Clinical and Preclinical Studies of Inflammatory Cytokines Impact on Endometrial Versus Ovarian Cancer with Obesity: A Comprehensive Literature Review

Sabrina Afroz¹², Azma Parhin²³, Shamima Akter Somi S²⁴, Tarannum Y. Munir⁵⁶ and Salma Khan²⁶⁷*

¹Tri-City Medical Group, 11900 S Avalon Blvd # 100, Los Angeles, California, United States of America.
²Bangladesh Medical Association of North America, 20707 Hillside Ave, Jamaica, NY, United States of America.
³Department of Neurology, University of Washington, 325 9th Ave, Seattle, WA.
⁴Schervier Rehabilitation and Nursing Center, 2975 Independence Ave, Bronx, Newyork.
⁵University of California, San Diego, California, United States of America.
⁶Center for Health Disparities & Molecular Medicine, Loma Linda University School of Medicine, Loma Linda, California, United States of America.
⁷Loma Linda University, Cancer Center, Loma Linda University School of Medicine, Loma Linda, California, United States of America.


ABSTRACT

**Aim:** In obesity-linked cancers in women, especially endometrial and ovarian cancer pathways are linked to hormones, inflammation, immunological, and metabolic functions, defects in DNA repair, and alterations in gene function. However, a compilation of the literature on how these inflammatory pathways are linked to endometrial and ovarian cancers is lacking. We, therefore, discuss the pathways linked to obesity and discuss whether these can be exploited for therapeutic interventions in both in vitro and in vivo studies of these two important cancers in women.

**Methods:** A literature search was done from the last ten years and discussed the data on obesity-induced cytokines and female hormones, and their signaling pathways: in vitro, in vivo, and clinical trials in endometrial and ovarian cancer. We also determine the FDA-approved drugs currently used to enhance obesity research and the future niche in obesity research.

**Results:** We found some unique pathways which were linked to obesity-induced cytokines and hormones that are mainly correlated to the occurrence of endometrial cancers not as much as in ovarian cancers. Some clinical trials are ongoing for these endometrial cancer patient populations with overweight.

**Conclusion:** We summarized the literature on the expression of novel inflammatory markers for the prognosis, prevention, and potential therapy of endometrial cancer linked to obesity but not in ovarian cancer. Further studies are required in a larger population with ovarian cancer who are obese.
Keywords
Cytokines, Endometrial cancer, Ovarian cancer, Leptin, Adiponectin.

Introduction
In women, endometrial cancer is the sixth most common cancer in the world. It is a complex gynecological neoplasm with several clinical, histopathological, and genetic features. Its survival rate is high because it is often diagnosed at an early stage. Endometrial cancer has been the first tumor to be identified as obesity-linked cancer. A recent summary by the International Agency for Research on Cancer (IARC) reinforced obesity as a risk factor for many cancer types, including endometrial carcinoma [1]. In the United States, with >60,000 new cases and >11,000 deaths estimated for 2018 due to this neoplasm. In endometrial cancer, women with obesity have a six-fold increased risk of developing malignancy [2].

Ovarian cancer, on the other hand, is among the most common gynecologic neoplasms in females with a general 5-year survivability of 40 percent [3]. Epidemiological data support the contribution of adiposity/obesity to the carcinogenesis of ovarian cancer. Studies established the association between ovarian cancer and obesity [4]. The ovaries are the primary sex organ in the female, which produces progesterone and estrogen in premenopausal females. Three cell types in the ovaries can develop ovarian cancer: germ cells producing ova, stromal cells producing hormones, and epithelial cells lining the surface of the ovary. Among them, ovarian epithelial cell tumors are the most abundant (95%) [5]. About 98% of ovarian cancers are the following tumor types: low-grade serous carcinoma 3%, mucinous carcinoma 5%, clear cell carcinoma 19%, endometroid carcinoma 10%, and high-grade serous carcinoma 70%. The presence of excessive body fat enhances the risk of ovarian cancer [6,7]. In 2014, obesity and overweight were listed as possible associated risks for ovarian cancer by the American Institute for Cancer Research/World Cancer Research fund [8]. On the other hand, the United States Cancer Institute shows that ovarian cancer is not associated with obesity; however, a strong association between ovarian cancer and obesity cannot be ruled out [9].

Obesity is linked to many cancers. In our previously published paper, we found a clear correlation of obesity-induced inflammatory pathways in breast and thyroid cancer [10]. In this study, we discuss: 1) obesity-induced inflammation on endometrial and ovarian carcinogenesis \textit{in vivo} and \textit{in vitro} and their pathways, and 2) drugs available for clinical trials on obesity-induced inflammatory cytokines/chemokines. Our main goal was to provide a comprehensive literature search on the critical role of obesity in endometrial versus ovarian cancer and the mechanistic pathways of inflammatory cytokines. We also discussed the implications of these pathways for future treatment outcomes.

Obesity and Endometrial Cancer

Obesity influencing endometrial cancer
In 2010, meta-analysis announced that the combined risk ratio of developing endometrial cancer per 5 kg/m$^2$ increase in BMI above 27 kg/m$^2$ was 1.60 (95% CI 1.52e1.68). Because of secular trends in obesity worldwide, it is expected that endometrial cancer will increase its incidence in future years [11]. Two types of endometrial cancer have been described: type-I (estrogen-dependent), representing 85% of endometrial cancers, and type II (estrogen-independent). Type-I cancers are most commonly low-grade endometrioid tumors, occur more frequently in obese women, and are preceded by complex atypical hyperplasia. They are estrogen predominant and confined to the uterus. Conversely, type II tumors occur more frequently in thin, older patients with an atrophic endometrium; the histology is typically high-grade serous or clear cell with poor prognosis [2,11].

Obesity is a well-known causal factor for endomaterial cancer disease. The local and systemic effects of adipose tissue promote subclinical chronic inflammation. This inflammation plays a vital role in the pathogenesis of different tumors, including endometrial

Figure 1: Schematic representation of the association of obesity, cytokines, adipokines, with endometrial cancer. IL-1, interleukin-1; IL6, interleukin-6; TNF, tumor necrosis factor; NILCO, Notch, IL-1, and leptin crosstalk outcome.
cancer [12]. Many molecular and pathologic markers have been described for early diagnosis, prognosis, therapy response, and endometrial cancer monitoring [11,13].

Inflammatory pathways related to endometrial cancer
The fat cell is a true endocrine cell that secretes various peptides named (TNF-α and IL-6 and Adipokines-leptin, adiponectin, NILCO, etc.) [14]. The inflammatory cytokines secreted by visceral adipocytes regulate the process of angiogenesis and signaling pathways such as PI3K/AKT/mTOR, which result in altered pathogenesis of endometrial cancer [12]. The study involved 519 endometrial cancer cases and 964 age-matched controls in Alberta (Canada) from 2002 to 2006 with the following observations: endometrial cancer cases had persistently greater mean levels of TNF-α, IL-6, and CRP than controls in these predominantly postmenopausal women [15]. Other studies show among various inflammatory cytokines, the risk of endometrial cancer is mainly associated with the elevated level of leptin.16 The association between obesity-induced cytokines and endometrial cancer was shown in Figure 1.

Obesity-induced factors in endometrial carcinoma
Fujimoto et al. found higher vascular endothelial growth factor (VEGF) levels in well-differentiated cells. Moderately to well-differentiated cells, HEC-1A and Ishikawa cells expressed higher levels of VEGF mRNA. Thus, VEGF expression could be decreased during endometrial cancer progression with dedifferentiation and may contribute to the early process of tumoral growth via angiogenic activity. In the Ishikawa cell line, Insulin-like growth factor (IGF-I) failed to increase VEGF mRNA expression. The difference could be the result of large amounts of IGF-binding proteins (IGFBPs), especially IGFBP-3 secreted by Ishikawa cells, which inhibit the action of IGF-I. Here, the low affinity of insulin for the IGFBPs did not impede insulin action on Ishikawa cells. Thus, insulin might regulate the expression of other angiogenic factors by endometrial carcinoma cells, namely, VEGF B, VEGF C, VEGF D, or basic fibroblast growth factor (FGF), which could cooperate with VEGF to promote vascular growth. In summary, insulin could contribute to vascular growth due to its ability to regulate VEGF expression in endometrial carcinoma cells. Thus, the increased risk of endometrial carcinoma linked to morbid obesity might be partially due to hyperinsulinemia via the induction of VEGF expression, a potent angiogenic factor, by tumor cells [17].

Notch, IL-1, and leptin crosstalk outcome (NILCO)
The expression of NILCO mRNAs and proteins were analyzed in endometrial cancer from 29 African American and 120 Chinese patients. Results showed NILCO molecules were expressed higher in type II endometrial cancer, regardless of ethnic background or obesity status of patients. Besides, endometrial cancer from obese African American patients had higher levels of NILCO molecules than endometrial cancer from lean patients. Thus, obesity is associated with higher expression of NILCO in endometrial cancer.

Leptin-induced cell invasion depends on NILCO molecules and is halted by NILCO inhibitors. Hence, NILCO might be involved in tumor progression and could represent a new target/biomarker for type-II endometrial cancer [2,13]. NILCO is also a potent stimulus for leptin-induced tumorigenic activity (leptin-mediated angiogenic and proliferative activity) in endometrial cancer. A study indicated leptin’s involvement in more aggressive tumor types [2,18]. Immunohistochemical staining, western blot, and real-time PCR analyses confirmed that NILCO expression was higher in type II endometrial cancer. Therefore, NILCO expression in endometrial cancer may serve as a new tumor marker [18].

NF-κB signaling, TNF-α, RelA
Several studies showed that early-stage/grade endometrioid (obesity-related) endometrial cancer had upregulated glucose transporter GLUT6. Multiple members of the NF-κB signaling pathway are positively correlated with GLUT6 gene expression in this malignancy, including NFKB2, RelB, NFKBIE, and TNF-α. Further investigations identified RelA and TNF-α as positive regulators of GLUT6 expression in endometrial cells. The NF-κB signaling pathway has 2 distinct pathways: the canonical and noncanonical pathways. The activation of the canonical NF-κB signaling pathway (via TNF-α and RelA) may be a critical mediator of GLUT6 expression in obesity-related endometrial cancer. After stimulation by TNFα, GLUT6 may play a vital role in the response of endometrial cells to this pleiotropic inflammatory molecule. The noncanonical NF-κB signaling pathway is considered slow and persistent and is activated by a specific subset of TNFR superfamily members. NFKB2 encodes p52 and p100, of which p100 is the predominant product in most cell types. Phosphorylation-induced processing of p100 mediates the activation and nuclear translocation of the RelB/p52 complex. Interestingly, RelB expression is elevated in endometrioid endometrial cancers, and knockdown of RelB expression altered cell cycle regulatory proteins’ expression and inhibited the growth of human endometrial cancer cell lines (HEC1A and RL95-2) in vitro and in vivo. These findings reveal a novel relationship between GLUT6 and members of both the canonical and noncanonical NF-κB signaling pathways. However, there are multiple RelA binding sites within both human GLUT6 (SLC2A6) and mouse GLUT6 (Slc2a6) genes, and the ChIP Atlas database has identified the presence of RelA at the GLUT6 promoter in blood cells. Luciferase reporter assays have also confirmed that 2 RelA binding sequences within the human GLUT6 gene and 1 sequence within the mouse GLUT6 gene were induced in response to lipopolysaccharide (LPS); a known activator of RelA. These results suggest that RelA binds to the GLUT6 gene at multiple locations. In summary, this study revealed that the NF-κB signaling pathway is a potentially an essential regulator of GLUT6 expression in endometrial cells and may contribute to increased GLUT6 expression in endometrial cancer [19]. In Table 1, we show the mechanism of action of obesity-induced cytokines on endometrial cancer.
Mechanism non-inflammatory pathways [21]. IL-23) reverse the risk of endometrial cancer. There are also some (IL-13, IL-21), other proinflammatory markers (CCL3, IL-1B, and endometrial cancer. On the other hand, anti-inflammatory markers cytokines, and acute-phase proteins escalate the pathogenesis of obesity-related inflammatory biomarkers- adipokines, proinflammatory cytokines, and acute-phase proteins escalate the pathogenesis of endometrial cancer. On the other hand, anti-inflammatory markers (IL-13, IL-21), other proinflammatory markers (CCL3, IL-1B, and IL-23) reverse the risk of endometrial cancer. There are also some BMI-independent risk factors of endometrial cancer, which follow non-inflammatory pathways [21].

Table 1: Obesity-induced cytokines and adipokines in endometrial cancer.

<table>
<thead>
<tr>
<th>Cytokines/Adipokines</th>
<th>Mechanism</th>
<th>Types of Endometrial Carcinoma</th>
</tr>
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<tbody>
<tr>
<td>Leptin</td>
<td>• Increases TNF-α, IL-6. • Increases VEGF, which helps in angiogenesis and vascular permeability. • Bind to Ob-Rb activates jak/stat and AKT pathways.</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td>Adiponectin (decreases)</td>
<td>• No AMPK and P53 activation. • No mTor pathway inhibition.</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td>NF-κB, TNF-α RELA</td>
<td>Regulate of GLUT6 expression in endometrial cells through both the canonical and noncanonical signaling pathways</td>
<td>Endometroid endometrial carcinoma</td>
</tr>
<tr>
<td>The Transforming Growth Factor B(TGF-β)</td>
<td>Inactivated mutation of TGF-β gene: • Nonfunctional TGF-B cell surface receptors (TGFBR1/ALK5 and TGFBR2), which cause impaired endometrial hemostasis and tumor suppression.</td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>TNF-α, IL-6</td>
<td>• Induces C-reactive protein. • Stimulates estrogen biosynthesis and induces insulin resistance. • Increases the migratory and invasive capacity of cancer cells.</td>
<td>Type-I Endometrial cancer</td>
</tr>
<tr>
<td>NILCO (Notch, IL-1, and leptin crosstalk outcome)</td>
<td>Stimulate leptin-induced tumorigenic activity (leptin-induced angiogenic and proliferative activity) in endometrial cancer.</td>
<td>Type-II Endometrial cancer</td>
</tr>
<tr>
<td>NF-κB and signal transducer and activator of transcription (STAT3) pathways</td>
<td>Increased expression of midkines (MK) and decreased E-cadherin levels in EC cells.</td>
<td>This leads to the development and progression of EC</td>
</tr>
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</table>

Roles of leptin in endometrial cancer

Among several established endometrial cancer risk factors, particularly obesity is hypothesized to operate through this pathway by increasing proinflammatory cytokines such as TNF-α, IL-6, and C-reactive protein (CRP). After adjusting for age, all markers were associated with statistically significant increased risk for endometrial cancer; however, after multivariable adjustment, only the risk of CRP remained elevated. Similarly, upon stratification by cancer type, only CRP was associated positively with an increased risk for type I endometrial cancer. All markers were associated with an elevated risk for more rare and aggressive type II cancers; however, these findings were statistically nonsignificant, likely because of the small number of cases in this group. In conclusion, we found epidemiologic evidence for an association between CRP and the risk of endometrial cancer, which was slightly stronger for type I cancer [15].

Obesity-induced inflammatory cytokines and endometrial cancer in vivo (human) models:

Studies demonstrate the association between obesity-induced cytokines and endometrial cancer. Luminex measurement of IL-8 levels in three anatomical locations of endometrial cancer patients shows a difference in the level of IL-8 in different anatomical sites. IL-8 level is highest in the omental depot and lowest in the retroperitoneal depot in endometrial cancer patients. IL-8 is a proinflammatory chemokine whose expression correlates with the angiogenic, tumorigenic, and metastatic potential of several in vivo tumor models. Increasing IL-8 levels have been linked with the increase in obesity and waist circumference, as well as to endometrial cancer progression, suggesting that IL-8 is an important marker to investigate in future research [20].

In another study, endometrial cancer risk was most pronounced among obese women with the highest inflammation score. Obesity-related inflammatory biomarkers- adipokines, proinflammatory cytokines, and acute-phase proteins escalate the pathogenesis of endometrial cancer. On the other hand, anti-inflammatory markers (IL-13, IL-21), other proinflammatory markers (CCL3, IL-1B, and IL-23) reverse the risk of endometrial cancer. There are also some BMI-independent risk factors of endometrial cancer, which follow non-inflammatory pathways [21].

Sharma et al. found that when endometrial cancer cell lines were treated with leptin, cell proliferation increased via activation of STAT3 and ERK2 signaling pathways via JAK/STAT activation. Additionally, leptin increased the invasion of endometrial cancer cells, which was inhibited by a JAK/STAT inhibitor (AG490) and PI3K inhibitor (LY294002). Leptin has been found to regulate angiogenic activity in a dose-dependent manner in endometrial carcinoma, with leptin-mediated signaling pathways including JAK2, PI3K, and mTOR [2].

Leptin level highlights the grading and staging of endometrial cancer. Some studies exhibit a higher stage of endometrial cancer with lower grade differentiation being associated with elevated leptin levels. It also inhibits cancer cell apoptosis, which leads to cancer cell invasion, infiltration in the lymph vessels, metastasis to the lymph nodes. Therefore, elevated levels of leptin and its receptors are an indicator of poor prognosis.

Endometrial cancer is a hormone-dependent neoplasm. Leptin is known to activate aromatase, an enzyme catalyzing the transformation of androstenedione to estrone in adipose tissue. The study demonstrates the effect of estrogen hormone in the initiation and progression of endometrial cancer. Increased estrogen level has a direct correlation to developing endometrial cancer. Leptin increased estrogen levels by activating aromatase P450 in endometrial fibroblasts. Besides aromatase activation, leptin also...
enhances cellular proliferation and angiogenesis by acting as a growth factor. Another study shows that serum concentrations of leptin and Ob-R in endometrial cancer are higher than in controls with normal endometrium [22].

Leptin modulates different inflammatory cytokines such as VEGF, LIF, IL-1β, IL-6, TNF-α, resistin, etc., and their corresponding receptors. VEGF, IL-1β increase in benign endometrial cells. On the other hand, IL-6, TNF-α, resistin elevates in endometrial cancer cells [23]. Leptin is capable of inducing the production of IL-6, IL-12, and TNF-α by macrophages. The association between leptin and endometrial cancer was shown in Figure 2.

**Figure 2:** Schematic representation of leptin Pathway in Endometrial Carcinoma. OBR, leptin receptor; VEGF, vascular endothelial growth factor; LIF, lymphokine inhibitory factor; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-12, interleukin-12; TNF-α, tumor necrosis factor-α.

**IL-6:** Progressive infiltration of macrophages in obese patients leads to the secretion of proinflammatory cytokines such as IL-6 and TNF-α; these induce CRP, an acute-phase protein. In endometrial cancer, they stimulate estrogen biosynthesis and induce insulin resistance [24]. CRP is associated mainly with an increased risk for type I endometrial cancer [15].

**TNF-α** has also been suggested to increase the migratory and invasive capacity of cancer cells; class 1 cytokines and PGE2 may induce aromatase expression in stromal cells in obese women with endometrial cancer [11].

**Role of adiponectin in endometrial cancer**

Adiponectins are biologically active molecules that assist in angiogenesis, adipose tissue metabolism, and inflammation, and modulate tissue sensitivity for insulin. Adiponectins are produced in adipose tissue, so an abnormal amount of this tissue leads to impaired levels of these factors [25].

A study showed plasma levels of adiponectin were 53% higher in nonobese subjects compared to obese subjects. The results also showed that adipose-derived stem cells (ASCs) have a stimulating effect on the endometrial tumor cells with a decrease in the intracellular level of adiponectin and associated with proliferative status. Similar results have been reported by other studies that have shown the role of leptin secreted by adipose cells in stimulating the secretion of VEGF, IL-1β, and leukemia inhibitory factor (LIF) in endometrial cancer cell lines. Adipose-derived stem cells (ASCs) have different sources such as omentum and subcutaneous tissue. The omentum is an important resource for endometrial cancer progression.

The low level of adiponectin is associated with endometrial cancer could be explained by its antiangiogenic properties. Adiponectin inhibits angiogenesis both in vivo and in vitro [25]. It has also been reported in the literature that adiponectin inhibits tumor growth by suppressing the development of neovessels in rats. These findings support the idea that low levels of adiponectin are associated with increased angiogenesis required for the development of endometrial cancer.

Klopp et al. have shown that adipose cells derived from the omentum stimulate vascularization in endometrial cancer. Adipose-derived stem cells (ASCs) play a role in the adipose tissue, which functions as a stem cell reservoir. Other studies have shown a pericapillary location of migrated adipose-derived stem cells (ASCs) in tumors. This suggests that adipose-derived stem cells (ASCs) could stimulate tumor progression through angiogenesis. In contrast, adiponectin, an adipokine that increases the sensitivity of cells to insulin and is elevated in lean individuals, may protect against cancer [26].

Moon et al. hypothesized that adiponectin mediates activation of the adenosine monophosphate-activated protein (AMPK) pathway by LKB (Liver Kinase B), an adapter molecule with growth-suppressing effects on tumor cells. Adiponectin-mediated AMPK activation inhibits cell proliferation, colony formation, adhesion, and invasion properties of endometrial cancer cells. In vitro and in vivo studies have shown that adiponectin inhibits angiogenesis. Furthermore, in a mouse model, adiponectin has been observed to suppress tumor growth by decreasing the neovascularization process. These findings give solid support to the notion that low adiponectin concentrations may allow angiogenesis, which leads to the development of endometrial cancer. Similarly, circulating, and periitoneal fluid levels of angiogenic factors, such as angiogenin, hepatocyte growth factor, and VEGF are increased in women with endometrial cancer. Decreased expression of cyclin D1 and E2, different progrowth regulators of the cell cycle, and the signaling proteins ERK1/2 and Akt are all associated with PTEN (phosphatase tensin homolog, tumor suppressor gene) activity and LKB1-mediated adiponectin signaling in inhibiting endometrial carcinogenesis. These results suggest that additional studies are needed to determine the significance of adiponectin and adiponectin receptors as prognostic markers and therapeutic targets in endometrial cancer [27].

**Obesity-induced inflammatory cytokines and endometrial cancer in vitro models**

A study is conducted in vitro to compare endometrial cancer cell proliferation, migration, and survival rate between adipocyte-conditioned medium (ACM) and preadipocyte-conditioned...
medium (PACM). The result reflects the elevated levels of cytokines, including VEGF signaling pathways in ACM. VEGF protein expression was upregulated in visceral adipose tissue (VAT) in obese patients, which is correlated with increased tumor growth in vivo xenograft model [17].

In another study, omental adipose-derived stem cells (O-ASC) are isolated from the omental adipose tissue of eight patients who are diagnosed with EC aged from 35 to 56 years. According to the patients’ BMI, the O-ASC is divided into two groups: the obesity group (BMI ≥ 30) and the standard group (18.5 < BMI ≤ 24.9). A broad-spectrum cytokine antibody array is used to measure 62 paracrine cytokines secreted by the O-ASC. MTS assays, direct and indirect coculture assays, are used to assess O-ASC’s effects on the proliferation and migration of Hec-1A (estrogen receptor−/progesterone receptor−) and Ishikawa (estrogen receptor+/progesterone receptor+) endometrial cancer cells [28]. Eight samples of O-ASC are successfully isolated, including four samples in the obesity group and four in the normal group. The O-ASC displayed typical characteristics of mesenchymal stem cells and possessed similar secretory functions as 26 cytokines are identified in the conditioned medium of O-ASC based on cytokine antibody array. The proliferation of Ishikawa cells is gently stimulated by O-ASC in the two groups whereas without any effect on Hec-1A cells. Both horizontal and vertical migrations of EC cells are promoted by O-ASC.

Obesity, a state of chronic inflammation, is associated with poor fertility and low implantation rates and is a well-documented risk factor for endometrial cancer. Adipokines, such as TNF-α, play an important role in the initiation of endometrial cancer. The study aimed to evaluate the in vitro effects of human adipocyte cells (SW872) on the growth of endometrial glandular epithelial cells (EGE). The cell proliferation and expression of cell growth proteins proliferating cell nuclear antigen, cyclin D1, cyclin-dependent kinase-1, and apoptotic markers (BCL-2 and BAK) in human EGE cells co-cultured with SW872 cells. EGE cells are also evaluated in SW872-conditioned media neutralized with an anti-TNF-C antibody. A significant increase in EGE cell proliferation is observed in both SW872-conditioned media and coculture (P < 0.05). An upregulation of proliferation markers PCNA, cyclin D1, CDK-1, and BCL-2 and decrease in BAK (P < 0.05). Neutralization of SW872-conditioned media using anti-TNF-α antibodies reversed EGE cell proliferation as indicated by BCL-2 expression. In conclusion, adipocytes have a potent proliferative paracrine effect on EGE cells, which may be, in part, mediated via TNF-α. Further understanding of the role of obesity in endometrial carcinogenesis should lead to better Preventive and therapeutic strategies [29].

Obesity-induced inflammatory cytokines in the preclinical model

Vitamin D3 has been proposed to reduce the risk of endometrial cancer. It exerts the antitumor effect by regulating the expression of genes for osteopontin and E cadherin. Osteopontin is a glycoprotein that plays a crucial role in the abnormal proliferation of tumor cells and subsequent metastasis. It keeps the cells alive after their detachment from the primary site. On the other hand, E cadherin maintains cell adhesion and prevents invasion and metastasis of cancer cells. Vitamin D3 is also thought to decrease estrogen receptor (ER) expression on endometrial cells, thus preventing estrogen-mediated abnormal cell proliferation and tumor growth.

A study on obese mouse models treated with Vitamin D3 revealed that it prevented the development of cancerous and pre-cancerous lesions of the endometrium, decreased osteopontin, and increased E cadherin levels. However, it did not show any effect on estrogen receptor expression on endometrial cells. This preclinical model’s promising results should be explored further in the clinical model to invent novel targeted therapies for endometrial cancer [30].

Obesity-induced inflammatory cytokines in Clinical trials

Chemotherapy

The study exhibited in obese endometrial cancer patients, tumor vasculature and VEGF-mTOR activity are elevated compared to non-obese endometrial cancer patients. The results provided evidence that VEGF-mTOR signaling drives endometrial cell growth leading to hyperplasia and cancer [17]. Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF). The addition of bevacizumab to chemotherapy offers meaningful improvements in progression-free survival [16].

Metformin

Metformin has a significant effect on cellular energy production and usage. It also interferes with intercellular and hormone-based interactions. Based on these criteria, metformin now considers a component of combination therapy with other treatment modalities impeding the tumor metabolic pathways [31].

Metformin exerts modulating effects on progesterone receptors in endometrial cancer, inhibiting both endometrial cell proliferation and aromatase expression. This explains this biguanide’s potential role in the prevention and treatment of endometrial cancer [11].

Metformin decreases systemic insulin and IGF-1 levels, which are strongly mitogenic and induce cancer cell proliferation and metastasis by activating the PI3K/AKT/mTOR pathway, which is called insulin-dependent (indirect) effects. Additionally, Metformin inhibits the activation of the PI3K/AKT/mTOR and MAPK/mTOR pathways through AMPK-dependent and AMPK-independent pathways, which is also known as insulin’s direct effect. This leads to decreased protein synthesis and cell growth and increased autophagy and apoptosis [32].

Metformin has been investigated as a therapeutic agent given its inhibition of this pathway and indirect inhibition of downstream leptin signaling. Metformin directly activates AMP-activated protein kinase, which then phosphorylates tuberous sclerosis 2 protein and subsequently inhibits mTOR signaling, leading to a reduction in cell proliferation. Metformin also indirectly...
affects cell growth by increasing insulin sensitivity, causing increased intracellular glucose uptake and decreased insulin levels peripherally. Metformin also has been found to cause leptin sensitivity via upregulation of LEPR expression.

In a prospective trial by Soliman et al., patients with newly diagnosed endometrial cancer underwent pretreatment blood draw and endometrial biopsies, then were treated for ≥7 days with Metformin, and subsequently underwent posttreatment blood draw and definitive surgery. After treatment, serum IGF-1, omentin, insulin, C-peptide, and leptin levels were significantly lower. Posttreatment tissue analysis indicated decreased phosphorylated AKT, phosphorylated S6rp, and phosphorylated p44/42MAPK. A systematic review of the literature analyzing 19 different studies supports Metformin as a potential adjuvant therapeutic agent in endometrial cancer, Metformin was found to reverse atypical endometrial hyperplasia in normal endometrium, decrease cell proliferation from 51.9% to 34.5%, and increase overall survival in metformin users with endometrial cancer. Currently, a Gynecologic Oncology Group clinical trial is in progress, randomly assigning patients with advanced or recurrent endometrial cancer undergoing standard chemotherapy with or without Metformin as adjuvant therapy [2].

Conclusion
Based on the review, obesity happens to be one of the significant risk factors for developing many cancers, including endometrial carcinoma [1]. The relationship between obesity, enhanced cytokine activity, and adipokines (e.g., leptin, adiponectin) contributes to the development of endometrial cancer from the above discussion. A review of in vivo, in vitro, and preclinical models was also done to illustrate the link. The role of metformin and bevacizumab to treat this cancer is also discussed. The identification of inflammatory biomarkers released by adipose tissue and alterations in their pathway in endometrial cancer’s pathogenesis could help improve diagnostic accuracy, identifying targets of therapy, suggesting good lifestyle behaviors [12]. Future studies are required to explore the precancer inflammatory marker level and how it is essential for the detection, prevention, treatment, and prognosis of endometrial carcinoma [15].

Obesity-linked inflammatory markers in ovarian cancer

Obesity influencing Ovarian Cancer
Globally, ovarian cancer is ranked seven out of the most common cancers in females and ranked second for fatal gynecological malignancies with approximately 0.15 million deaths and 0.23 million new cases back in 2012 [33]. A mild reduction in ovarian cancer has been observed in the United States of America from 1998 to 2008. It was probably because of a decrease in using postmenopausal hormone therapy [34]; however, an increase in the occurrence of obesity was overserved during the same time frame [35]. This rise in the prevalence of obesity supports a relationship between ovarian cancer and obesity. Ovarian cancer is a heterogeneous disorder having histologically different subtypes, demonstrating various development pathways [36]. Such etiological heterogeneity may cover the possible role of obesity in the formation and progression of ovarian cancer.

Inflammatory pathways related to ovarian cancer
Apart from other functions, adipose tissue in the body functions as an endocrine organ that can affect physiological processes in the body, i.e., immunity, metabolism, hemostasis, and reproduction [37]. Based upon this close association of adipose tissue with altered normal physiology, it has been considered as an important risk factor for ovarian cancer, deregulation of sex hormones, and bioavailability of growth factors, e.g., insulin-like growth factor-I (IGF-I) [38]. Table 2 represents the list of obesity-induced cytokines and their actions on ovarian cancer.

Table 2: Different obesity-related cytokines in ovarian cancer.

<table>
<thead>
<tr>
<th>Cytokines/adipokines</th>
<th>Mechanism/pathways</th>
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<tbody>
<tr>
<td>Leptin</td>
<td>• Excessive growth in ovarian cells by mitogen-activate protein kinases (MAPKs).&lt;br&gt;• Suppression of inhibitors through increased expression of cyclin D and A.&lt;br&gt;• Inhibition of apoptosis by decreasing Bad, TNFR1, caspase-6 protein expression.&lt;br&gt;• Activation of ERK, JNK pathway that promotes MMPs, thus playing a vital role in tumor invasion and metastasis.</td>
</tr>
<tr>
<td>IL-6 and TNF-α</td>
<td>• Promotes inflammation and plays a role in tumor genesis.</td>
</tr>
<tr>
<td>IGF-1</td>
<td>• Mitogenesis&lt;br&gt;• Inhibition of apoptosis</td>
</tr>
<tr>
<td>Monocyte chemoattractant protein-1 (MCP-1)</td>
<td>• Tumor formation&lt;br&gt;• Distant metastasis</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>• Malignant transformation of ovarian cells.&lt;br&gt;• Angiogenesis</td>
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Researchers have demonstrated a direct relationship between obesity and increased blood levels of estrogen and androgens after menopause [39]. High levels of sex hormones in the body have been related to the pathogenesis of ovarian carcinoma [40]; increased estrogen concentration enhances epithelial cell growth in the ovary [41]. A recent study showed that increased estrogen concentration is not a direct risk factor, although it has a positive association with another endometrioid subtype. Although epidemiological evidence is deficient, the relationship of long-term use of estrogen with ovarian cancer is consistently observed [42].

Another essential gynecological disorder, polycystic ovarian syndrome (PCOS), is characterized as an important risk factor for ovarian carcinoma. Although this evidence is not supported by some studies [42], a recent study showed the association of increased concentration of sex hormones with low-grade serous tumors only [43]. Overall, androgens may act as a risk factor for different subtypes of ovarian cancer, thus, supporting the examination of ovarian cancer with histologic subtypes.

Insulin-associated pathways are also altered by obesity, e.g., enhanced blood levels of IGF-I. Research has shown that increased blood levels of IGF and its receptors promote ovarian cancer cell
growth while inhibiting the IGF-signaling pathways with anti-cancerous properties [44]. This evidence is not supported by many epidemiological studies [42], but some have shown a direct link between increased circulating levels of IGF and ovarian cancer. However, other studies show an increased concentration of IGF-1 and its receptor in patients with ovarian cancer [45]. Ovarian cancer patients with a very poor prognosis showed increased levels of IL-6 and TNF-alpha [46]. Ovarian cancer risk has also been attributed to high blood levels of C-reactive protein (CRP), especially in obese women [43].

Lipid metabolism and synthesis are also dysregulated in ovarian tumors [47]. The association of circulating blood levels of cholesterol, HDL, and LDL has been studied as risk factors for ovarian cancer, but no link was observed for cholesterol [48]. In another study, three-time higher risk for ovarian cancer was found due to increased cholesterol [49]. A registry study observed no link of HDL or cholesterol with ovarian cancer [50]. Nonetheless, a positive relation between pre-diagnostic LDL with ovarian cancer was demonstrated [51]. An 8-fold increased uptake of radiolabeled LDL was observed in patients with ovarian tumors undergoing gynecological surgery compared to normal tissue / benign tumors [52]. Ovarian cell line proliferation can be enhanced by LDL, thus indicating the close association of LDL with ovarian cancerous cell growth and proliferation. Recent research has shown that the use of statins, which controls the cholesterol level, showed a lower risk of ovarian cancer [53].

**Obesity-induced factors in ovarian cancer**

Abnormal secretion of hormones like cytokines adipokines from the adipose tissue, especially Leptin, plays vital roles. Overexpression of leptin and its transmembrane receptor(obR) has been related to an aggressive form of ovarian tumor [54].

The ovarian tumor arises from one of the following three components: surface epithelium, stromal cells, and germ cells. Most of the tumors arising from surface epithelial cells are subdivided into five classes: high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous cancers [34]. Among the primary tumors arising from ovarian surface epithelium-borderline serous, low grade invasive serous, invasive endometrioid, and invasive mucinous tumors’ the risks were greater with higher body weight/BMI [55]. Adipose tissue’s role in different cancers and active influence in the tumor microenvironment was shown. Adipocytes that are activated can be transformed into cancer-associated adipocytes and ultimately produce free fatty acids and nutrients for the cancer cells [56] as shown in Figure 3.

Reactive oxygen species (ROS) from inflammatory cells, mainly lymphocytes and macrophages, can function as tumor promoters. Additionally, adipocytes, secrete adipokines, and other cytokines facilitate tumor growth [56]. Prolinflammatory cytokines like TNF-α, IL-6, IL-8, MCP-1, and ROS from the adipocytes play important role in tumorigenesis [57]. Insulin resistance promotes carcinogenesis via IGF-1 and causes mitogenesis as well as inhibits apoptosis [58].

Chronic hypoxia in adipose tissue of obese individuals promotes tumor growth by hypoxia-inducible factor (HIF) pathway. Stromal tissues from activated adipocytes helps in the distant spread of tumor cells by promoting angiogenesis [59]. Another study found patients with synchronous primary endometrial and ovarian cancer in premenopausal, nulliparous, and obese. The hyper estrogenic state is thought to be a common cause [60]. There are direct nutritional and physiological effects of leptin on both ovaries and follicles via JAK/STAT, MAPK/ERK, and PI3K pathways [61].

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**Figure 3:** Schematic representation of adipocyte function in ovarian cancer oncogenesis. IGF-1, insulin-like growth factor-1.
Obesity-induced inflammatory cytokines and ovarian cancer

in vivo (humans) study

Although the influence of obesity-related factors in ovarian carcinogenesis is supported by in vitro studies, epidemiological studies failed to show a direct association of obesity with increased risk for ovarian cancer. More intense research is required for the understanding of obesity-linked pathways in ovarian cancer.

Role of leptin in ovarian cancer

Leptin treatment caused excessive growth in different cell lines of ovarian cancer by mitogen-activated protein kinases (MAPks) in the BG-1 ovarian cancer cells. Leptin receptor isoforms are expressed in IOSAE-80, PC, BG-1, OVCAR3, SKOV-3 cells. Growth is also stimulated in BG-1 cells by ERK1/2 and inhibition of the P38 MAPK pathway [62]. Leptin's impacts on the stimulation of cells in the S and G2/M phases by upregulation of of cyclin D and A were noted. Leptin also inhibited p21WAF1/CIP1 protein as well as suppressed both extrinsic and intrinsic apoptotic pathways, decreasing Bad, TNFR1, and six caspase protein expression [63].

Ghasemi et al. found adipose tissue-secreted leptin-adipokines facilitated cellular invasion and distant metastasis. Members of the matrix metalloproteinase family MMP-7, MMP-2, MMP-9 are promoted by the activation of ERK, JNK pathways. These promoted MMPs then degraded the extracellular matrix and thus play a crucial role in the invasion of cancer cells and metastasis. This study also included urokinase plasminogen (uPA) that can contribute to tumor cell migration by degrading ECM components. 

Role of adiponectin in ovarian cancer

Adipose tissues are formed by lipid-containing adipose cells called adipocytes, vasculature, immune cells, loose connective tissue containing collagen fibers, and preadipocytes. Two types of adipose tissue do exist in the human body, i.e., brown and white adipose tissue. White adipose tissue preserves energy in the form of triglycerides and is primarily present in the visceral pads and subcutaneous parts of the body, while brown adipose tissue is associated with heat production by uncoupling the respiratory chain in the mitochondria. Although brown adipose tissue is primarily present in infants and neonates, recently, it has been detected in the visceral fat of the adult [69]. Generally, 5% of the adipose tissue is distributed as visceral fat present around organs such as lymph nodes, kidneys, and the heart. The adipose tissue is present 10% of those in the omentum and 85% in the subcutaneous space [70].

Adipokines (also called adipokines are the proteins released by adipocytes, which can act systemically such as via endocrine function) and locally (such as paracrine or autocrine) to locally impact metabolism, immune response, and steroidogenesis. Adipocytes are thought to secrete a basal amount of these effector proteins, making this a vital tissue with key immunomodulatory, metabolic, and endocrine roles. A recently published study has associated adipokines with the growth and progression of endometrial and ovarian carcinomas. For each 5 kg/m² rise in body mass index, the risk of developing ovarian cancer rises by a factor of 1.03 compared to 1.52 for endometrial cancer [38].

Obesity-induced inflammatory cytokines and ovarian cancer

in vitro models

Preovulatory follicles from goose ovarian cells cultured with leptin showed a proliferative and antiapoptotic role via PI3K/AKT/mTOR pathway. Further analysis showed leptin increased Cyclin D3, Cyclin D2, Cyclin D1, and BCL-2 expression while
also decreasing P21 and caspase-3 expression. S6K, PI3K, p-S6K, Akt1, mTOR, Akt2, and Raptor pathways were enhanced by leptin treatment. After blockade of the PI3K/AKT/mTOR pathway, a conclusion was drawn that leptin’s downstream effect was reduced by either 20 μM LY294002 (a PI3K inhibitor) or 10 μM rapamycin (an mTOR inhibitor) [71]. A separate study found that ovarian estradiol release was stimulated by leptin and Ob-R expression also induced in the granulosa cells of the ovarian follicles [72].

Obesity-induced inflammatory cytokines in the preclinical model
Metformin arrests cancer growth by inhibiting cellular proliferation and anti-inflammatory effects on cancer cells. It stimulates AMPK, an inhibitor of protein synthesis, which ultimately represses cellular proliferation. The effect of metformin in ovarian cancer was observed in mouse models. The results showed a dose-dependent decrease of ovarian cancer cell proliferation after administering metformin. Commonly used neoadjuvant chemotherapeutics for ovarian cancer are carboplatin, paclitaxel, bevacizumab, etc. Maintenance chemotherapeutics administered after first-line treatment with platinum, doxorubicin, paclitaxel, erlotinib [50,72]. Another in vitro study showed an increase efficacy of chemotherapeutic agents such as cisplatin, paclitaxel with metformin [19,22].

Melatonin
Melatonin is another available option to co-administer along with radiotherapy and chemotherapy to escalate the efficacy of them. Melatonin with chemotherapeutics increases the apoptotic action of cisplatin, the most used chemotherapeutic agent. It also protects normal ovarian cells from the destructive nature of cisplatin and improves fertility. Besides, melatonin enhances the therapeutic effects of radiotherapy and protects normal cells from DNA damage caused by ionizing radiation [73,74].

Conclusion
Regarding ovarian cancer, the risk of obesity-associated ovarian cancer varies, which depends on the subtypes of cancer. Current studies advocate a strong link between obesity with ovarian cancer in premenopausal females. Notably, the pattern and strength of such relations seem to differ for case-control study designs versus prospective cohorts. Additional studies are required to further clarify the role of obesity in the risk assessment of ovarian cancer and survival. Consortia, which gather primary data from studies to perform pulled investigations using harmonized variables, will be vital to enhance the sample size. In summary, adiposity is not a potentially stronger risk factor for ovarian cancer, specifically compared to hormonal and reproductive aspects; future studies are vital to detect specific populations and ovarian cancer subtypes for which weight reduction may be most useful.

Acknowledgements
We would like to thank McPherson summer program for supporting the scholar (RD). We also thank Dr. MD. Mamoon for making it possible to recruit SA, AP, and SAS in the BMANA Research fellowship program.

List of Abbreviations

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