer screenings to promote primary prevention from which many may benefit from early detection of malignancies (Suh and Kim, 2019).

## CRediT authorship contribution statement

**Cristian Espinoza:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Javiera Veas-Torres:** Writing – original draft, Investigation, Conceptualization. **Daniela I. Miranda:** Writing – original draft, Investigation, Conceptualization. **Gareth I. Owen:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used NCBI Pubmed and Consensus Ai as deep literature search engines to help identify publications related to the review. Once written, Chat GTP from Open AI and Anara were used to improve the organization, readability and language of the manuscript. The authors reviewed and edited all content and take full responsibility for the content of the published article.

## Funding

This work was supported by ANID-FONDAP-152220002, PROGRAMA ICM-ANID, ICN2021_045, ANID FONDECYT 1220586.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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