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REVIEW

Linking obesity-induced leptin-signaling pathways to common endocrine-related cancers in women

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Abstract

Obesity is related to many major diseases and cancers. Women have higher rates of obesity and obesity is linked to commonly occurring cancers in women. However, there is a lack of knowledge of the unique mechanism(s) involved in each type of cancer. The objective of this review is to highlight the need for novel experimental approaches and a better understanding of the common and unique pathways to resolve controversies regarding the role of obesity in cancer. In women, there is a link between hormones and obesity-associated genes in cancer development. Leptin is an obesity-associated gene that has been studied exten sively in cancers; however, whether the defect is in the leptin gene or in its signaling pathways remains unclear. Both leptin and its receptor have been positively correlated with cancer progression in some endocrine-related cancers in women. This review offers an up-to-date and cohesive review of both upstream and downstream pathways of leptin signaling in cancer and a comprehensive picture of cancer pathogenesis in light of current evidence of leptin effects in several major types of cancer. This work is intended to aid in the design of better therapeutic strategies for obese/overweight women with cancer.

Keywords Leptin · Thyroid · Ovary · Breast cancer

Introduction

Despite the increasing application of innovative technology and diverse lifestyle and diet choices, obesity remains a prevalent global public health issue [1–3]. In the United States, obesity remains a leading cause of morbidity, affecting a third of the population [4]. Furthermore, stroke, heart disease, type 2 diabetes mellitus, and other systemic diseases are also influenced by obesity. There are other contributing factors to these diseases that cannot be altered include age, sex, and genetics. Recently there has been a shift in emphasis by considering modifiable environmental factors such as diet, exercise, smoking, and alcohol intake. Medical interventions could be tailored for susceptible patient groups by altering the modifiable factors to impede diseases.

Epidemiological studies show a connection between obesity and some cancer types. The molecular mechanisms of these obesity-linked cancers are still not well understood. Inflammation and altered adipokine signaling occur along with the disruption of energy homeostasis in the adipocytes. A better understanding of these molecular pathways has the potential to aid in the development of therapies to reduce the incidence and improve prognosis of cancer in the growing population of obese patients. Expression of hormone receptors like the estrogen receptor (ER) in breast cancer are associated with increased body mass index (BMI) [5] Tissue estradiol levels also vary with BMI and are very high in receptor-positive breast cancer [6]. Obesity-linked factors that may potentially contribute to carcinogenesis are well discussed in the literatures. Adipose tissue contributes to various metabolic diseases and cancers; however, it is unknown whether adipose tissue-induced factors and their pathways differ in cancers compared to metabolic diseases.

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Adipose tissue is recognized as an organ of the endocrine system that produces adipokines, the most important member of which is leptin. Leptin is a 16 kDa hormone, with numerous biological functions including acting as a mitogen, suppressing appetite, and regulating energy homeostasis [7, 8]. Serum leptin level directly correlates with obesity with a higher BMI resulting in a higher level of circulating leptin [9–12]. Understanding the role of leptin in obesity-linked malignancies such as endometrial, postmenopausal breast, ovarian, and thyroid cancer is crucial. In cancer cell lines, leptin can be both mitogenic and anti-apoptotic. Recent studies suggested that the ratio of leptin to adiponectin is more important than the exact amounts of these hormones in relation to carcinogenesis [13]. Its actions depend on its capacity to bind with its membrane-bound receptor protein (ObR), which is demonstrated in two forms of hypothalamic neurons. Research shows that leptin and ObR are demonstrated in a number of tumor cells [14] Once bound to ObR, leptin exerts its effects by initiating the Janus Kinase/Signal Transducers and Activator of Transcription (JAK/STAT) pathway by phosphorylating Tyr986 and Tyr1141 of ObR [15–17]. Leptin has been associated with carcinogenesis via initiating tumor cell proliferation, angiogenesis, and metastasis [18]. The mechanisms by which leptin affects pathways in hormone-related cancers like breast, cervical, ovarian, and endometrial cancers are still unclear.

A 2003−2004 study showed that 31.5% of women aged 60 and older were obese. However, a 2011−2012 study showed that this number had risen to more than 38% [4, 19]. The increase in the incidence of hormone-related cancers in women could be related to the increase of obesity in postmenopausal women. The aim of this review is to compile and assess the published studies over the past 10 years that provide evidence for a biological link between leptin and estradiol-mediated pathways in breast, ovarian, endometrial, and thyroid cancer.

Leptin in breast cancer

Breast cancer is the most prevalent cancer and the second leading cause of cancer-related death among women. Obesity is thought to promote breast cancer and to be an important risk factor for this disease [19]. In both pre- and postmenopausal women, breast cancer frequently recurs and results in death [20, 21]. Native Hawaiian women with a BMI ≥ 30 kg/m^2 show 82% higher risk of developing breast cancer as opposed to those with BMI of 20−24.9 kg/m^2 [22].

The incidence of breast cancer is also associated with higher levels of estrogen from the aromatization of androgens in adipose tissue in postmenopausal women [23–25]. Shimizu et al. reported that leptin gene expression in adipose tissue could be regulated by estrogens [26]. Higher levels of leptin and estrogen increase breast cancer oncogenesis as well as survival of cancer cells [27, 28]. CYP1B1, an extrahepatic enzyme found in ER-alpha-positive MCF-7 cells, is upregulated by leptin [27]. When the enzyme combines catechol estrogens with oxygen, they become chemically reactive semi-quinone and quinine intermediates that then form DNA adducts to promote breast cancer development [27].

In vivo studies of leptin-induced breast cancer

Serum leptin and insulin levels have been shown to correlate with breast cancer occurrence [24, 25, 28]. These studies appear to show the involvement of inflammatory pathways although no clear proinflammatory connection has been proposed. Grossman et al. found that when leptin-deficient mice and leptin receptor-deficient mice were crossed with transgenic mice that develop mammary tumors, mice without leptin or leptin receptors did not develop tumors. This was in contrast to mice with leptin and leptin receptors, which developed tumors at a rate of 50−69% [29]. The study suggests that leptin is expressed in malignant epithelial cells of the breast [30]. While a number of studies point to leptin as having a direct correlation with the occurrence of breast cancer, a number of studies show contradictory results, failing to exhibit a positive correlation between the risk of breast cancer and leptin levels [31, 32]. The studies of Gunter et al. showed that although there was little correlation between the levels of leptin and breast cancer risk, there was a positive correlation between estradiol and the occurrence of breast cancer [25]. It is possible that these different results were due to small sample size or factors such as hormone status and/or the stage of the disease [29]. Stage of disease may be particularly important given the weight loss that frequently occurs in late stage cancer. According to Al-Shibli et al., based on immunohistochemistry results, it is the overexpression of leptin receptor rather than leptin that contributes to breast cancer [33]. Although both adiponectin and leptin are implicated in oncogenesis, it is leptin that may stimulate invasion, angiogenesis, and metastases. The increased morbidity and mortality of cancer in overweight and obese breast cancer patients could be related to decreased effectiveness of cancer therapy in these patients as a result of leptin activity [34].

Adipose stromal/stem cells were found to influence the primary tumor growth and metastasis of breast cancer cells through a leptin-mediated pathway utilizing SERPINE1 and matrix metalloproteinase-2 (MMP-2) [35, 36]. An in vivo study in rats by Imaoka et al. shows that an increase of serum leptin/insulin levels associated with obesity raise the

energy required for protein synthesis in cancer cells and expedite oncogenesis [37]. Another study shows that tumorigenesis related to leptin is brought about by inducing autophagy through the p53/FOXO3A axis [38].

In vitro studies of leptin effects on breast cancer

In vitro studies show that leptin increases breast cancer cell proliferation and survival by upregulating protein kinase (MAPK) stimulated by mitogen, Janus kinase 2-signal transducer, and activator of transcription 3 (JAK2-STAT3), and phosphatidylinositol 3-kinase protein kinase B (PI3K-AKT) [23, 32, 33, 36, 39–41].

The induction of cyclic AMP was shown to down-regulate adhesion molecules and leptin-induced migration of breast cancer cells in vitro [42]. Activation of the leptin receptor, OBR has been shown to enhance cell migration and invasive activity of breast cancer cells [19]. OBR has two primary isoforms, a long and a short fors. When leptin binds to OBR1, the long form of the receptor stimulates the JAK2/STAT3, MAPK/ERK1/2, and Phophoinositide 3-Kinase (PI-3K)/AKT1 pathways, as established by in vitro studies [41] (Fig. 1). Studies also show that the knockdown of leptin genes cause the downregulation of a series of downstream genes [7]. Transcription of vascular endothelial growth factors (VEGF)/VEGFR2 was upregulated by leptin in ER+ and ER− cells [43] (Fig. 1). A different study showed that leptin signaling was positively regulated and leptin-caused proliferation and migration of cancer cells was encouraged by the adaptor protein, APPL1 [44]. In conclusion, leptin has been shown to activate leptin receptors and stimulate many downstream signaling pathways that are important for breast cancer progression (Table 1).

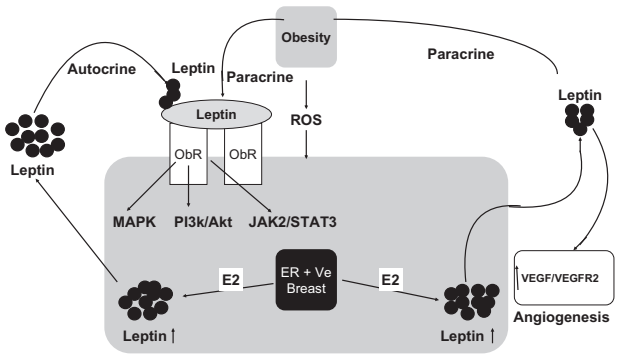

Fig. 1 Schematic representation of obesity-linked leptin-signaling pathways in breast cancer. Leptin produced from adipose tissues can directly or indirectly via ROS production, induce leptin receptor expression in cancer cells (paracrine manner). ER-positive breast cancer cells can induce leptin production endogenously in cancer cells by estradiol (E2), which in turn activate leptin receptor in cancer cells (autocrine manner) and activate MAPK, PI3K/Akt, and JAK2/STAT3 pathways. Exogenous leptin can upregulate VEGF/VEGFR2 in the endothelial cells and induce angiogenesis. ObR leptin receptor, ROS reactive oxygen species

Inflammatory pathways of leptin in breast cancer

Leptin is also secreted from breast cancer cells and acts both in an autocrine and paracrine manner to assist angiogenesis, tumor cell proliferation, migration, and invasion. Leptin induces expression of proinflammatory cytokines [45]. Research has shown that obesity produces an imbalance between proinflammatory and anti-inflammatory markers and local inflammation creates a microenvironment that favors tumorigenesis [9]. A greater concentration of leptin could influence metastasis as leptin is implicated in inflammatory pathways, given its effects on tumor cell migration and invasion. Both proinflammatory and anti-inflammatory cytokines have been associated with mammographic density, which is a strong breast cancer risk indicator, thus supporting the notion that inflammation can induce breast tumorigenesis [46]. An interleukin (IL-1) signal is associated with leptin's proangiogenesis signature in breast cancer [47]. Leptin was found to activate multiple signaling pathways, contributing to the upregulation of the IL-1 pathway at the transcriptional and translational levels in breast cancer cells. When IL-1 signaling is blocked, leptin upregulation of VEGF/VEGFR2 is also blocked [47]. By inducing nonstop cellular proliferation, genomic instability, and cellular membrane damage, suppressing the antitumor immune response, and raising estrogen levels, proinflammatory factors, like leptin, play a crucial role in breast cancer oncogenesis [46].

Role of estrogen in leptin-induced breast cancer

In obese patients with ER-positive breast cancer, leptin is overexpressed [48]. In an in vivo study, adipose cells were taken from obese patients and inserted into mice, which ultimately led to enhancement of tumorigenicity of breast cancer cells and modified their gene expression profile [35]. Additionally, elevated leptin levels were correlated with increased proliferation, migration, and invasion capacity of several ER+ breast cancer cell lines [35]. Further, the higher levels of leptin varied directly with the rise in proliferation, migration, and invasion capacity of multiple ER+ breast cancer cell lines [35]. Catalano et al. found that leptin can transactivate ER through activation of MAP kinase pathway and increase aromatase expression in MCF7 cells, promoting cancer progression [40]. Studies have established a bidirectional interaction between OBR and ERs [49]. Knockdown of OBR significantly enhanced the inhibitory effects of tamoxifen on cell proliferation and survival in tamoxifen-resistant breast cancer cell lines [50]. A multivariate regression analysis showed that BMI, leptin, IL-6

Table 1 Signaling pathways in breast cancer

Pathway	Name	References
Inflammatory	VEGF/VEGFR2	Zhou et al. [47]
Angiogenic	VEGF	Bouraget et al. [55]
	SERPINE1/MMP-2	Strong et al. [35]
	JAK2/STAT, MAPK/ERK1/2 and PI-3K/AKT1	Guo et al. [41]
	MAPK, JAK2-STAT3, PI3k-AKT	Guo et al. [41], Liu et al. [23], Niu et al. [32], Wolfson et al. [36]
Estrogenic	MAPK	Catalano et al. [39]
	LKB1/AMPK	Swami et al. [52], William et al. [53]
	JAK/STAT: Tyr986 and Tyr1141	Basu et al. [19]

and reactive oxygen species (ROS) were predictive for the staging of ER+ patients but not for ER− patients, indicating that obesity, inflammation, and ROS play important roles in estrogen-dependent breast cancer prognosis [51]. Studies also demonstrated that vitamin D treatments decreased insulin resistance, reduced leptin, increased adiponectin signaling and also regulated LKB1, the primary upstream kinase of adenosine monophosphate-activated protein kinase (AMPK) pathway contributing to an overall decrease in local estrogen synthesis in obese mice [52, 53]. Research has shown that changes in gene expression in breast epithelial and cancer cell lines exhibiting cancer stem cell properties or during epithelial mesenchymal transition can be attributed to leptin [54] via transforming growth factor β-1 (TGFβ1) pathway and is independent of ER status.

Angiogenic pathway of leptin in breast cancer

Angiogenesis is an important feature of breast cancer progression that requires physiological and pathological stimuli. When isolated endothelial cells (HUVEC) were cultured in the presence of supernatants obtained from mature adipocyte (paracrine) derived from obese women and breast cancer cell lines (autocrine) cultures, both demonstrated an impact on angiogenesis through proliferation, migration, and tube formation [55]. Angiogenesis is induced by VEGF binding to its receptors, VEGFR-1 and VEGFR-2. Solid tumors are treated by inhibiting VEGF-signaling. However, resistance to this blocking effect complicated the treatment strategies due to redundant receptors and/or other proangiogenic factors. One of them is obesity. Adipose tissue secretes many factors, such as leptin, IL6, and tumor necrosis factor α (TNFα) [56]. VEGF is upregulated by several cytokines released by adipose tissue, namely IL-1β, IL-6, IL-8, and TNF-α. In postmenopausal women, the primary source of estrogen is adipose tissue, which may contribute to the development of ER+ breast cancer [57]. Obesity increases cancer cell resistance to therapy via production of IL-6 and/or fibroblast growth factor 2 (FGF-2) [58]. In conclusion, breast cancer is influenced by obesity via many pathways (Table 1) that can trigger drug resistance to therapy. Therefore, the impact of weight reduction on breast cancer progression would provide an important prospective study in a clinical setting.

Leptin in ovarian cancer

Ovarian cancer is the most lethal cancer and fifth leading cause of death in women. Erondu et al. found that obesity was observed in the majority of epithelial ovarian cancer patients [59]. It has been well documented that ovarian cancer is linked to obesity [60]. Vysotskii et al. discovered that patients with benign and malignant ovarian tumors did not exhibit any difference in leptin levels; however, they found a stage-dependent increase in leptin levels in ovarian cancer, and a twofold increase in leptin among those with poorly and moderately differentiated serous ovarian cancer [61]. In both ovarian and endometrial cancers, high OBR expression was noted [62]. In another study, BMI and age but not leptin/adipokine ratio were shown as independent risk factors for ovarian cancer [63].

Role of estrogen on leptin function in ovarian cancer

Obesity has been shown to increase levels of estrogen via conversion of androgens to estrone by the aromatase enzyme in adipose tissue [64]. Thereby high levels of estrogen impact the progression of ovarian cancer. According to Shen et al. the motility and invasion of ovarian cancer is influenced by estrogen. A strong link between obesity and ovarian cancer with inter-study heterogeneity in its incidence has been linked [65] with controversial findings in correlation between obesity and ovarian cancer [66], which could be due to the inter-study heterogeneity. This could be due to confounding factors

such as premenopausal versus postmenopausal discrepancies, infertility, polycystic ovarian syndrome, hormone therapy users versus nonusers or other unknown factors [67]. It may also depend on the study design, for example prospective studies versus case-control studies with population controls, or case-control studies with hospital controls.

Although there have been in vitro studies, the lack of animal models has hindered the elucidation of leptin's role during in vivo cancer progression and invasion. The development of animal models is crucial for future investigations.

In vitro studies of leptin in ovarian cancer

An in vitro study showed that 17β-estradiol has an antagonistic effect on leptin-induced cell migration as well as matrix metalloproteinase-9 (MMP-9) expression and activity and that this occurs via the PI3K pathway in OBR- and ER-positive ($OBR^{+}/ER^{+)}$ ovarian cancer cells [68]. The study showed that the activity and expression of caspase-3 can be inhibited by the interaction of leptin and bisphenol A/estradiol through modulation of the STAT3 and ERK1/2 signaling pathways in an ovarian cell line [69]. According to Choi et al., leptin induces ER transcriptional activation via STAT-3 signaling pathways, thus stimulating ovarian cancer cell growth [18]. The study shows that leptin regulates ovarian cancer cell invasion by stimulating MMP7 expression via ERK and JNK pathways [70]. Ghasemi et al. showed that leptin-induced urokinase plasminogen activator expression requires the involvement of the OBR, RhoA/ROCK, PI3K/AKT, and JAK/STAT pathways as well as nuclear factor activation [71]. It has been shown that superactive human leptin antagonists (SHLA) and leptin mutein are very effective leptin receptor inhibitors in epithelial ovarian cancer cell lines, which could be used to block leptin activity, thereby eliminating its negative effects on carcinogenesis [72]. Leptin has been shown to promote a more aggressive phenotype of ovarian cancer cells [73] and to stimulate migration and invasion, as well as cancer stem-like properties in ovarian cancer cells [74]. Leptin has been shown to promote growth of an ovarian cancer cell line via upregulating cell-cycle-associated genes, as well as downregulating proapoptotic genes [69]. Wei et al. illustrated that blocking leptin can significantly suppress malignant ovarian ascites induced metastatic aggravation of ovarian cancer cells. These studies indicate that leptin is highly expressed in ovarian cancer and correlate with the poor outcome of ovarian cancer patients. They also provide evidence that recombinant leptin promotes ovarian cancer cells migration, invasion, and proliferation [75]. Therefore, it is very critical to understand the signaling pathways involved in ovarian carcinogenesis.

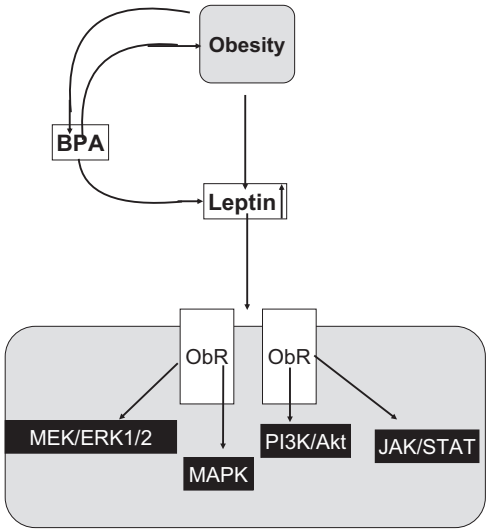

Fig. 2 Schematic representation of obesity-linked leptin-signaling pathways in ovarian cancer. Leptin produced directly from adipose tissues stimulates leptin receptor expression or via activation from BPA in the circulation in ovarian cancer cells. This in turn activates MEK/ERK1/2, MAPK, PI3K/Akt, and JAK/STAT pathway. ObR leptin receptor, BPA bisphenol A

Leptin-signaling pathways in ovarian cancer

It is well documented that leptin induces ovarian cancer cell migration and cell growth via the PI3K/Akt pathway [76, 77] (Fig. 2). Leptin/LEPR signaling via JAK2/STAT3 has been reported by another group (Fig. 2) and has the potential to significantly impact pathogenesis in a subset of ovarian cancer [78]. High coexpression of leptin and LEPR show a significant correlation with decreased patient survival. Studies found that cell growth could be induced when leptin activates the MEK/ERK1/2 pathway (Fig. 2) [18, 76]. Additionally, it has been observed that apoptosis can be inhibited if leptin upregulates the expression of cyclin D1 and Mcl-1 [76]. Choi et al. have shown the expression of multiple short and long forms of leptin receptors in multiple ovarian cancer lines [18]. It was shown that with leptin treatment, the growth of ovarian cancer cells occurred via the ERK pathway but also via inhibition of phosphorylation of p38 MAPK [79] (Fig. 2). Hoffmann et al. observed that when the E2 and leptin were combined, E2 acted as an antagonistic agent by inhibiting leptin-induced cell migration through the activation of the PI3K/AKT pathway (Fig. 2). The signaling pathways in ovarian cancer are summarized in Table 2.

Leptin in endometrial cancer

Endometrial cancer (EC) is one of the most common cancers in women in developed countries. A higher incidence

Table 2 Signaling pathways in ovarian cancer

Pathway	Name	References
Inflammatory	None specified	NA
Angiogenic	PI3K	Hoffmann et al. [68]
	STAT3/ERK1&2	Ptak et al. [69]
	ERK and JNK	Ghasemi et al. [70]
	RhoA/ROCK, PI3K/AKT, and JAK/STAT NF-kB	Ghasemi et al. [70]
	MEK/ERK1/2	Choi et al. [18], Chen et al. [76]
	JAK2/STAT3	Kumar et al. [78]
	STAT3	Choi et al. [18]
Estrogenic	PI3K/Akt	Chen et al. [76]

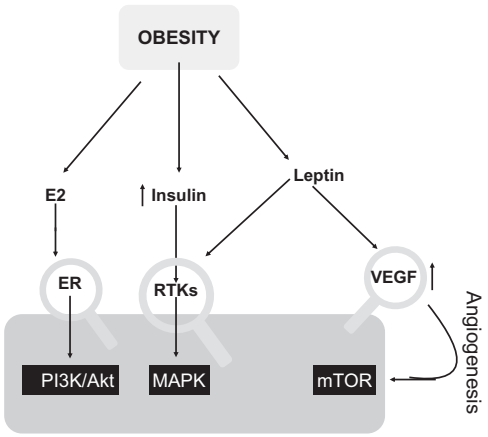

Fig. 3 Schematic representation of obesity-linked leptin-signaling pathways in endometrial cancer. Obesity-induced leptin can activate RTKs directly and activates mTOR pathway indirectly via upregulation of VEGF through angiogenesis; estradiol (E2) stimulates ER in endometrial cells and induce PI3K/Akt pathway and insulin can stimulate MAPK pathway through RTKs activations. RTKs receptor tyrosine kinase superfamily

rate is observed between 55 and 64 years of age. More than half of EC is associated with obesity, which is considered an independent contributor to EC [80]. Despite an increased EC risk in obese women, the impact of obesity on clinical and histological phenotypes is poorly understood. The strong positive association between EC incidence and BMI warrants further research to understand the mechanisms involved in this obesity-driven oncogenesis and implications for patient therapy.

Leptin-signaling pathway in endometrial cancer

Excess body weight is thought to influence EC development primarily through three different mechanisms which include excess estrogen levels, insulin-mediated effects, and secretion of proinflammatory mediators from the adipose tissue [2, 80, 81]. These systemic signals mediate cellular effects, including activation of the ER and receptor tyrosine kinases (RTKs), which induce activation of a wide range of intracellular signaling pathways, including expression of ER target genes and increased PI3K- and MAPK pathway signaling (Fig. 3) [80].

Two large population-based studies report that increased BMI is strongly associated with cancer-specific mortality from EC [82–84]. In contrast, other studies show an association of obesity with less aggressive pathologic features [85, 86] or improved outcomes [84–90]. This discrepancy may be due to the inclusion of both serous and endometrioid subtypes, which have different genomic underpinnings [91].

Loss of phosphatase and tensin homolog (PTEN) is the most common PI3K pathway alteration in EC and is reported in over 50% of cases. The loss occurs via mutation, methylation, or chromosomal loss [92–94]. PTEN protein loss can be induced by microRNA and protein degradation [95]. EC shows 50% mutations in *PIK3CA*, the gene that encodes the catalytic subunit of PI3K (p110α), and 30% *PIK3R1* mutations, the gene that encodes the regulatory subunit of PI3K (p85α) [91, 96–98]. A report showed an improved outcomes in obese patients with concurrent p27Kip and PTEN loss [99]. Interestingly, the study showed that PTEN loss in obese patients was associated with an improved outcome while PTEN loss in nonobese patients was associated with a worse outcome. This indicates a close link between metabolism and the consequence of tumor suppressor loss. A recent study showed an increased association of the MAPK pathway in nonobese patients with early stage tumors [100]. In contrast, some studies showed no significant association between obesity and estrogen signaling pathways in histological subtypes of ECs [101, 102]. These studies conclude that there is no association between histological grading and the weight of women affected by EC.

Reports indicate that angiogenesis plays an important role in EC progression. EC oncogenesis depends on angiogenesis for oxygen and nutrients and obesity can facilitate both growth and progression via many angiogenic factors. An increased angiogenesis is associated with unfavorable outcome of EC; therefore, it is important to understand the pathways involved in EC angiogenesis so that these can be targeted for future therapy.

Obesity-induced angiogenic pathway in endometrial cancer

Studies showed that VEGF protein expression is upregulated in visceral adipose tissue (VAT) in obese patients [90, 103, 104], and is linked with increased tumor growth in an in vivo xenograft model [105]. Activation of the PI3K/

AKT/mTOR pathway increases tumor size, a downstream target of VEGF signaling and its suppression decreased the growth-promoting effects of VAT on endometrial cancer cells [106]. In a hyperphagic obese mouse model that mimics human obesity, pathologic changes in endometrial cells are associated with obesity via hyperactive mTOR signaling (Fig. 3). An increase in tumor vasculature and VEGF-mTOR activity were observed in human tissues from obese endometrial cancer patients compared with nonobese patients [103, 107, 108]. These results indicate that VEGF-mTOR signaling is critical for endometrial cell growth that leads to hyperplasia and cancer [103, 109]. The peroxisome proliferator-activated receptor (PPAR)/retinoid X receptor (RXR) pathway contributes to EC oncogenesis by VEGF secretion; PPARα activates VEGF secretion, whereas PPARγ reduces VEGF [110]. Recently, angiogenesis inhibitors have been used in endometrial cancer, alone or in combination with chemotherapy. These include anti-VEGF monoclonal antibodies (bevacizumab and aflibercept), together with mammalian target of rapamycin inhibitors (mTORi) (everolimus, temsirolimus and ridaforolimus), PI3K inhibitors (BKM120), tyrosine kinase inhibitors (brivanib, sunitinib, dovitinib and nintedanib) and thalidomide [108]. Some of these agents show benefit whereas others show no benefit; therefore, identifications of tumor subtypes and specific-pathways where specific treatments are effective will be important to improve outcomes with molecularly targeted agents used combination therapy.

Obesity-induced inflammatory pathways in endometrial cancer

Obesity can induce both local and systemic inflammation. It is very important to identify the mechanistic link between obesity-induced inflammation and EC progression to improve prognosis and therapeutic strategies via targeting these pathways. There are multiple inflammatory pathways involved in EC pathogenesis [111]. Inflammatory pathways mediating EC pathogenesis can be (1) estrogen-dependent (STAR) or (2) metabolic-dependent (AKRB10, aldo-keto reductase). AKRB10 is a common mediator of different inflammatory pathways [111], including lipid synthesis that stabilizes acetyl-CoA carboxylase-α to promote de novo fatty acid/lipid synthesis. Adipose tissue-induced proinflammatory cytokines can trigger inflammation and mediate cancer progression. A study of the role of inflammation and obesity in the context of EC biomarkers showed that the levels of sex hormone binding globulin, C-peptide, insulin, insulin-like growth factor binding protein 1 (IGFBP1), adiponectin, C-reactive protein (CRP), and TNFα after bariatric surgery approached the level of markers in the control group. Multiple regression analyses revealed significant relationships between changes in BMI and biomarker levels. Changes in IL-1Rα were significantly associated with race [112]. It was also shown that decreasing BMI was associated with lower levels of these inflammatory markers. This implicates obesity as a component of the inflammatory pathway in cancer and suggests that it could be reversed by weight loss. Table 3 shows all signaling pathways involved in EC.

Table 3 Signaling pathways in endometrial cancer

Pathway	Name	References
Inflammatory	None specified	NA
Angiogenic	PI3K/AKT/mTOR	Chen et al. [106]
	VEGF/mTOR	Sahoo et al. [104], Westin et al. [107], Papa et al. [108]
Estrogenic	PI3K/MAPK	Onstad et al. [80]
	MAPK	Mauland et al. [84]

Leptin in thyroid cancer

Epidemiologic evidence indicates that obesity is associated with a high risk of thyroid cancer (TC). Several studies indicated that that sex influences the association of obesity status with TC and obesity was only associated with TC in women [113–117]. In a separate population study performed in New Caledonia, BMI was found to be strongly related to TC risk [118, 119] in women but not in men [120]. A similar association was reported in a prospective European study by Rinaldi et al. [121], who found an association of TC risk with obesity only in women (HR highest versus lowest BMI quintile 1.41 [CI 1.03–1.94]). Likewise, in an American cohort studied by Meinhold et al., only women with a BMI > 35 kg/m^2 (and not men) had a significantly higher risk of TC compared to normal-weight individuals [122]. Higher BMI was also related to increased TC incidence in women in the prospective European cohort study by Almquist et al. [123]. Similarly, in a recent large Korean study that used thyroid ultrasonography screening in 15,068 euthyroid subjects, obesity was found to be significantly related to TC risk in women. This finding was independent of age, smoking, and TSH levels. Again, this relation was not significant in males [124].

Obesity on thyroid cancer subtypes

The role of obesity among different TC subtypes has also been examined [125]. Engeland et al. performed a histopathology-focused analysis showing that the relative risk for follicular and papillary thyroid cancer (PTC) increased with higher BMI values, and this was linked to both men and women [126], which is contradictory to other

analyses. Additionally, in a large U.S. prospective study, the relative risk for PTC increased with rising BMI values, whereas only a trend was noted for follicular and anaplastic TCs and no relation could be demonstrated for medullary TC [125, 127].

Given the rising prevalence of both TC and obesity, it is important to clarify their connection with TC to the mediating pathways. Leptin is an essential component of thyroid cancer progression [14, 128–131]. Researchers have found that, in contrast to controls, serum leptin levels were notably higher in well-differentiated thyroid cancer (WDTC) patients with a remarkable decrease after surgery [131]. The levels of serum leptin differed in follicular lesions, which is an ongoing challenge in diagnosis for pathologists. Tumor size is influenced by leptin and/or ObRs in PTC [132]. Fan et al. showed a strong correlation of leptin expression with ObR expression in PTC, follicular (FTC) and anaplastic thyroid cancer (ATC) [14]. Leptin and ObR showed negative prognostic significance in PTC as opposed to FTC and ATC [14]. In some cases of PTC, overexpression of adiponectin receptors was noticed and linked with an improved prognosis [133, 134]. Therefore, leptin-signaling pathways are important for thyroid cancer in obese individuals. It is also important to differentiate the signaling pathways for thyroid cancer from that of metabolic syndrome related to obesity [114, 135].

Obesity-induced signaling pathway in thyroid cancer

Obesity-induced signals and TC-promoting effectors have displayed a direct link. It was formerly demonstrated that leptin stimulates the STAT3 pathway (Fig. 4) [136, 137]. In recent studies, it was shown that activation of the STAT3 pathway is inversely related to PTC behavior, presented in both clinical specimens [138], as well as in mouse models [136, 139]. According to others, a rise in circulating insulin and bioavailable IGF-1 in obese individuals depicts another logical participating factor, particularly in reference to the key role of IGF-1 signaling in thyroid proliferation [140]. The elevated basal activation status of the PI3K/AKT pathway (Fig. 4) in the mice harboring both thyroglobulin PV gene ($Thrb^{Pv/Pv}$)/Pten heterozygous ($Pten^{+/-}$) crossing develops aggressive FTC. Another study showed the contributions of activated ERK1/2 and STAT3 in leptin-induced thyroid cancer cell growth and invasion, but not by a new functional OB3 peptide, which is a derivative of leptin with lack of mitogenic effects of leptin on thyroid cancer cells [141]. This compound may be functional to induce metabolic effects in obese individuals but not cancer, which requires further investigations. All the signaling pathways in TC are summarized in Table 4.

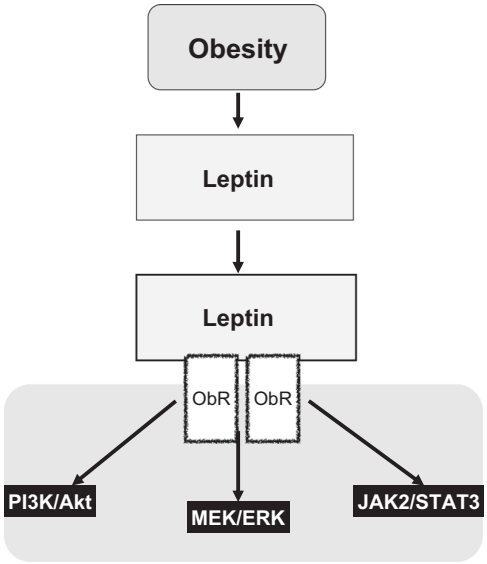

Fig. 4 Schematic representation of obesity-linked leptin-signaling pathways in thyroid cancer. Leptin produced from adipose tissues can directly induce leptin receptor expression in thyroid cancer cells and activates PI3K/Akt, MEK/ERK, and JAK2/STAT3 pathways. ObR leptin receptor

Table 4 Signaling pathways in thyroid cancer

Pathway	Name	Reference
Inflammatory	None specified	NA
Angiogenic	PI3K/AKT	Uddin et al. [137]
	ERK1/2 and STAT3	Kim et al. [142]
	STAT3	Kim et al. [138], Couto et al. [139]
	JAK/STAT3	Kim et al. [142]
Estrogenic	PI3K/AKT	Uddin et al. [137], Liu et al. [23]
	STAT3	Park et al. [136]

In vivo studies of leptin on thyroid cancer

In humans, serum leptin levels in thyroid cancer patients are significantly higher than controls [129]. In PTC, leptin and leptin receptors are expressed and associated with cancer aggressiveness [137]. Control group patients had much lower serum leptin levels compared to WDTC patients. WDTC patients' serum leptin levels significantly dropped after surgery. Even though leptin's prognostic value is still undetermined, it aids in the diagnosis of WDTC. In medullary thyroid carcinomas and control groups, adiponectin and leptin levels were not greatly different [131]. In a mouse model of TC (Thrb (PV/PV) Pten (±) mice), the obese phenotype was caused by feeding the mice a high-fat diet (HFD). This obesity-induced thyroid carcinogenesis can be delayed by inhibiting STAT3 activity in the mouse

model [136]. In ATC, increased serum levels of leptin and increased activation of the JAK/STAT3 pathway cascade has been shown (Fig. 4), which is one of leptin's downstream effector pathways [142]. Earlier reports have shown an association of increased STAT3 activation with ATC. It is interesting, however, that STAT3 activation has recently been inversely associated with PTC behavior, both in clinical specimens [138] and in mouse models [139]. Kim et al. [127] proposed a mechanism that applies to a distinct subset of thyroid tumors, i.e., FTCs and their dedifferentiated derivatives [142]. ERα may be a useful immunohistochemical marker for differential diagnosis of PTC as shown by the differential expression patterns of the two ER subtypes between PTC and normal thyroid gland [143]. The study shows that leptin is a potential prognostic marker associated with an aggressive phenotype and poor disease-free survival and also plays an important role in PTC pathogenesis through the PI3K/AKT pathway via OBR [137]. Elevated leptin levels were decreased after total thyroidectomy, which indicates that leptin may be associated with thyroid papillary carcinogenesis [128]. The serum concentrations of leptin and resistin are influenced by thyroid hormones, which are important regulators of energy balance and intermediate metabolism [144].

It is reported that the increase in circulating insulin and bioavailable IGF-1 in obese individuals represents an additional logical contributing factor, especially in view of the key role of IGF-1 signaling in thyroid proliferation [140]. Via a variety of mechanisms, hyperinsulinemia from obesity leads to the inactivation of AMPK [145] and impaired AMP-activated protein kinase function in the thyroid. This in turn, reduces the activity of PPAR-gamma coactivator-1α. This leads to the coordinated down-regulation of the expression of the Krebs cycle and oxidative phosphorylation genes, impairing mitochondrial function and inducing a compensatory glycolytic switch that favors the transformation process [145]. The authors established a direct role of diet-induced obesity in increasing the aggressiveness of these tumors by feeding regular chow or HFD and comparing the incidence and biological behavior of follicular thyroid tumors in thyroid cancers heterozygous for the Pten mutation ($Thrb^{Pv/Pv}$, $Pten^{+/-}$). The tumors were measured by size, proliferative index, and presence of focal anaplasia [142]. The capsular invasion and prevalence of hyperplasia did not exhibit any differences. This implies that preexisting thyroid lesions, rather than their initiation rate, are biologically impacted by obesity.

In vitro studies of leptin in thyroid cancer

All thyroid cancer cell lines—anaplastic (ARO), follicular (WRO) and papillary (CGTH-W3)—express the long form of leptin receptors, but leptin stimulation does not alter the expression of the sodium-iodide symporter, cell growth or cell cycle [133, 134]. Leptin stimulated migration of PTC cells whereas it diminished migration of ATC and FTC cells [133]. However, in a contradictory in vitro study, leptin stimulated cell proliferation and inhibited apoptosis of PTCs, via activation of PI3K/AKT [137]. Kim et al. previously demonstrated that an HFD effectively induces the obese phenotype in a mouse model of aggressive FTC [142]. They showed that HFD promotes cancer progression through aberrant activation of the leptin-JAK2-STAT3 signaling pathway. Thyroid cancer progression induced by HFD allowed testing for other molecular targets as potential therapeutic interventions in obesity-induced thyroid cancer. Leptin was added to cultures of different thyroid cancer cells that were evaluated for gene expression, proliferation, and invasion. Leptin failed to stimulate cell proliferation, but stimulated cell invasion, and reduced adhesion in ATC cells. Activated ERK1/2 and STAT3 (Fig. 4) contributed to leptin-induced invasion [142]. Both in vivo and in vitro studies implicate obesity-induced leptin and its receptors activation in thyroid cancer oncogenesis and progression. Future studies are needed to determine the relevant signaling pathways in different subtypes of thyroid cancer and the benefit of reversing the impact of obesity through weight reduction.

Conclusion

Obesity continues to be a major global health problem. Numerous cancers are linked to obesity. It is important to understand the etiology and molecular biology linked to obesity for early diagnosis and better treatment. We also found report on sexual dimorphism that has been found in obesity and cancer correlation; a higher association was shown with obese females cancer than that of their male counterparts. Genes may play an important role in the development of obesity as leptin and leptin receptor genes were linked to obesity. The leptin-induced signaling pathway is different from other metabolic pathways. Leptin can function in both autocrine and paracrine manners to trigger the onset of tumorigenesis. Leptin produced either from adipose tissues or from cancer cells binds to leptin receptor. Leptin can stimulate several signaling pathways that are commonly activated by many cytokines in both canonical, i.e. JAK2/STAT/MAPK/ERK1/2 and PI-3K/AKT1 pathways as well as PKC, JNK, and p38 MAP kinase, which are noncanonical signaling pathways [41]. A summary of the signaling pathways is shown in Tables 1–4.

It has been reported that leptin actions are commonly reinforced through crosstalk with multiple oncogenes, cytokines, and growth factors. Procarcinogenic effects of leptin and the anticarcinogenic effects of adiponectin are

two pathways involved in cell proliferation and apoptosis that can be modulated [146]. It is important to emphasize that there are a number of additional leptin-mediated pathways that might further contribute to the increased aggressiveness of thyroid tumors in a predisposed population.

The role of leptin and OBR have been studied in preclinical models of both breast and thyroid cancer. However, very few or no preclinical models have studied their role in endometrial and ovarian cancer. Given the role of leptin and leptin receptor in obesity, a preclinical model, orthotopic patient-derived xenograft would be ideal to test a novel therapy that acts by blocking leptin signaling. Once such a preclinical model is successfully tested, inhibitors of leptin signaling (leptin inhibitors or OBR antagonists alone or in combination) could ultimately lead to clinical trials. Therefore, targeting these pathways in a preclinical model will not only be critical for identifying treatments for obesity-induced cancer, but also for determining the potential impact of lifestyle changes on cancer aggressiveness with relevance for future cancer prevention.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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