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## REVIEW

# The impact of obesity and adipokines on breast and gynecologic malignancies

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## Abstract

The link between obesity and multiple disease comorbidities is well established. In 2003, Calle and colleagues presented the relationship between obesity and several cancer types, including breast, ovarian, and endometrial malignancies. Nearly, 20% of cancer-related deaths in females can be accounted for by obesity. Identifying obesity as a risk factor for cancer led to a focus on the role of fat-secreted cytokines, known as adipokines, on carcinogenesis and tumor progression. Early studies indicated that the adipokine leptin increases cell proliferation, invasion, and inhibition of apoptosis in multiple cancer types. As a greater appreciation of the obesity–cancer link has amassed, we now know that additional adipokines can impact tumorigenesis. A deeper understanding of the adipokine-activated signaling in cancer may identify new treatment strategies irrespective of obesity. Moreover, adipokines may serve as disease biomarkers, harnessing the potential of obesity-associated factors to serve as indicators of treatment response and disease prognosis. As studies investigating obesity and women's cancers continue to expand, it has become evident that breast, ovarian, and uterine cancers are distinctly impacted by adipokines. While complex, these distinct interactions may provide insight into cancer progression in these organs and new opportunities for targeted therapies. This review aims to organize and present the literature from the last 5 years investigating the mechanisms and implications of adipokine signaling in breast, endometrial, and ovarian cancers with a special focus on leptin and adiponectin.

## KEYWORDS

adipokines, breast, cancer, endometrial, obesity, ovarian

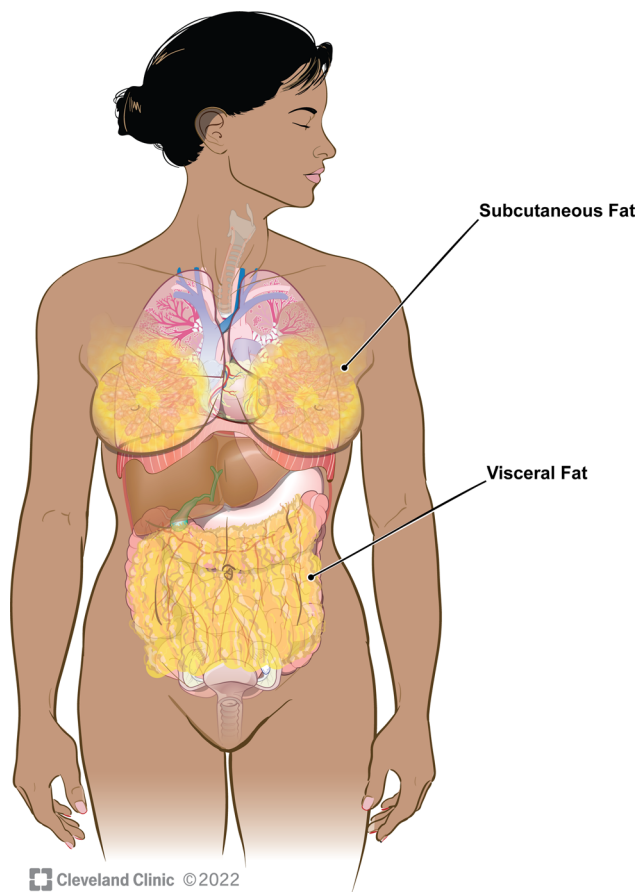
## INTRODUCTION

Obesity is a leading public health crisis, with rates of obesity increasing at an alarming rate over the last several decades. Projections estimate that by 2030, over 50% of the United States population will be obese with a 130% increase in people with a body mass index (BMI)

of greater than 40 kg/m<sup>2</sup>.<sup>1,2</sup> Obesity is a known risk factor for many disease states, including cardiovascular disease, type 2 diabetes mellitus, hypertension, and dyslipidemia.<sup>3</sup> Obesity has also been linked to cancer, including malignancies impacting the female sex.<sup>1</sup> This includes postmenopausal breast cancer, as well as endometrial and ovarian cancers.<sup>1,2,4</sup> Several mechanisms linking obesity to cancer have been

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**FIGURE 1** Adipose tissue depots are primarily involved in cancers impacting the female sex. The two main adipose tissue depots are visceral and subcutaneous. Differential cytokine profiles may alter their impact on different target organs. Subcutaneous breast adipose primarily regulates the tumor microenvironment in breast cancer, whereas visceral adipose tissue more impacts pelvic organs, such as the uterus and ovaries. Reprinted with permission, Cleveland Clinic Foundation ©2022. All rights reserved.

proposed, including insulin resistance, chronic low-grade inflammation, oxidative stress, tumor-microenvironment alterations, and adipokine signaling.<sup>4–8</sup>

Adipokines are bioactive cytokines secreted by adipocytes, and their discovery established adipose tissue as not only an energy storage organ but also an endocrine organ.<sup>9,10</sup> Visceral, subcutaneous, and additional adipose depots, such as those found in breast tissue, all secrete adipokines. However, the metabolic profile and risk associated with disease differs between each distinct adipose depot (Figure 1).<sup>6,11,12</sup> Further, obesity modifies the secretory status of adipose tissue, shifting its homeostasis from anti-inflammatory to proinflammatory via the regulation of secreted adipokines.<sup>11</sup> Adipokines have also been shown to promote tumorigenic pathways, including increased tumor cell proliferation, enhancement of cell migration, and promotion of cancer stem cell (CSC) populations.<sup>7,13</sup> CSCs are generally considered as tumor-initiating cells implicated in cancer recurrence, metastatic invasion, and tumor heterogeneity.<sup>14,15</sup>

The association between obesity and breast, endometrial, and ovarian cancer has led to an interest in investigating the role of adipokines

in each of these malignancies. Studies have identified both mechanistic and clinical roles for adipokines in tumorigenic pathways. Although there is a breadth of literature analyzing the role of adipokines and obesity in each cancer type, there is a unique opportunity to compare their roles among these three cancers impacting the female sex. Here, we organize and present the mechanisms studied underlying adipokine signaling in all three cancer types, drawing attention to the vastly different mechanisms in which these adipokines, especially leptin and adiponectin, the most studied, modulate tumor behavior in each organ. We survey the most significant discoveries in the last 5 years that focus on adipokines as both key molecular mediators and biomarkers in breast, endometrial, and ovarian cancer in distinct manners.

## METHODS

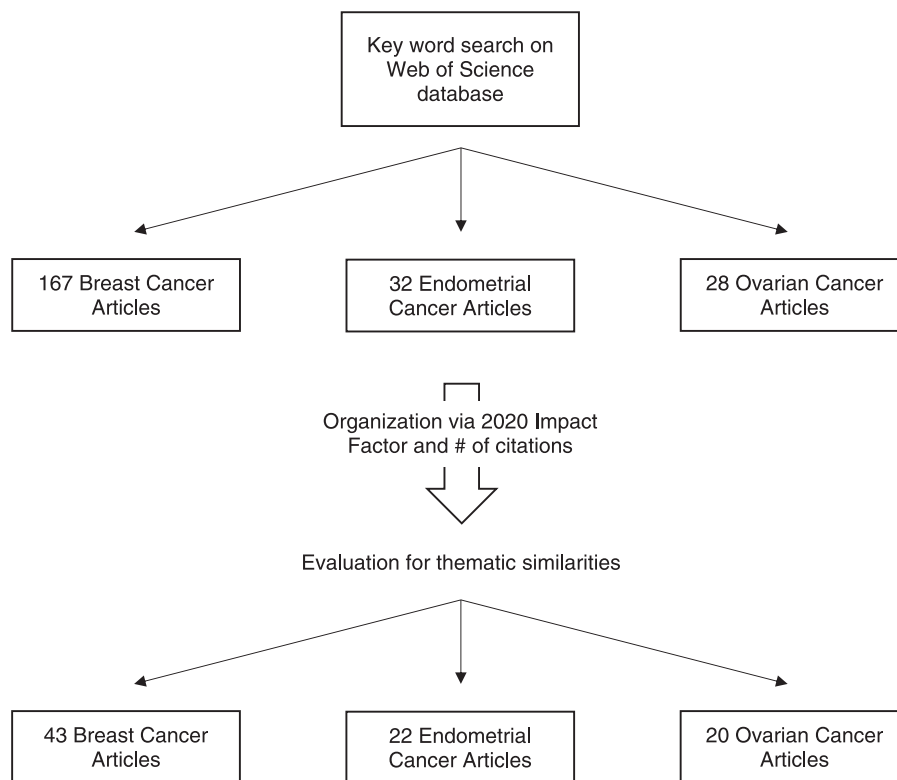
We searched the Web of Science database to identify clinical and pre-clinical studies using the following keywords (Figure 2): adipokines OR resistin OR leptin OR adiponectin along with either breast cancer OR breast neoplasm, endometrial cancer OR endometrial neoplasm, or ovarian cancer OR ovarian neoplasm. Additional search terms included study OR studies OR trial OR trials OR randomized OR randomised OR placebo OR cohort OR RCT OR multicenter OR retrospective OR longitudinal OR observational OR comparative OR ([clinical OR control\* OR phase] NEAR/4 [study OR trial\*]). Searches were limited to articles published between 2018 and 2022, and review articles, proceedings, abstracts, and editorials were removed. Articles written in a language other than English were excluded. A total of 167 results were identified for breast cancer articles, 32 results were identified for endometrial cancer, and 28 results were identified for ovarian cancer. Articles were organized by the journal's 2020 impact factor and number of citations. Articles were evaluated for thematic similarities between the three cancer types. A total of 43 breast cancer, 22 endometrial cancer, and 20 ovarian cancer-related articles were included from this search.

## Breast cancer

### Obesity as a risk factor for breast cancer

One in eight females in the United States will be diagnosed with breast cancer in their lifetime.<sup>16</sup> Several factors, including established genetic linkages, environmental exposures, and excess adiposity, increase the risk for the development of the disease.<sup>17</sup> The relationship between obesity and breast cancer is nonetheless complex. In postmenopausal patients, obesity is an independent risk factor for the development of breast cancer and outcomes, such as disease progression, distant metastases, and overall survival.<sup>18,19</sup> This relationship holds true for the different subtypes of breast cancer, including estrogen receptor-positive (ER+) and triple-negative breast cancer (TNBC).<sup>19,20</sup>

Conversely, the relationship between premenopausal breast cancer and obesity appears to be inverse, especially with regard to ER+ breast cancer.<sup>21</sup> The reasons for these divergent findings are not well understood, especially given the low incidence of premenopausal breast cancer. Pathophysiological explanations underscoring the negative



**FIGURE 2** A schematic representation for paper selection evaluating adipokine effects in breast, endometrial, and ovarian cancer. Web of Science keywords are as defined in the text. Thematic similarities were evaluated by S.T. and O.R.

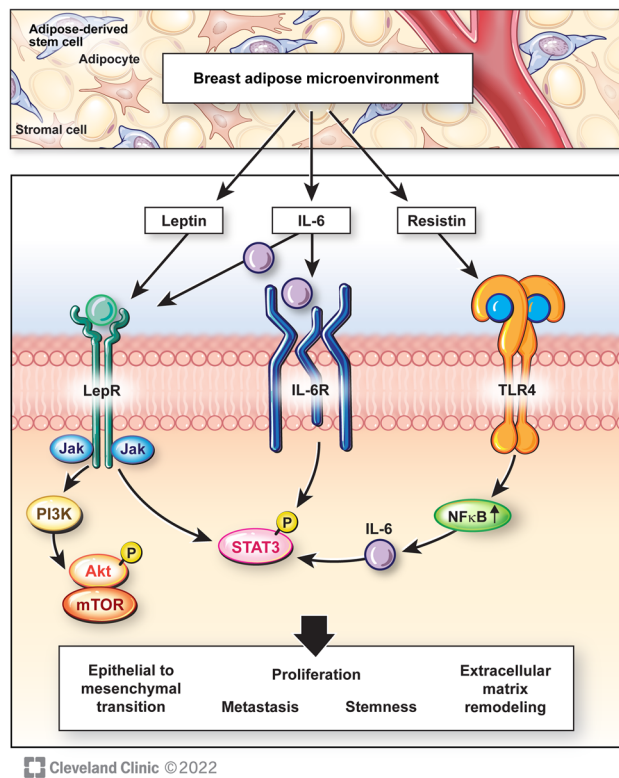
feedback mechanisms regulating the hypothalamic–pituitary–ovarian axis from excess peripheral estrogen exposure have been proposed.<sup>21</sup> Although estrogen synthesis through peripheral conversion via the enzyme aromatase represents around 5% of the total estradiol synthesis in premenopausal women, extreme obesity can lead to dysregulation of the hypothalamic–pituitary–ovarian axis due to excessive estrogen production.<sup>21</sup> This dysregulation coupled with amenorrhea could alter breast cancer risk, although studies have demonstrated mixed results.<sup>21–24</sup> Hormonal profile alterations due to premenopausal obesity shift the normal balance between androgens, estrogens, and progesterone. Studies have shown that estradiol and total testosterone, both inversely correlated with BMI in premenopausal women, may be positively associated with ER+/progesterone receptor (PR)+ breast cancer.<sup>21,25–30</sup> Adipokine leptin has demonstrated similar effects.<sup>31</sup>

Various mechanisms linking obesity and postmenopausal breast cancer, including metabolic dysregulation, immunologic alterations, epigenetic modifications, and microbiome perturbations, have been proposed.<sup>32</sup> Adipokine signaling pathways are an extensively studied facet of obesity-driven tumorigenesis in breast cancer. Much of this prior research has focused on the role of the adipokine leptin.<sup>33</sup> The past several years have also established additional adipokines, such as resistin and interleukin-6 (IL-6), as mediators of disease via modulation of signaling cascades and participating in the crosstalk between the tumor microenvironment and breast cancer cells (Figure 3).<sup>34</sup> Adipokines may also serve as biomarkers of disease for those patients with increased truncal fat mass. The nature of their predictive value is complex, however, as studies demonstrate varying results regarding

circulating adipokine concentrations and associations with different breast cancer subtypes.<sup>35,36</sup>

### Breast cancer invasiveness: Leptin and the extracellular matrix

Leptin, a 16-kD adipokine produced by the obesity (*OB*) gene, is secreted primarily from adipose tissue although low levels are found in the placenta, brain, and skeletal muscles.<sup>9,33</sup> Leptin and leptin receptor (LepR) overexpression in postmenopausal breast cancer is well established, and recent data implicate the concordance of *LEPR* polymorphisms with a sustained increase in BMI to enhance the risk for breast cancer even in premenopausal patients.<sup>33,37</sup> The binding of leptin to LepR, especially the long isoform LepRb, results in downstream activation of signaling pathways that are implicated in breast cancer progression. For example, leptin binding to LepRb leads to homoisomerization of Janus kinase 2 (JAK2) and downstream activation of signaling transducer and activator of transcription 3 (STAT3).<sup>38</sup> Leptin binding of JAK2 also activates phosphoinositide 3-kinase (PI3K), subsequently stimulating the phosphorylation of insulin receptor substrate (IRS). IRS-mediated phosphorylation of protein kinase B (Akt) activates target mammalian target of rapamycin complex 1 (mTORC1).<sup>7,38</sup> Leptin-mediated signaling via JAK/STAT3 and PI3K/AKT/mTORC pathways has been shown to increase CSC frequency, chemoresistance, and tumor progression in breast cancer.<sup>7,39,40</sup> Recently, Tenvooren et al. demonstrated that



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**FIGURE 3** Intracellular pathways driven by adipokines secreted from breast-associated adipose tissue. Adipokines secreted from breast adipose tissue act on their respective receptors to regulate signaling pathways. These pathways enhance tumorigenic behaviors in breast cancer, leading to the progression of the disease. Abbreviations: IL-6, interleukin-6; IL-6R, interleukin-6 receptor; Jak, Janus kinase 2; LepR, leptin receptor; mTOR, mammalian target of rapamycin; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; STAT3, signaling transducer and activator of transcription 3; TLR-4, toll-like receptor 4. Reprinted with permission, Cleveland Clinic Foundation ©2022. All rights reserved.

leptin-mediated signaling via the PI3K/AKT pathway leads to the mislocalization of apical polarity proteins in normal mammary glands, indicating a possible role for leptin in the premalignant phase as well.<sup>41</sup>

Recently, studies have demonstrated an interaction between leptin, the extracellular matrix, and breast cancer cell invasion via JAK2/STAT3 signaling. Haque et al. demonstrated that leptin plays a role in stemness, cell migration, and cell viability in ER $\alpha$  breast cancer cells through the suppression of extracellular matrix-associated cysteine-rich protein, CCN5, at the transcriptional level via the JAK2/AKT/STAT pathways.<sup>42</sup> CCN5 expression has been previously reported as inversely correlated with aggressiveness with breast cancers.<sup>42</sup> Leptin signaling via JAK2/STAT3 also mediates extracellular matrix remodeling in a noncanonical pathway by activating focal adhesion kinase and Src, a nonreceptor tyrosine kinase. This study by Juárez-Cruz et al. demonstrated that the Fak-Src signaling complex in response to leptin signaling leads to mesenchymal pattern cell migration via matrix metalloproteinase (MMP)-2 and MMP-9 secretion.<sup>43</sup>

Beyond LEPR, He et al. found leptin signaling in conjunction with adipokine IL-6 signaling through the GP130 receptor induces

transcription of procollagen-lysine 2-oxoglutarate 5-dioxygenase (PLOD), specifically PLOD2, encoding lysyl hydroxylase-2, a matrix remodeling protein that is a protumorigenic, prometastatic marker in several cancer types. PLOD2 upregulation was mediated by both IL-6 and leptin-mediated enhancement of JAK2/STAT3 signaling. PI3K/AKT signaling upregulation via leptin also further enhanced the upregulation of PLOD2, leading to increased extracellular matrix remodeling and metastatic potential.<sup>44</sup> These findings implicate leptin in combination with additional adipokines, such as IL-6 in promoting extracellular matrix remodeling and enhancing the metastatic potential of breast cancer.

### Leptin promotes hormone-sensitive breast cancer proliferation

In premenopausal women, most of the estrogen is produced by the ovaries. In contrast, postmenopausal estrogen production is predominantly produced through the peripheral conversion of androgens produced by the adrenal cortex and ovaries to estrogens via the enzyme aromatase.<sup>45</sup> Both adipose tissue and epithelial breast cells produce aromatase. Thus, increased adiposity enhances postmenopausal estrogen production to augment hormone-sensitive breast cancer growth both in autocrine and paracrine manners.

Leptin can stimulate aromatase expression in MCF-7 human breast cancer cells via mitogen-activated protein kinase (MAPK) and STAT3 signaling cascades.<sup>46</sup> Supporting this concept, Zahid et al. demonstrated that adipose stromal cells treated with leptin exhibited a dose-dependent increase in aromatase expression through modulation of the p53-HIF1 $\alpha$ /PKM2 axis.<sup>47</sup> These findings indicate leptin-stimulated extracellular signal-regulated kinase 1/2 (ERK1/2) activity leading to activation and translocation of protein kinase C (PKC) to the plasma membrane and decreased levels of the tumor suppressor p53. Loss of p53 activity enhanced expression of the activator of Hsp90 ATPase (Aha1) and the 90 kD heat shock protein (Hsp90) ATPase. Increased expression of HSP90 ATPase stabilized both hypoxia-inducible factor-1-alpha (HIF1 $\alpha$ ) and pyruvate kinase M2 (PKM2). In turn, HIF1 $\alpha$  and PKM2 bind to the aromatase promoter region PII resulting in enhanced aromatase expression, estrogen production, and hormone-driven breast cancer progression in obese women.<sup>47</sup> The findings highlight the positive influence of leptin in promoting estrogen-driven breast cancer in postmenopausal women.

The impact of leptin is not limited to promoting estrogen. Tamoxifen, a selective estrogen receptor modulator (SERM), is a commonly used hormone therapy that targets ER in breast cancer. Acquired resistance to tamoxifen in ER+ breast cancer remains a challenge. Proposed mechanisms for tamoxifen resistance focus on the cross-talk between ER and its comodulators, including growth factors, stress-response elements, and cytokine-related kinases, resulting in ER activation and downstream signaling in spite of antiestrogen SERM activity.<sup>48</sup> Diminished tamoxifen efficacy and increased recurrence of disease in obese, postmenopausal women indicate a putative link between obesity and chemoresistance. Tamoxifen treatment can increase leptin



expression, underscoring the link between adipokine signaling pathways and chemoresistance.<sup>49</sup>

Supporting evidence comes from a study by Bougaret et al. finding that an obesity-altered tumor microenvironment leads to increased cell proliferation and expression of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and IL-6 in the presence of tamoxifen. Further, leptin, TNF $\alpha$ , and IL-6 treatment of MCF-7 breast cancer cells at a dose equivalent to levels in the plasma of patients with comorbid obesity appeared to decrease the efficacy of tamoxifen.<sup>50</sup> Likewise, Linares et al. found that *in vitro* exposure to leptin mitigates the efficacy of tamoxifen—a consequence of enhanced expression of LEPR at the protein level in ER+ breast cancer.<sup>51</sup> Decreased efficacy of tamoxifen is induced by a high-fat diet driving hyperleptinemia, revealing both enhanced expression of ER-responsive genes and diminished tamoxifen-induced recruitment of tumor-suppressive genes.<sup>52</sup> Thus, obesity and leptin in the postmenopausal state lead to chemoresistance via suppression of SERM activity.

## Adipose-derived stem cells regulate the impact of adipokines in breast cancer

The mammary tissue microenvironment is heterogeneous, consisting of both adipocytes and stromal cells, such as adipose-derived stem cells (ADSCs), endothelial and immune cells, fibroblasts, and the extracellular matrix.<sup>53,54</sup> Interactions between the stromal components, such as ADSCs and breast epithelial cells, impact the malignant potential and migration of breast epithelial cells.<sup>55</sup> Further, cross-talk between breast cancer cells and surrounding breast stroma can impair the adipogenic differentiation potential of ADSCs.<sup>56</sup>

Obesity has been shown to modulate the impact of ADSCs on tumorigenesis. ADSCs isolated from obese patients (obADSC) are sufficient to enhance the proliferation, migration, and invasion of ER+ breast cancer through increased leptin expression, leading to the induction of ER $\alpha$  and aromatase.<sup>57,58</sup> However, this relationship is complex and may be independent of ER signaling. Sabol et al. demonstrated that obADSCs in a constitutively active model of ER $\alpha$  enhance metastasis but not tumor growth via upregulation of *SERPINE1*, a member of the serine proteinase inhibitor (serpin) superfamily and a key player in extracellular matrix remodeling, neoangiogenesis, and cell migration during wound healing.<sup>59</sup> A separate investigation found leptin signaling via obADSC increases the expression of metastasis-related genes in TNBC. Knockdown of leptin expression in obADSC suppressed the metastatic potential *in vivo* in patient-derived xenograft (PDX) models of TNBC. This study did not find leptin expression via obADSC to enhance TNBC tumor cell proliferation itself, demonstrating that the obesity-altered tumor microenvironment, especially its impact on ADSCs, may play a larger role in epithelial-to-mesenchymal transition (EMT) and migration in TNBC in comparison to tumor growth.<sup>60</sup>

In addition to cell migration, leptin and additional adipokines derived from obADSC may impact treatment response as patients with obesity tend to respond less favorably to both chemotherapy and endocrine therapy.<sup>17,18</sup> Leptin expression in obADSC has also been shown to promote radiation resistance in ER+ breast cancer via the

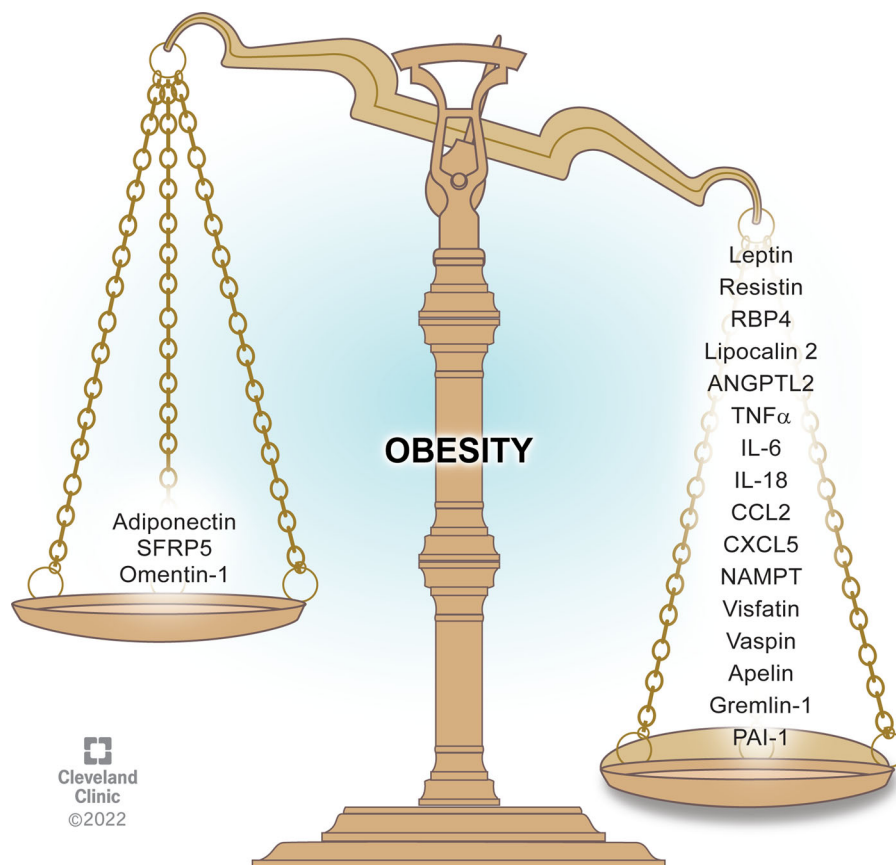
promotion of NOTCH and IL-6 signaling, promoters of tumorigenic properties, such as stemness, proliferation, and metastasis.<sup>61</sup> Delort et al. further investigated the role of obesity in hormone therapy resistance in breast cancer finding that upregulation of *STAT3* may link tamoxifen resistance in MCF-7 breast cancer cells in the presence of human ADSCs in a leptin-independent manner.<sup>54</sup>

Goto et al. explored the relationship between adipokines beyond leptin that are expressed by ADSCs in the context of breast cancer to identify a complementary role. Their studies focused on establishing breast cancer PDX models and collecting ADSCs from the surgical specimen of patients with breast cancer. Their findings indicated that dissociated breast cancer PDX cells cocultured with ADSCs had enhanced sphere-forming ability, a proxy assay for CSCs, and cell growth. Screening for known adipokines identified enhanced expression of adipisin, or complement factor D, in the culture media of ADSCs and the tumor specimen of breast cancer patients, especially those with increased BMI. C3a, a product of adipisin-mediated cleavage of complement C3, cultured with PDX cells expressing its receptor (C3aR) further increased the expression of CSCs. Notably, the introduction of a selective antagonist for C3aR diminished this ability. Knockdown of adipisin in ADSCs further mitigated the CSC properties of the PDX cells *in vitro* and diminished the rate of tumor growth *in vivo*. This study demonstrated that the adipisin/C3a complement pathway production from ADSCs enhances stemness and cell proliferation in breast cancer.<sup>62</sup>

## Anti-inflammatory effects of adiponectin confer a protective influence on breast cancer

An inflammatory milieu created by unopposed estrogen, menstruation, and diabetes mellitus is purported to impact endometrial carcinogenesis.<sup>63</sup> Obesity itself is a proinflammatory state, as hypertrophy of adipose tissue leads to the recruitment of activated M1 macrophages and T cells. Lean adipose tissue on the other hand recruits M2, or alternatively activated, macrophages. The balance between pro- and anti-inflammatory adipokines also shifts in obesity with increased production of inflammatory adipokines, such as leptin, resistin, TNF $\alpha$ , IL-6, and IL-8. The relative production of anti-inflammatory cytokines, such as adiponectin and secreted frizzled-related protein 5 (SFRP5), is diminished (Figure 4).<sup>11</sup>

Adiponectin, a multimeric protein belonging to the complement 1q family, is classically associated with insulin sensitization and exerts protective effects against breast cancer, negatively regulating breast cancer cell development and growth.<sup>11,34,64,65</sup> Adiponectin's role in insulin sensitization highlights the key interplay between insulin resistance and several types of cancers, including breast cancer. In the obese state, decreased sensitivity of peripheral target tissues to insulin results in a compensatory increase in insulin production, resulting in hyperinsulinemia and metabolic syndrome. Increased levels of circulating insulin enhance IRS signaling, resulting in downstream activation of protumorigenic signaling via the PI3K/AKT/mTORC and rat sarcoma (Ras)-MAPK/ERK pathways. Hyperinsulinemia also decreases the hepatic production of sex hormone binding globulin (SHBG), increasing



**FIGURE 4** Alteration to the inflammatory milieu in the setting of obesity. Obesity in general enhances the secretion of proinflammatory adipokines and decreases the secretion of anti-inflammatory cytokines, such as adiponectin. Decreased expression of the anti-inflammatory adipokine in particular is implicated in increased risk for endometrial cancer progression. Abbreviations: ANGPTL2, angiopoietin-like protein 2; CCL2, C-C motif chemokine ligand 2; CXCL5, C-X-C motif chemokine ligand 5; IL-6, interleukin-6; IL-18, interleukin-18; NAMPT, nicotinamide phosphoribosyltransferase; PAI-1, plasminogen activator inhibitor; RBP4, retinol-binding protein 4; SFRP5, secreted frizzled-related protein 5; TNF  $\alpha$ , tumor necrosis factor  $\alpha$ . Reprinted with permission, Cleveland Clinic Foundation ©2022. All rights reserved.

circulating levels of sex steroid hormone and tumor progression in hormone-sensitive disease.<sup>66</sup> In fact, a prospective cohort study by Park et al. found that the biguanide metformin treatment in patients with type 2 diabetes was associated with a lower risk of ER+ breast cancer in comparison to no type 2 diabetes, but this relationship was inverse for ER- disease and TNBC.<sup>67</sup> These findings were in contrast to previously reported relationships between metformin, ER- breast cancer, and TNBC, highlighting the complex relationship between insulin resistance, metformin, and cancer progression as it relates to hormone status.<sup>67,68</sup>

In addition to biguanides, thiazolidinediones (or glitazones) and glucagon-like peptide-1 receptor agonists are approved for the treatment of type 2 diabetes and increase adiponectin expression.<sup>69,70</sup> Glitazones activate the nuclear receptor peroxisome proliferator-activated receptor-gamma leading to downstream anticancer effects, such as increased cell apoptosis, decreased cell migration, mitigated cell proliferation, and enhanced anti-inflammatory effects.<sup>69,71,72</sup> Interestingly, Shea et al. demonstrated that exposure to adipose tissue loaded with glitazones decreases the proliferation of breast cancer cell lines MCF-7 and MBA-MD-231 along with the normal breast epithelial

cell line MCF-10A. This was also correlated with increased production and release of adiponectin, identifying a possible role for adipose tissue serving as a drug depot for breast cancer treatment in conjunction with lumpectomy.<sup>69</sup>

Adiponectin may also serve roles beyond insulin sensitization in breast cancer since increased adiponectin levels have been observed at earlier stages of the disease.<sup>73</sup> Studies have also identified lower expression of adiponectin in obese women with breast cancer in comparison to women with normal BMI.<sup>74,75</sup> The expression of adiponectin receptors 1 and 2 in breast cancer tissue as it relates to BMI is complicated as Orozco-Arguelles et al. recently demonstrated an increase in adiponectin receptor 1 in breast cancer tissue of women with higher BMI compared to those with normal BMI. This may reflect the upregulation of compensatory mechanisms in the setting of decreased adiponectin expression.<sup>74</sup> Increased adiponectin levels may be indicative of improved overall survival and disease-free survival in breast cancer.<sup>73,76</sup> However, Obi et al. found in a large cohort of women with breast cancer that doubling the adiponectin concentration is associated with increased breast cancer-specific mortality in ER- PR- breast cancer. This relationship was not seen in adipokines leptin and resistin

(discussed below), any of the three evaluated adipokines nor in ER+ PR+ breast cancer. These findings indicate a possible hormonal interaction.<sup>36</sup>

Genetic and epigenetic regulation of adiponectin has been of interest given *ADIPOQ* gene is highly polymorphic, with over 600 reported variants to date.<sup>77</sup> Genetic and epigenetic regulation of *ADIPOQ* and circulating levels of adiponectin may modify breast cancer risk. Changes due to an obesity environment may further alter breast cancer risk in such genetic alterations.<sup>78</sup> In particular, the single nucleotide polymorphisms (SNPs) rs1501299 and rs2241766 have been associated with altered circulating adiponectin levels and are predictors of increased breast cancer risk.<sup>78–81</sup> Further, Pasha et al. found that in patients with obese women with breast cancer, epigenetic regulation of *ADIPQ* via promoter site methylation is associated with altered disease risk.<sup>80</sup>

### The role of resistin in breast cancer stemness and migration

Resistin is a cysteine-rich, proinflammatory protein present in mice and humans. Because of its secretion from mouse adipocytes, enhancement of an obesity phenotype, and role in hepatic insulin resistance, resistin was originally introduced as a novel adipokine. However, the classification of resistin in humans remains controversial as it is primarily produced from mononuclear cells with only low levels of expression in adipocytes.<sup>11,82</sup> Although the specific roles and receptors of resistin have not been fully elucidated, studies propose an immunomodulatory, proinflammatory role for resistin in humans, which is distinct from that in animal models. In humans, resistin is associated with several disease states, including cardiovascular disease, rheumatologic conditions, and cancer.<sup>82</sup>

Recent studies demonstrate the role of resistin in breast cancer progression and metastasis via the promotion of EMT and stemness.<sup>83,84</sup> Wang et al. demonstrated that serum resistin levels were elevated in patients with breast cancer in comparison to age-matched controls when controlling for BMI.<sup>83</sup> Serum resistin was also positively associated with tumor stage, size, and metastasis. *In vitro*, exposure to resistin enhanced markers of EMT and tumorsphere formation with upregulation of CSC markers SOX2, NANOG, and OCT4. These findings were also replicated *in vivo*. Most interestingly, Wang et al. demonstrated that resistin signaling via toll-like receptor 4 mediated activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) to upregulate IL-6 production, subsequently activating the JAK/STAT3 signaling cascade to promote these tumorigenic behaviors.<sup>83</sup>

In parallel, Avtanski et al. demonstrated that resistin upregulated EMT markers *in vitro* in both MCF-7 and MDA-MB-231 breast cancer cells as well as MCF-10A breast epithelium cells. Complementary studies showed that silencing adenylyl cyclase-associated protein 1 (CAP1) suppressed resistin-mediated upregulation of these markers as well as MCF-7 cell migration.<sup>84</sup> Interestingly, SNPs in both *RETN*, which encodes for resistin, and *CAP1* have been associated with an increased

risk of breast cancer.<sup>85</sup> Thus, resistin may play a role in EMT in breast cancer, but its relationship to the obesity phenotype remains to be further investigated.

### The impact of diet and exercise on breast cancer

Dietary and lifestyle interventions to manage weight and adiposity may have therapeutic potential in patients with breast cancer. However, there is much to be learned about the impact of weight loss on the various stages of the disease, from diagnosis to survivorship. For example, the impact of weight loss on breast cancer diagnosis is unclear. A randomized trial comparing basic nutrition and exercise counseling with additional instruction on caloric restriction and aerobic exercise in patients with early-stage breast cancer found that in spite of decreased presurgical weight and serum leptin concentrations at the surgery in the intervention group, there was upregulation of TNF $\alpha$ , vascular endothelial growth factor (VEGF), and IL-6 within their tumor specimens. These findings were in contrast to the enhanced tumor immune-cell infiltration and NK-cell expression observed in the intervention group.<sup>86</sup> On the other hand, the addition of the biguanide metformin to sustained dietary and exercise interventions for 1 year in women without signs of breast cancer has resulted in improved BMI, adiponectin levels, and patients' Breast Imaging Reporting and Data System scores. The addition of metformin was also associated with decreased positive pathological biopsy rate.<sup>87</sup> Thus, presurgical weight loss counseling, dietary modification, and additional interventions demonstrate mixed pro- and antitumorigenic effects.<sup>86,87</sup>

In contrast, the impact of exercise and weight loss on breast cancer survivors appears to be less ambiguous. Several supervised exercise programs have demonstrated decreased expression of proinflammatory adipokines and insulin resistance as a result of intervention as well as enhanced expression of anti-inflammatory markers, such as adiponectin in survivors of breast cancer who are exposed to supervised weight loss management (Table 1).<sup>88–93</sup> In a cohort of patients with stage I–III breast or colon cancer who had completed standard treatment, exercise in combination with metformin was associated with a greater decrease in BMI and circulating concentrations of leptin than exercise alone.<sup>94</sup> Metformin in combination with exercise has also been shown to lead to favorable hormone profiles.<sup>95</sup> Such data demonstrate a possible added benefit of insulin regulation via metformin in breast cancer survivors.

The impact of different dietary modifications in mouse models of breast cancer provides additional mechanistic insights linking breast cancer to lifestyle interventions. For example, some studies indicate that mice fed on a high-fat diet have accelerated breast cancer recurrence and increased accumulation of PD-1<sup>+</sup> CD8<sup>+</sup> exhausted T cells.<sup>96,97</sup> Exposure to a high-fat diet also correlates with increased expression of the proinflammatory markers leptin, resistin, IGF-1, TNF $\alpha$ , and NF- $\kappa$ B *in vivo*.<sup>96,98</sup> Interestingly, the composition of dietary fat appears to modulate the risk of breast cancer. For example, a diet rich in omega ( $\omega$ )–3 fatty acids in comparison to  $\omega$ –6 fatty acids was associated with lower ductal end-point density, branching density,



**TABLE 1** Trials investigating the impact of exercise in breast cancer survivors

Study	Trial design	Population	Intervention	Outcome
Dieli-Conwright et al. <sup>88</sup>	Prospective RCT	BCS (heterogenous population)	Aerobic and resistance exercise intervention versus UC	SS improvement in metabolic syndrome variables
Dieli-Conwright et al. <sup>89</sup>	Prospective RCT	Obese postmenopausal BCS	Aerobic and resistance exercise versus UC	SS improvement in inflammatory markers, including proinflammatory M1 macrophages in adipose tissue
Travier et al. <sup>90</sup>	Prospective biomarker study	Overweight and obese BCS	Diet and exercise sessions versus UC	SS improvement in metabolic risk biomarkers, insulin resistance indicators. NS decrease in leptin
Brown et al. <sup>91</sup>	Phase II RCT	Survivors of solid tumors and hematologic malignancies; 77% BCS	Caloric restriction and physical activity versus UC	SS decrease in weight, fat mass, insulin levels, and leptin levels. SS improvement in physical fitness
Dittus et al. <sup>92</sup>	Prospective biomarker study	Overweight, early-stage breast cancer survivors	Behaviorally based weight loss intervention (calorie reduction, exercise, and behavior modification)	SS improvements in indices of insulin resistance with $\geq 5\%$ weight loss
Hooshmand Moghadam et al. <sup>93</sup>	Prospective RCT	BCS	High-intensity interval training (HIIT) versus moderate-intensity continuous training (MICT) versus UC	Greater improvements in body mass, fat mass, TNF- $\alpha$ , leptin, and lower body strength with HIIT in comparison to MICT and UC

Abbreviations: BCS, breast cancer survivor; NS, nonsignificant; RCT, randomized controlled trial; SS, statistically significant; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; UC, usual care.

thinner ductal stroma, and fewer proliferating epithelial cells along with lower expression of ER in an *in vivo* model of breast cancer.<sup>98</sup>

Restricted dietary patterns also impact breast cancer tumor progression *in vivo*. In the MMTV-PyMT breast cancer mouse model, a high-fat diet restricted to dark-phase feeding (12 h per day) had similar tumor growth and levels of circulating adipokines compared with control diet-fed mice. Unrestricted feeding of the same diet accelerated tumor growth and enhanced plasma inflammatory adipokines including, leptin, plasminogen activator inhibitor 1 (PAI-1), and monocyte chemoattractant protein-1 (MCP-1).<sup>99</sup> These findings underscore the impact of dietary timing on the induction of leptin and circulating adipokines.

The impact of diet timing is further supported by Caffa et al. investigating the role of the fasting-mimicking-diet (FMD) on hormone therapy response. FMD in combination with endocrine therapies tamoxifen and fulvestrant decreased tumor growth in comparison to the control, ad libitum diet. Additionally, FMD was associated with decreased expression of insulin, IGF1, and leptin, decreasing the activity of the PI3K-AKT-mTOR pathway and enhancing its negative regulators PTEN and early growth response protein 1. Combining fulvestrant with the cyclin-dependent kinase 4/6 inhibitor palbociclib in the presence of FMD propagated the therapies' antitumor benefits *in vivo*. A limited patient sample also demonstrated clinical benefits of FMD as evi-

denced by tumor shrinkage on imaging as well as decreased glucose, IGF, insulin, and leptin plasma levels.<sup>100</sup>

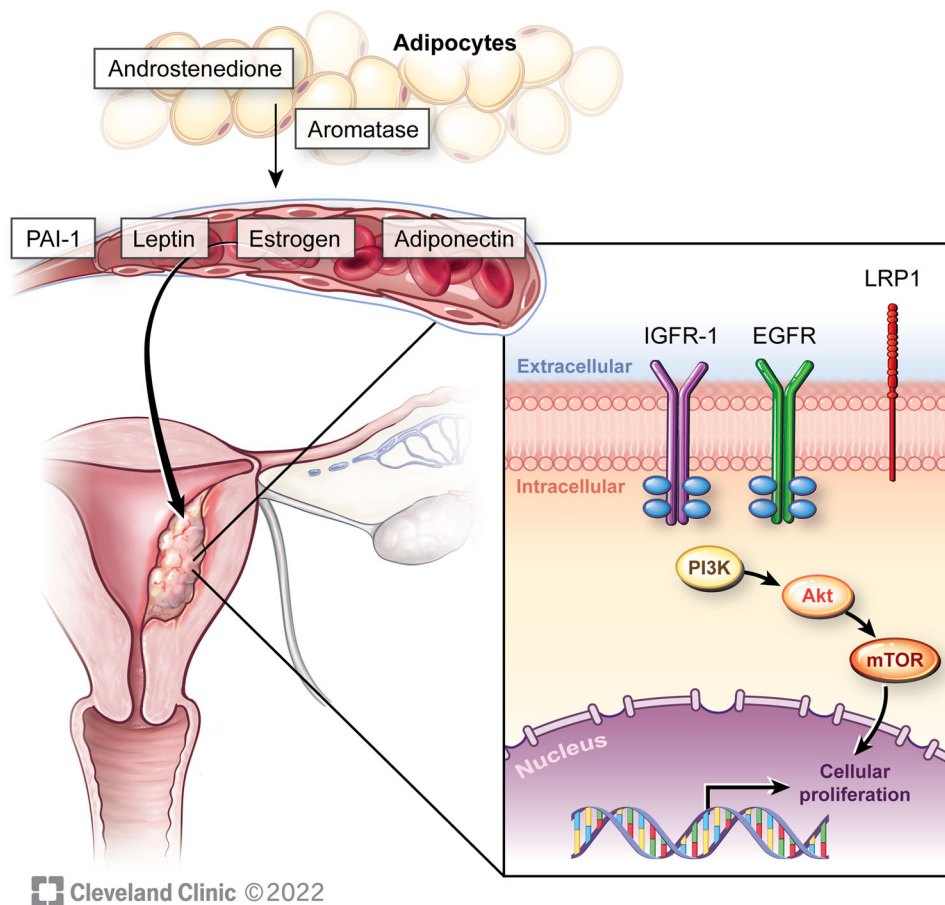
## Breast cancer and adipokines: A summary of recent discoveries

The studies linking obesity and breast cancer are supportive of direct activation of cancer signaling pathways by adipokines, enhancing progression, invasion, and chemoresistance. As we continue to identify opportunities to therapeutically inhibit leptin and related adipokines in breast cancer, we must also focus on the impact of dietary and lifestyle modifications in the realm of obesity-driven disease.

## Endometrial cancer

### The complex relationship of obesity and endometrial cancer

Endometrial cancer is the most common gynecologic cancer, with recent data demonstrating the incidence of uterine corpus cancer similar to that of ovarian cancer.<sup>101</sup> The increased prevalence of obesity in females has been postulated to be a contributor to these



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**FIGURE 5** Circulating adipokine-mediated signaling enhances endometrial proliferation and tumorigenic behavior in endometrial cancer. Peripheral conversion of androgens to estrogen via aromatase along with adipokines PAI-1, leptin, and adiponectin enhances endometrial cell proliferation. The PI3K-AKT-mTOR pathway induced by IGFR-1 and EGFR signaling is a key modulator of these processes. PAI-1 signaling on lipoprotein receptor-related protein 1 (LRP1) has also been shown to increase the invasiveness of endometrial cancer. Abbreviations: EGFR, epidermal growth factor receptor; IGFR-1, insulin-like growth factor I receptor; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PAI-1, plasminogen activator inhibitor; Akt, protein kinase B. Reprinted with permission, Cleveland Clinic Foundation ©2022. All rights reserved.

alarming statistics.<sup>101</sup> Approximately 57% of endometrial cancers in the United States can be attributed to obesity, and endometrial cancer in comparison to other cancers has the strongest association with obesity.<sup>102</sup>

The peripheral conversion of androgens to estrogen via adipocyte-derived aromatase and the relative depletion of SHBG after menopause results in increased bioactive circulating estrogen with increasing adiposity. Excess endogenous estrogens stimulate endometrial proliferation via the activation of ER $\alpha$ . Estradiol, the most potent endogenous estrogen compound, acts on insulin-like growth factor I receptor (IGFR-1) and epidermal growth factor receptor (EGFR) to activate the phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin (PI3K-AKT-mTOR) pathway, stimulating proliferation of the endometrium (Figure 5).<sup>103</sup> Several adipokines, including leptin, TNF $\alpha$ , IL-6, IL-8, and MCP-1, are implicated in endometrial cancer progression and may serve as valuable biomarkers of disease.<sup>103-105</sup> These studies parallel the findings of adipokine promotion of breast cancer in postmenopausal women.

### Adiponectin activation of anti-inflammatory pathways in endometrial cancer

As in breast cancer, adiponectin serves as an anti-inflammatory adipokine in endometrial cancer that is diminished in the obese state.<sup>11</sup> A meta-analysis of 20 studies that evaluated circulating adipokine concentrations and risk of endometrial cancer identified adiponectin as an independent marker for a decreased risk of endometrial cancer, even when controlling for comorbid risk factors.<sup>106</sup> However, the mechanisms underlying the protective role of adiponectin in endometrial cancer remain unresolved.

The AMPK-mTOR pathway has been recently identified as a mediator of adiponectin activity in endometrial cancer. Jin et al. studied human endometrial carcinoma RL95-2 cells, finding decreased cell proliferation and migration when exposed to increasing concentrations of adiponectin.<sup>107</sup> Adiponectin treatment increased the expression of activated, phosphorylated-AMPK (p-AMPK) and decreased phosphorylation both of mTOR (p-mTOR) and its downstream mediator

4E-binding protein 1 (p-4EBP1). Further, MMP-9 and B-cell lymphoma-2, an inhibitor of apoptosis, were both downregulated with adiponectin exposure. Introducing an AMPK inhibitor significantly increased cell proliferation and migration in spite of adiponectin treatment.<sup>107</sup> Roque et al. similarly studied the AMPK-mTOR signaling pathway in endometrial cancer.<sup>108</sup> Endometrial cancer cell lines ECC-1 and Ishikawa were treated with either the biguanide metformin or a novel biguanide NT-1044, both with AMPK activating properties. Both compounds inhibited cell proliferation in a dose-dependent manner and decreased activation of proteins downstream to the mTOR signaling cascade.<sup>108</sup> In parallel, a separate study found that metformin treatment decreases endometrial CSC populations, but this effect is diminished by exposure to patient-derived adipocyte-conditioned media.<sup>109</sup> Therefore, AMPK activation either by circulating adiponectin or exogenous biguanide exposure may mediate anticancer properties in endometrial carcinoma.

### Adipokine-mediated endometrial cancer cell migration and metastasis

Adipokine signaling also impacts the migratory and invasive potential of endometrial cancer cells. For example, PAI-1, a member of the serine protease inhibitor family, is overexpressed in most human cancers, including breast, ovarian, and endometrial cancers. 4G/5G polymorphisms (guanosine insertion/deletion gene polymorphism) in the promoter region of the *PAI-1* gene are associated with an increased risk of endometrial cancer.<sup>110</sup> PAI-1 is highly expressed in the visceral adipose tissue in obesity and is implicated in several hallmarks of cancer, including metastasis and invasion.<sup>110,111</sup> In a study by Polusani et al., coculturing nontumorigenic endometrial cancer cells with adipocyte stromal cells (ASCs) expressing PAI-1 repressed transcription of *GJA1*, which encoded for the gap junction connexin protein Cx43, both *in vitro* and *in vivo* models. Tumor specimens from patients with endometrioid endometrial cancer harbored hypermethylation at the *GJA1* gene and other gap junction-related loci, repressing their expression, which was further exacerbated in obese and morbidly obese patients. Restoration of *GJA1* (Cx43) gene transcription via demethylation decreased endometrial cancer cell migration, and depletion of Cx43 led to immortalized endometrial cells. Thus, Polusani et al. demonstrated that adipokine-mediated signaling, especially from PAI-1, enhances endometrial cancer migration due to epigenetic regulation of gap junction proteins.<sup>112</sup>

Further investigation into the mechanisms that underly paracrine signaling of ASC derived from PAI-1 on endometrial epithelial cells has identified lipoprotein receptor-related protein 1 (LRP-1) as a mediator of downstream pathways. PAI-1 signaling via LRP-1 downregulated expression of genes was related to a cellular junction and adhesion complexes via transcriptional repression and enhanced ubiquitination of SMAD4. This attenuated SMAD4/transforming growth factor- $\beta$  tumor suppressive signaling impaired intracellular communication.<sup>113</sup> Repression of key junction and adhesion complex factors under the regulation of SMAD4 via PAI-1/LRP-1 signaling may enhance the

cellular motility and invasiveness seen in endometrial cancers in an obese state.<sup>113</sup>

### Leptin induction of canonical signaling augments novel pathways in endometrial cancer

Leptin, LEPR, and leptin-associated proteins are expressed at the mRNA and protein level in the endometrial tissue of patients with endometrial cancer, posing a relationship between cancer progression and adipokines enhanced by obesity.<sup>114</sup> Mechanisms underlying this relationship are being investigated. For example, leptin and exogenous estradiol treatment in an ovariectomized mouse model of endometrial cancer synergistically increased the expression of tumorigenic proteins, including Igf1 and VEGF via upregulation of both the JAK/STAT and MAPK-ERK pathways.<sup>115,116</sup> Dai et al. further demonstrated that leptin, in conjunction with estrogen and insulin, activated the PI3K/AKT signaling cascade to enhance the translocation of phosphorylated ATP-citrate lyase (p-ACLY), a metabolic enzyme involved in glucose and lipid metabolism, to the nucleus.<sup>117</sup> Finding nuclear p-ACLY is highly novel and is capable of mediating histone acetylation and enhanced expression of dihydroorotate dehydrogenase, an enzyme involved in *de novo* biosynthesis of pyrimidine nucleotides and a known therapeutic target of several cancers.<sup>117</sup> These studies highlight leptin as an obesity-associated target regulating key tumorigenic signaling pathways that enhance the activity of estrogen and obesity-associated cytokines to augment endometrial cancer progression.

### Adipokines as biomarkers of endometrial cancer

As in breast cancer, identifying circulating adipose-derived biomarkers in endometrial cancer is an ongoing area of investigation. Linkov et al. in a pilot study of patients with endometrial cancer classified the adipokines secreted by adipose tissue from distinct fat depots. The proinflammatory adipokine IL-8 was the most differentially expressed adipokine, highest in the omental fat and lowest in the retroperitoneal depot.<sup>118</sup> A case-control study utilizing the European Prospective Investigation into Cancer and Nutrition database identified that both reduced circulating adiponectin and increased circulating inflammatory factors mediated nearly 70% of the increased odds of endometrial cancer in patients with obesity in comparison to those with normal weight.<sup>119</sup> Weight loss interventions, including bariatric surgery, also impact circulating adipokine concentrations, although prospective weight loss intervention studies demonstrate mixed results (Table 2).<sup>120-125</sup> Although such exploratory studies highlight associations between adipokines and endometrial cancer in the context of obesity, further studies are needed to establish their predictive value for both presence and prognosis of the disease.

Isolated studies have identified the diagnostic efficacy of adiponectin in endometrial cancer as decreased serum adiponectin independently predicts an increased risk for endometrial cancer.<sup>126,127</sup>

**TABLE 2** Trials investigating weight loss interventions in endometrial and ovarian cancers over the last decade

Disease site	Trial design	Population	Intervention	Outcome
Endometrial <sup>121</sup>	Prospective RCT	Endometrial cancer survivors	Text message versus EUC	No difference in weight loss
Endometrial <sup>122</sup>	Prospective RCT	Endometrial cancer survivors	Technologic interventions versus EUC	EUC led to more activity, telemedicine increased health
Endometrial <sup>123</sup>	Prospective RCT (REWARD trial)	Endometrial cancer survivors	Assisted versus voluntary exercise intensity cycling	Pending—Accrual complete 2019
Endometrial <sup>124</sup>	Phase II RCT (FenME trial)	Endometrial cancer /hyperplasia patients	Levonorgestrel IUD +/- metformin +/- weight loss intervention	Accrual completion expected 2022
Endometrial <sup>125</sup>	Prospective biomarker study	Overweight postmenopausal females	Randomization metformin/placebo and lifestyle modification/UC	Lifestyle modification led to SS increase in weight loss. No biomarker changes
Ovary <sup>163</sup>	Prospective RCT (PADOVA study)	Front-line ovarian cancer therapy	Exercise and dietary intervention versus UC	Ongoing accrual
Ovary <sup>164</sup>	Open-label RCT (LIVES study)	Ovarian cancer survivors after primary therapy	Diet and physical activity versus UC	Ongoing accrual

Abbreviations: EUC, enhanced usual care; IUD, intrauterine device; RCT, randomized controlled trial; SS, statistically significant; UC, usual care.

**TABLE 3** Diverse roles of leptin in women's cancers

Breast		
Function	Summary	Citations
Invasion/migration	Leptin via ER-dependent and independent mechanisms promotes migration <i>in vitro</i> and <i>in vivo</i>	42, 43, 59, 60
Aromatase induction	Regulation by leptin of aromatase via p53/HIF1a in adipose stromal cells is linked to cancer progression	47
Chemoresistance	Hyperleptinemia via leptin results in refractory response to hormonal therapy	52, 54
Endometrial		
Function	Summary	Citations
Estrogen/leptin axis	Cotreatment of estrogen and leptin promotes malignancy	115, 116
Novel pathways	Nuclear ATP-citrate lyase induced in obesity regulation of histone acetylation	117
Ovarian		
Function	Summary	Citations
Reciprocal function of leptin/estrogen axis	Opposing roles of leptin and estrogen in cancer progression	145, 146

Note: Summary of major *in vitro* and *in vivo* findings relating leptin to breast, endometrial, and ovarian cancers over the last 5 years as presented in this review. Abbreviations: ER, estrogen receptor; HIF1a, hypoxia inducible factor 1 alpha subunit.

Leptin similarly has been studied as an independent predictor of endometrial cancer.<sup>128,129</sup> Wang et al. investigated the relationship between endometrial cancer and visfatin, an inflammatory adipokine that promotes tumorigenic behavior of endometrial cancer via PI3K/AKT and MAPK/ERK signaling pathways.<sup>11,130</sup> When controlling for comorbid risk factors associated with endometrial cancer, serum visfatin was independently associated with endometrial cancer.<sup>126</sup>

Adipokines may also predict the histologic grade, pathologic stage, and ultimately clinical outcomes of disease. A prospective, case-control pilot study identified significantly increased neuropilin-1, an adipokine expressed by adipose tissue-associated macrophages, in

patients with higher-grade cancers in comparison to low-grade or control patients. Adipokines follistatin and IL-8 were associated with lymphovascular space invasion and metastases, respectively.<sup>128</sup> In a similar study, decreased concentration of both serpin and omentin-1, an adipose stroma-derived adipokine suggested to enhance insulin sensitization, predicted higher stage of endometrial cancer.<sup>129</sup> Thus, specific and validated adipokines may predict not only the presence but also the extent of the disease.

These results must be interpreted cautiously given the limitations of a nonrandomized study design as well as conflicting results. For example, Terlikowska et al. measured levels of inflammatory markers

associated with obesity and angiogenesis in preoperative serum samples of 176 patients with endometrial cancer. Although both angiopoietin-2 and C-reactive protein were predictive of clinical stage and significantly associated with poor prognosis, no measured obesity-associated factors, including adiponectin, IGF-1, and insulin, were significantly associated with stage or outcomes.<sup>131</sup> Similarly, a prospective, case-only study of the Nurses' Health Study database identified no relationship between BMI, all-cause mortality, or endometrial cancer-specific mortality. The study did find expression of several obesity-associated factors, including adiponectin 1/2, LEPR, and IGFR-1/2, in tissue specimens from 360 patients.<sup>132</sup> Further studies are needed to establish the clinical utility of using adipokines as biomarkers for endometrial cancer risk, progression, and outcomes.

## Endometrial cancer and adipokines: A summary of recent discoveries

The ever-expanding obesity epidemic poses a significant concern, especially given its clear association with endometrial cancer. Collectively, these findings identify important relationships between obesity, several adipokines, and endometrial cancer progression but not necessarily initiation. Future investigations should establish the linkage of adipokines to endometrial cancer to advance therapeutic targets as well as validate the role of adipokines as biomarkers of endometrial cancer risk and extent.

## Ovarian cancer

### A proposed link between ovarian cancer and adiposity

Epithelial ovarian cancer is one of the most lethal gynecologic malignancies comprised of heterogeneous histologic subtypes. Patients often present with advanced-stage, metastatic disease.<sup>101</sup> Ovarian cancer cells often metastasize to the adipose-rich environment of the omentum. This predilection suggests a cross-talk between epithelial ovarian cancer cells and this fat pad covering the majority of abdominal organs.<sup>133,134</sup> As with breast and endometrial cancer, obesity is associated with a worse prognosis in epithelial ovarian cancer, albeit the correlation between the two is not as strong.<sup>134</sup> Several potential mechanisms underlie this relationship, including metabolic alterations, immune microenvironment modulation, and chronic low-grade inflammation due to obesity. Diet also contributes to inflammation as a high-fat diet has been shown to enhance ovarian cancer progression and upregulate inflammatory markers IL-6, IL-1 $\beta$ , and TNF $\alpha$ .<sup>135</sup> Estrogen-mediated signaling via ER $\alpha$  also links obesity to ovarian cancer as ovaries are both the primary producers and targets of estrone (E1) and estradiol (E2). ER $\alpha$  activation enhances downstream upregulation of proteins involved in cell proliferation, motility, and invasion.<sup>136</sup>

Adipokine-mediated progression, metastases, and chemoresistance are all implicated in epithelial ovarian cancer (Figure 6).<sup>137</sup> It is chal-

lenging to separate associations from the mechanistic impact that adipokines such as adiponectin and leptin may have on ovarian cancer, especially as studies demonstrate conflicting results regarding their significance.<sup>138-140</sup> Understanding the role of adipokines in epithelial ovarian cancer not only can improve therapeutic options for this lethal disease but also may aid with earlier diagnosis.

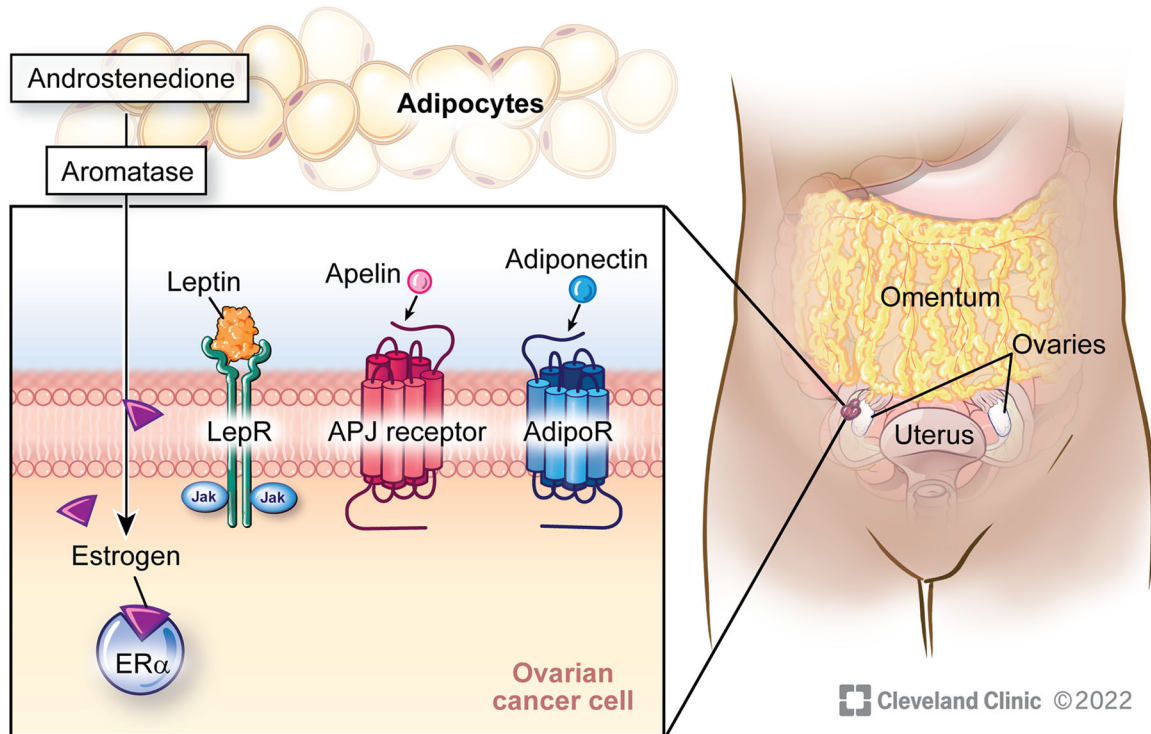
## Leptin and estradiol interactions in ovarian cancer

As in breast and endometrial cancer, leptin has been studied in relationship to cancer progression, metastases, and chemoresistance in ovarian cancer.<sup>141,142</sup> Isolated studies have identified leptin as a biomarker for disease although further randomized assessments are needed to validate these findings.<sup>143,144</sup> Leptin signaling via the JAK/STAT3 pathway upregulates ER $\alpha$  transcriptional activation, mediating ovarian cancer progression.<sup>141</sup> This effect may be independent of the E2 ligand. For example, in leptin treatment of human-derived SKOV3 ovarian cancer, estrogen-insensitive cells demonstrate activation of ER $\alpha$  independent of E2. Transcription of ER $\alpha$  resulted in enhanced cellular proliferation and invasion in an MMP9-dependent manner.<sup>141,145</sup> These findings contrast with those of Hoffmann et al. who demonstrated that leptin treatment does not enhance proliferation and migration in SKOV-3 cells, which are low LEPR expressing. However, OVCAR-3 human ovarian cancer cells, which are high LEPR expressing, demonstrate increased invasiveness via MMP9 with leptin treatment. Interestingly, E2 and leptin costimulation of OVCAR-3 cells antagonized MMP9-mediated cell migration. These findings were reversed by inhibiting the PI3K pathway, indicating that E2's regulation of leptin-induced OVCAR-3 migration is mediated by PI3K.<sup>146</sup> Therefore, the complexities underlying the relationships between leptin, ER $\alpha$ , and E2 are still under investigation.

## Adipokine-mediated chemoresistance in ovarian cancer

Chemoresistance in ovarian cancer poses a significant challenge as greater than 80% of patients will recur after the initial response to chemotherapy and develop chemoresistant disease.<sup>147</sup> The association of poor survival outcomes in ovarian cancer with obesity suggests a possible role for adipocyte-mediated inflammation, metabolic dysregulation, and adipokine signaling in chemoresistance.<sup>147,148</sup> Indeed, Gu et al. demonstrated that high leptin expression correlates with worse overall survival in a cohort of patients treated with first-line taxane therapy.<sup>149</sup> Leptin treatment of HO8910PM and OV-MZ-15 ovarian cancer cells increased chemoresistance to taxanes and cell viability. These same effects were not observed with platinum-based chemotherapy *in vitro*. Gene expression in patients with primary platinum-taxane chemotherapy demonstrated enriched gene sets in patients with high leptin expression, including EMT, NF $\kappa$ B-TNF $\alpha$ , and IL6-JAK-STAT3 signaling pathways.<sup>149</sup> These *in vitro* findings correlate with patient data, as the ratio of the serum tumor-antigen CA-125





**FIGURE 6** Adipokines as well as autocrine and paracrine estrogen signaling enhance the tumorigenic properties of ovarian cancer cells. The peripheral conversion of androgens to estrogen via aromatase drives ovarian cancer progression in a hormone-sensitive manner. Further, adipokine-mediated signaling may enhance, diminish, or yield a mixed tumorigenic effect. Abbreviations: AdipoR, adiponectin receptor; ER $\alpha$ , estrogen receptor alpha; LepR, leptin receptor. Reprinted with permission, Cleveland Clinic Foundation ©2022. All rights reserved.

to leptin levels in ascites has a specificity of nearly 90% for predicting chemoresistant disease. This study though focused on platinum rather than taxane resistance, limiting the conclusions that can be drawn from these findings.<sup>150</sup> While leptin has been the focus, Qiu et al. investigated the impact of resistin on cisplatin resistance in ovarian cancer. Resistin enhanced platinum resistance, EMT, and stemness by downregulating three miRNAs that are known inhibitors of EMT.<sup>151</sup> Together, these findings demonstrate that increased levels of adipokines may contribute to chemoresistance in ovarian cancer in a similar manner observed in breast cancer.

### Apelin and ovarian cancer

The adipokine apelin is an endogenous ligand for the G-protein coupled receptor APJ. Apelin has been studied in several cancer types, shown to promote proliferation, migration, and angiogenesis via the PI3K-Akt-mTOR and PKC-ERK pathways.<sup>152</sup> In high-grade serous ovarian cancer, apelin tumor expression is increased in patients with obesity. Increased apelin and APJ expression correlates with worse prognosis, enhanced proliferation, and cell migration via upregulation of STAT3, ERK, and AKT.<sup>153,154</sup> Dogra et al. studied the apelin-APJ-STAT3 signaling pathway. Apelin stimulated lipid uptake via the transmembrane facilitator of fatty acid transporter CD36, promoting lipid utilization to support cell proliferation and survival at the site of metastasis.<sup>155</sup> In contrast, Hoffman et al. identified a protective role of

apelin in ovarian cancer.<sup>156</sup> Although both apelin and E2 independently enhanced the proliferation of OVCAR-3 cancer cells, cotreatment abrogated the proliferative effects of E2 independent of canonical intracellular signaling. This argues for a cross-talk between apelin/APJ and ER $\alpha$  that results in decreased cell proliferation.<sup>156</sup> Although much research points to the tumorigenic nature of apelin in epithelial ovarian cancer, the mechanisms underlying apelin signaling are complex.

### Adiponectin and ovarian cancer

Decreased serum adiponectin and expression of adiponectin receptors AdipoR1 and AdipoR2 are associated with poor outcomes in ovarian cancer.<sup>157-159</sup> However, limited studies have investigated the underlying mechanisms related to these findings. The protective role of adiponectin in ovarian cancer was studied via AdipoRon, a small molecule agonist of the adiponectin receptor. Its activity on AdipoR1 and AdipoR2 enhances phosphorylation of AMPK, inhibiting cell cycle progression and promoting tumor cell apoptosis.<sup>160</sup> Further, adiponectin treatment of OVCAR-3 and SKOV-3 cells *in vitro* appears to reverse the stimulatory effects of E2 and IGF-1 via downregulation of their respective receptors.<sup>161</sup> The beneficial role of adiponectin in epithelial ovarian cancer is not without controversy, especially due to its role in angiogenesis. In a study by Ouh et al., adiponectin treatment of SKOV3 cancer cells with a VEGF knockdown demonstrated

enhanced angiogenesis via increased expression of CXC chemokine ligand 1, a known proangiogenic factor associated with ovarian cancer proliferation and migration.<sup>162</sup> Further investigations into the role of adiponectin in epithelial ovarian cancer are warranted.

## Ovarian cancer and adipokines: A summary of recent discoveries

Although the link between ovarian cancer, obesity, and adipokines is not as strong as endometrial and breast cancer, the propensity of ovarian cancer to hone to the omentum highlights a clear need to investigate pathways that activate ovarian cancer growth and promote metastases. The mechanisms underlying this preference are likely complex and may be better explained by metabolic derangements and inflammatory processes present in obesity rather than direct adipokine signaling. Investigations to identify the role of obesity in ovarian cancer progression and weight loss as a therapeutic option to mitigate metastases are needed, and results from ongoing trials may elucidate such links (Table 2).<sup>163,164</sup>

## CONCLUSION

Recent studies identify adipokines as key players in obesity-driven disease in breast, endometrial, and ovarian cancer. The upregulation of inflammatory adipokines and downregulation of anti-inflammatory adipokines by obesity alters tumor microenvironments which directly impact tumorigenic signaling cascades. Although obesity alters adipokine expression in a similar manner in all three cancer types, such as increased leptin expression, studies demonstrate widely varying tumor cell responses between each disease state (Table 3). Therefore, breast, endometrial, and ovarian cancer must continue to be studied as distinct diseases in relation to obesity. Further, therapeutic interventions targeting key emerging pathways may not demonstrate efficacy in all cancer types. Nonetheless, obesity in the three cancer types explored is a protumorigenic disease state. There is a critical need to address the obesity epidemic at the population level to mitigate its impact on various pathologies, including breast, endometrial, and ovarian cancers.

## AUTHOR CONTRIBUTIONS

S.T.: conception and design, literature acquisition and review, manuscript preparation, manuscript revision. R.V.: manuscript preparation, manuscript revision. O.R.: conception and design, manuscript preparation, manuscript revision, approval of the final submission.

## COMPETING INTERESTS

The authors report no competing interests.

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