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METABOLISM (M DALAMAGA, SECTION EDITOR)

The Role of Adipokines in Breast Cancer: Current Evidence and Perspectives

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Abstract

Purpose

The current review shows evidence for the role of adipokines in breast cancer (BC) pathogenesis summarizing the mechanisms underlying the association between adipokines and breast malignancy. Special emphasis is given also on intriguing insights into the relationship between obesity and BC as well as on the role of novel adipokines in BC development.

Recent Findings

Recent evidence has underscored the role of the triad of obesity, insulin resistance, and adipokines in postmenopausal BC. Adipokines exert independent and joint effects on activation of major intracellular signal networks implicated in BC cell proliferation, growth, survival, invasion, and metastasis, particularly in the context of obesity, considered a systemic endocrine dysfunction characterized by chronic inflammation. To date, more than 10 adipokines have been linked to BC, and this catalog is continuously increasing. The majority of circulating adipokines, such as leptin, resistin, visfatin, apelin, lipocalin 2, osteopontin, and oncostatin M, is elevated in BC, while some adipokines such as adiponectin and irisin (adipo-myokine) are generally decreased in BC and considered protective against breast carcinogenesis.

Summary

Further evidence from basic and translational research is necessary to delineate the ontological role of adipokines and their interplay in BC pathogenesis. More large-scale clinical and longitudinal studies are awaited to assess their clinical utility in BC prognosis and follow-up. Finally, novel more effective and safer adipokine-centered therapeutic strategies could pave the way for targeted oncotherapy.

Keywords Adipokine · Adiponectin · Apelin · Breast cancer · Chemerin · Irisin · Leptin · Lipocalin 2 · Nicotinamide phosphoribosyl-transferase · Obesity · Omentin · Oncostatin M · Osteopontin · Resistin · Visfatin

Abbreviations

ACC	Acetyl-coA carboxylase
ADSCs	Adipose-derived mesenchymal stem cells
AdipoR1/R2	adiponectin receptor 1/ 2
Akt: v-	Akt murine thymoma viral oncogene homolog

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AMPK	5′ AMP-activated protein kinase
APPL1	Adaptor protein phosphotyrosine interacting with PH domain and leucine zipper 1
bax	Bcl-2 associated X protein
BC	breast cancer
bcl-xL	B cell lymphoma-extra large
BMI	Body mass index
CAP1	Adenylyl cyclase–associated protein 1
CPT1B	Carnitine palmitoyltransferase 1B
CSC	Cancer stem cell
c-Src	Proto-oncogene tyrosine-proteine kinase Src
DM	Diabetes mellitus
EMT	Epithelial-mesenchymal transition
eNampt:	Extracellular nicotinamide phosphoribosyl-transferase (eNampt)
ER	Estrogen receptor
ERK 1/2	Extracellular signal-regulated kinase 1/2
FAO	Fatty acid b-oxidation
FASN	Fatty acid synthase
GRP78	Glucose-regulated protein 78
GTP	Guanosine-5′-triphosphate
HER	Human epidermal growth factor receptor
HIF-1a	Hypoxia-inducible factor-1a
HR	Hormone receptor
HRT	Hormone replacement therapy
hsCRP	High-sensitive C-reactive protein
IL	Interleukin
IARC	International Agency for Research on Cancer
IGF	Insulin-like growth factor
IRS	Insulin receptor substrate
JAK	Janus kinase
JNK	Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
MMTV	Mammary tumor virus
Lcn2	Lipocalin 2
LEPR	Leptin receptor
LIFR	Leukemia inhibitory receptor
LKB1	else known as STK11 (serine/threonine kinase 11)
MCF-7	Michigan Cancer Foundation 7
miR	Micro-RNA
MMP	Matrix metalloproteinase
mTOR	Mammalian target of rapamycin
MO25	Scaffolding mouse 25 protein
NAD	Nicotinamide adenine dinucleotide
Nampt	Nicotinamide phosphoribosyl-transferase
NF-κB	nuclear factor-κB
NGAL	Neutrophil gelatinase–associated lipocalin
NILCO	Notch, IL-1, and leptin
OPN	Osteopontin
OSM	Oncostatin M
OSMR	OSM receptor II
OR	Odds ratio
PBEF	pre-B cell colony–enhancing factor
PI3K	Phosphatidylinositol 3-kinase
PPAR	Peroxisome proliferator–activated receptors
PR	Progesterone receptor
RBP-4	Retinol-binding protein
ROCK	Rho-associated coiled coil-containing protein kinase
SHBG	Sex hormone–binding globulin
SIRT1	Sirtuin 1
SMD	Standardized mean difference
STAT	Signal transducer and activator of transcription
STRA6	Stimulated by retinoic acid 6
STRAD	STE20-related adaptor protein
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-α
VCAM-1	Vascular cellular adhesion molecule-1
VEGF	Vascular endothelial growth factor
Wnt	Wingless-related integration site
WC	Waist circumference
WHR	Waist-to hip ratio
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research

Introduction

By 2030 cancer is expected to surpass cardiovascular disease being the prevailing cause of death among all age categories, contributing to a 45% increase in the number of malignancies diagnosis during the next 10 years [1]. This is due to the emergence of the increased prevalence of risk factors, mainly diabesity (diabetes mellitus and obesity) in both developed and developing countries [2].

As a result of the adoption of the Western lifestyle which consists of decreased physical activity and consumption of energy-dense, low-quality foods, the prevalence of excess body weight encompassing overweight and obesity, characterized as a body mass index (BMI) between 25–29.9 and over 30 kg/m^2 respectively, has been dramatically increased worldwide with 18% of children and 40% of adults presenting excess body weight [3]. Moreover, obesity is more prevalent in females than males [4].

Based on reports from the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), there is a causal association between excess body weight/fatness and the risk of cancers in 15 anatomic positions: endometrium, esophagus (adenocarcinoma), colon and rectum, breast (postmenopausal), ovary, gallbladder, liver, kidney, thyroid, pancreas, stomach (cardia), meningioma, multiple myeloma, prostate (advanced cancer, probable evidence), and oropharyngeal space and larynx (probable evidence) [3, 5].

Across the world, breast cancer (BC) constitutes the most commonly diagnosed malignancy as well as the leading cause of cancer death in women [3, 6]. Furthermore, BC survivors represent the biggest category of women living with cancer in the USA and other developed countries [7]. The evidence for a causal association between excess body weight and postmenopausal BC is sufficient with almost 7% of all postmenopausal BC being attributed to overweight/obesity [8]. The pathological expansion of white adipose tissue in excess body weight, characterized as adiposopathy, provokes fat cell hypertrophy and/or hyperplasia; hypoxia and oxidative stress; perturbation in the protein secretory pathway; metabolic, inflammatory, immunologic, and epigenetic alterations promoting neoplastic transformation and growth [9••, 10••].

The current review examines the role of adipokines in BC pathogenesis summarizing the mechanisms underlying the association between adipokines and malignancy. Special emphasis is given also on intriguing insights into the relationship between obesity and BC as well as on the role of novel adipokines in BC development. Hence, elucidating mechanisms interconnecting excess body fatness with BC risk and mortality is of paramount importance for cancer prevention, diagnostics, and therapeutics.

Intriguing Insights into the Relationship Between Obesity and Breast Cancer

The relationship between obesity and BC is complex depending on histologic subtype, menopausal status, and hormone replacement therapy (HRT) [11]. In postmenopausal women, obesity is associated with BC risk, particularly hormone receptor (HR)–positive tumors in the majority of studies [3, 12, 13••] but not HR-negative or triple negative BC [13••]. However, the association between BC and obesity is attenuated in postmenopausal women taking HRT [14]. Moreover, there is robust epidemiological evidence for a dose-response association between visceral obesity, expressed by the anthropometric indices waist circumference (WC) and waist-to-hip ratio (WHR), and postmenopausal BC [3, 5]. Adult weight gain is also related to an increased risk of postmenopausal BC while, paradoxically, elevated weight in young adulthood (between 18 and 30 ages) is inversely related to postmenopausal BC [3, 15]. Interestingly, women with higher body fat levels, determined by dual-energy x-ray absorptionmetry, despite being within the normal BMI range, are at increased risk for invasive postmenopausal BC, underscoring the role of dysregulated metabolic and inflammatory biomarkers associated with excess body fat, particularly trunk fat [16, 17]. More importantly, obesity-associated metabolic disorders such as metabolic syndrome, diabetes mellitus (DM) type 2, and hypercholesterolemia are associated with increased risk for postmenopausal BC, particularly HR-positive tumors [11, 18].

In contrast to postmenopausal BC, obesity is linked to a decreased risk of premenopausal BC [3, 5]. However, many studies have highlighted that obesity is associated with an elevated risk for HR-negative, basal-like and triple negative BC in premenopausal women [11, 13••, 19]. Overall, regarding histologic subtype, obesity could be a potential risk factor of inflammatory and basal-like BC independently from menopausal status [13••, 20]. There is also preclinical evidence from mouse mammary tumors for connections between diet-induced obesity and both basal-like and luminal BC progression but not human epidermal growth factor receptor (HER)-2 and luminal B BC subtypes, despite the fact that these preclinical models do not fully represent human BC subtypes [11, 21, 22].

In both premenopausal and postmenopausal women, obesity is associated with decreased disease-free survival and increased risk of recurrence and mortality, particularly in HR-positive tumors [23, 24]. Besides, excess weight was correlated with increased tumor size and histopathological grade, and positive lymph nodes [13••, 25••]. Postdiagnosis weight gain is related to dismal prognosis especially in women with increased adiposity and sarcopenia [26, 27]. Moreover, obesity has been related with therapy-associated adverse effects comprising lymphedema, chemotherapy toxicity, and infections [11].

Overall, based on the etiologic diversity of BC, more larger prospective studies with sufficient power are required to explore the association between obesity and BC taking into account the menopausal status and the histologic subtype of BC.

Obesity Fat Tissue Promotes a Pro-inflammatory and Pro-oncogenic Environment

Recent evidence has underscored the contribution of the triad of overweight/obesity, insulin resistance, and adipokines in BC, particularly in postmenopausal women**.** Although the role of obesity in BC pathogenesis is not fully elucidated, the main mechanisms linking obesity and adiposopathy to BC comprise the following: (i) alterations in hormonal systems including both steroid hormones and their bioavailability as well as peptide metabolic hormones such as insulin and the insulin-like growth factor (IGF)-1 system; (ii) chronic low-grade systemic inflammation and oxidative stress; (iii) abnormal variations in the levels of adipokines; and (iv) intra-breast fat accumulation [3, 9••, 10••, 28].

As an endocrine tissue, adipose tissue regulates the production and bioavailability of sex hormones, which are considered to mediate the association of adiposity with BC risk by the following: (i) expressing aromatase enzymes, which transform androgens to estrogens, and less active (androstenedione, estrone) to more potent hormonal forms (testosterone,

estradiol) and (ii) by increasing the bioavailability of free estradiol and testosterone, through hyperinsulinemia, elevated IGF-1 bioavailability, and decreased hepatic secretion of sex hormone–binding globulin (SHBG) [3, 29]. In postmenopausal women, the rate of transformation of androgens to estrogens is higher amid obese women [29].

Besides its energy-storage properties, white adipose tissue represents a metabolically dynamic secretory organ producing by a variety of cells (including adipocytes and macrophages) a wide range of functional heterogeneous adipokines, which regulate numerous physiologic and pathologic pathways comprising insulin sensitivity, appetite, inflammation, innate and adaptive immunity, hematopoiesis, and angiogenesis [10••, 30–32]. To date, more than 10 adipokines have been linked to BC, and this catalog is continuously increasing [9••, 33–37]. As fat tissue expands in excess weight, more preadipocytes produce leptin. Hypoxia promotes alterations in the gene expression of adipocytes, particularly in pro-inflammatory adipokines, and the immune environment [13••]. Chronic inflammation in obese adipose tissue is stimulated and sustained by the nuclear factor-κB (NF-κB) [38]. Therefore, obese fat tissue promotes a pro-inflammatory and pro-oncogenic environment. Interestingly, emerging evidence from epidemiologic and translational studies has shown that the local ectopic breast adipose tissue presents deleterious and tumorigenic effects for the development and progression of BC, being associated with a more pronounced hormonal and inflammatory milieu impacting on tumor promotion and progression [10••, 39]. The breast adipose tissue, mostly occupied by adipocytes, represents the breast stroma which secretes adipokines participating in the crosstalk with BC cells and contributing to increased BC cell proliferation, invasion, and resistance to therapy [40]. Cancer-associated adipocytes, which are mainly characterized by their small size and the modification of lipid droplets, are situated in the invasive front of BC cells and represent cardinal mediators of tumor progression via their paracrine and endocrine actions [41].

Whilst the constellation of circulating pro-inflammatory adipokines and cytokines, such as leptin, tumor necrosis factor (TNF)-α, interleukin (IL)-6, resistin, and extracellular nicotinamide phosphoribosyl-transferase (eNampt) is increased in BC, few adipokines such as adiponectin are decreased in BC and are considered protective against breast carcinogenesis [42, 43]. Classic adipokines, including leptin and adiponectin, have been sufficiently examined in BC [30, 44, 45]. Figure 1 shows the main variations of plasma adipokine concentrations and implicated mechanisms in BC.

The connection of adipokines with BC risk and progression is based on the following: (1) altered plasma concentrations in BC patients compared with controls as shown in meta-analyses; (2) their association with advanced stage and dismal prognosis in BC (prognostic biomarkers); (3) their differential expression in malignant and benign breast tissues and their upregulation in breast tumor tissues; (4) their association with cancer therapy resistance (predictive biomarkers); (5) their association with in vivo and in vitro models of BC; (6) the association of genetic polymorphisms of adipokines genes and their receptor genes with BC [9••]. Table 1 depicts meta-analyses examining the association between main adipokines and BC. Table 2 summarizes the main mechanisms of actions of adipokines in BC.

Adipokines and Breast Cancer

Adiponectin and Breast Cancer

Adiponectin is a polypeptide composed of 244 amino acids belonging to the C1q/TNF family of proteins [30]. It was discovered almost simultaneously by four different research groups in the 1990s [30]. Adiponectin is secreted into the circulation mainly by adipocytes and, to a lesser extent, by the skeletal muscle, heart, liver, bone marrow, and central nervous system [30, 46]. Adiponectin affects its target tissues through its receptors: AdipoR1 (specific for skeletal muscle and endothelial cells), AdipoR2 (specific for liver), and T-cadherin [47]. Adiponectin receptors are ubiquitously expressed in healthy as well as in cancerous tissue [30]. Other growth factors such as platelet-derived growth factor, basic fibroblast growth factor, and heparin-binding epidermal growth factor-like growth factor, are also bound by adiponectin [48]. The circulating levels of adiponectin exhibit an inverse association with adipose tissue mass and have been shown to exert protective roles against the development of obesity-related disorders, such as metabolic syndrome, diabetes, cardiovascular diseases, and malignancies [30].

Besides its other properties, adiponectin exhibits anti-proliferative, anti-migratory, and pro-apoptotic actions [9••, 49]. A large but heterogeneous body of data has shown that adiponectin negatively influences carcinogenesis [30]. The principal pathway that is activated by adiponectin is the AMPK/LKB1, a pathway involved in the regulation of cell proliferation, apoptosis, angiogenesis, and cellular metabolism. When adiponectin binds to its receptor, it facilitates the translocation of LKB1/STE20-related adaptor protein (STRAD)/scaffolding mouse 25 protein (MO25) from the cell nucleus to the cytoplasm and promotes the phosphorylation of LKB1. Simultaneously, it activates AMPK that, in turn, inhibits MAPK, PI3K/Akt, WNT-β-catenin, NF-κB, and JAK2/STAT3 pathways [50, 51].

Although the effects of adiponectin on carcinogenesis have been extensively studied, the exact mechanism of its action has not been fully elucidated in the context of BC.

Adiponectin's effects on BC cells depend on their estrogen receptor status. In ER-negative BC cells, it suppresses cell growth and apoptosis, and inhibits proliferation, invasion,

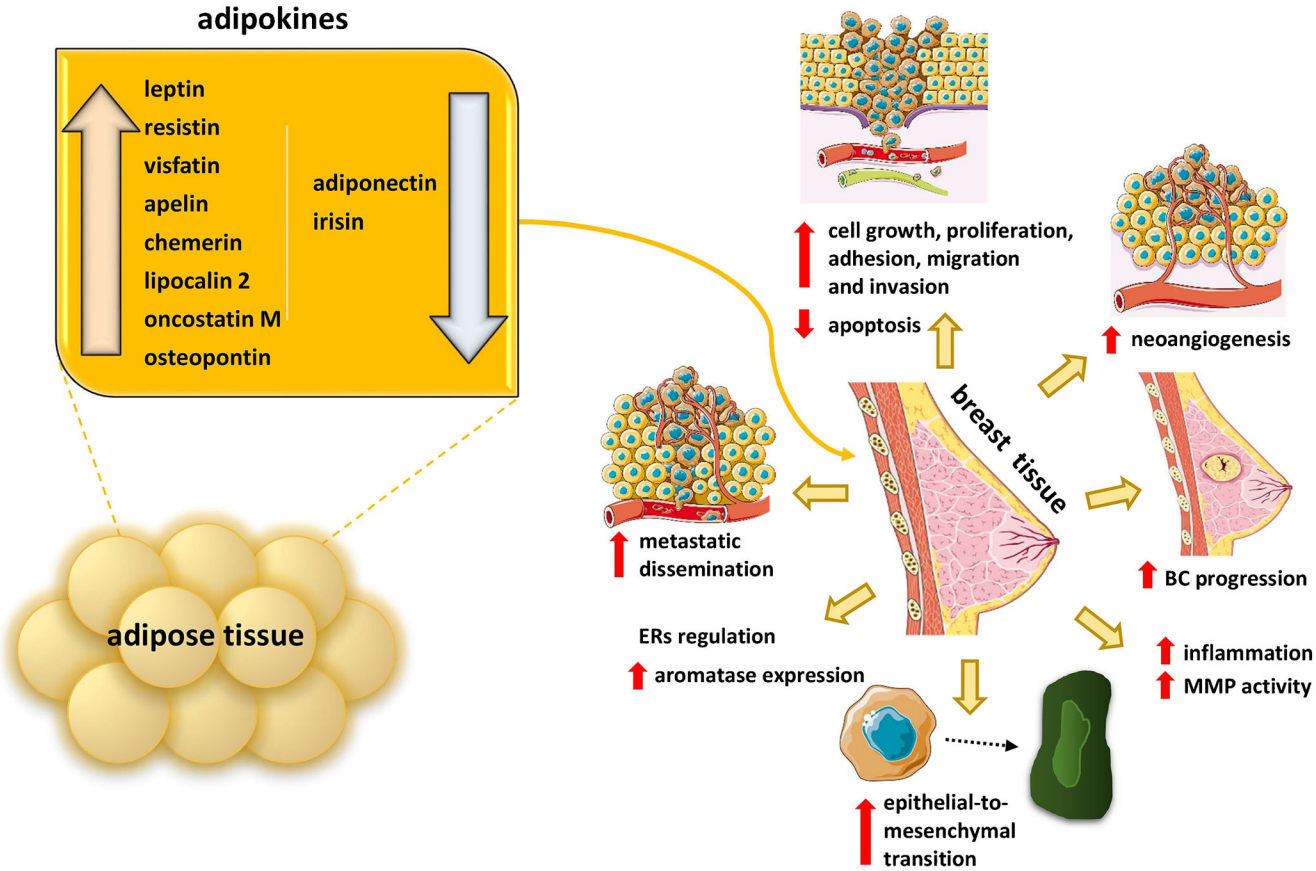

Fig. 1 Important variations of plasma adipokine concentrations and implicated mechanisms in breast cancer. BC, breast cancer; ERs, estrogen receptors; MMP, matrix metalloproteinase. (Both images of breast tissue and images of cancerous cell, angiogenesis, metastatic dissemination, and cell invasion are derived from the free medical site http://smart.servier.com/ by Servier licensed under a Creative Commons Attribution 3.0 Unported License)

and migration [49]. On the other hand, results are contradictory when examining its effects on ER-positive BC cells [52–56]. In ER-positive BC cells, low adiponectin levels permit the interaction of adaptor protein phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1) with AdipoR1, ERα, insulin-like growth factor (IGF-IR), and c-Src [57]. This complex activates MAPK signaling that promotes BC cell growth [57]. Moreover, adiponectin has a differential influence on cyclin D1 expression and tumor progression depending on ER status [58]. Cyclin is downregulated in ERα-negative cells and upregulated in ERα-positive cells, events that correspond to tumor reduction and growth respectively [58]. Studies have shown that ER status may modulate the effect of adiponectin on cell metabolism. Cancer cells rely mainly on aerobic glycolysis (Warburg effect), a property that is largely sustained by regulators such as fatty acid synthase (FASN) and Acetyl-coA carboxylase (ACC) [59, 60]. LKB1/AMPK is also a crucial pathway in regulating energy homeostasis, such as glucose uptake, glycolysis, fatty acid oxidation, and mitochondrial biogenesis [59, 61, 62]. In ERα-negative BC, adiponectin may inhibit fatty acid synthesis through activation of AMPK/ACC, while in ERα-positive BC, it cannot intervene in this process [58, 63].

Adiponectin has also been found in adipocyte exosomes—the lipid bilayer vesicles secreted by adipocytes [64], which constitute mediators of cell-to-cell signaling in the complex tumor microenvironment. Exosomes from human adipose-derived mesenchymal stem cells (ADSCs) and pre-adipocytes promote proliferation and migration of BC cells and BC stem cells respectively. Exosomes secreted by pre-adipocytes also regulate breast tumor stem cell formation and migration [65, 66]. More research is needed to explore the role of exosomic adiponectin in BC.

The most recent meta-analysis by Gu and colleagues investigated the association of serum adiponectin levels and BC finding that serum adiponectin was lower in BC patients irrespective of menopausal status [67•]. Interestingly, two other meta-analyses have found a significant association between adiponectin levels and postmenopausal BC patients but not premenopausal [68, 69]. Macis et al. compared "high" vs "low" adiponectin groups and found a 34% reduction in BC risk favoring the "high" adiponectin group while a subgroup analysis for menopausal status confirmed the association only

Table 1 List of recent meta-analyses examining the association between main adipokines and breast cancer

Meta-analysis (study)	Number of studies	Number of participants	Study outcomes	Comments
Adiponectin				
Gu L et al. Serum adiponectin in breast cancer: A meta-analysis. Medicine (Baltimore) 2018; 97:e11433.	31 case-control studies	7388 breast cancer cases and 8491 controls	SMD: 0.33 ($P < 0.001$)	Lower serum adiponectin levels in BC cases *Subgroup analysis:* Lower adiponectin levels in premenopausal and postmenopausal BC
Gui Y et al. The association between obesity related adipokines and risk of breast cancer: a meta-analysis. Oncotarget 2017; 8:75389–99.	23 case-control studies and 3 cross-sectional studies	3787 breast cancer patients and 5231 healthy controls	SMD: − 0.64 (95% CI: − 0.81, − 0.46; $P < 0.001$)	Lower serum adiponectin in breast cancer patients No significant association between adiponectin levels and menopausal status
Macis D et al. Circulating adiponectin and breast cancer risk: a systematic review and meta-analysis. Int J Epidemiol 2014; 43:1226–36.	15 case-control and cohort studies	4249 breast cancer cases and 5277controls	SRR: 34% (95% CI: 13–50%) Increase of 3 mg/ml of adiponectin corresponded to 5% risk reduction (95% CI: 1–9%)	"Highest" vs "lowest" adiponectin levels risk reduction in breast cancer risk *Subgroup analysis:* Remained significant only in postmenopausal women
Liu L et al. The Role of Adiponectin in Breast Cancer: A Meta-Analysis. PLoS One 2013; e73183.	13 case-control and cohort studies	3578 breast cancer cases and 4363 controls	OR: 0.902 (95% CI: 0.773–1.053)	Higher adiponectin levels did not significantly affect breast cancer risk
Leptin				
Pan H et al. Association between serum leptin levels and breast cancer risk: An updated systematic review and meta-analysis. Medicine (Baltimore) 2018; 97:e11345.	35 case-control and cohort studies	6086 breast cancer patients and 7158 healthy controls	SMD: 0.46 (95% CI: 0.31–0.60)	Higher leptin levels in breast cancer patients *Subgroup analysis:* Significantly higher leptin levels in overweight, obese, postmenopausal, Chinese women
Gui Y et al. The association between obesity related adipokines and risk of breast cancer: a meta-analysis. Oncotarget 2017; 8:75389–99.	23 case-control studies and 3 cross-sectional studies	3787 breast cancer patients and 5231 healthy controls	SMD: 0.96 (95% CI: 0.74, 1.18; $P < 0.00001$)	Higher leptin levels were associated with breast cancer ER+ and postmenopausal cases had significantly higher leptin levels than ER− and premenopausal cases
Niu J et al. The Association between Leptin Level and Breast Cancer: A Meta-Analysis. PLoS One 2013; 8:e67349.	23 case-control and cohort studies	2058 breast cancer patients, 2078 healthy controls and 285 breast benign controls	Combined effect: 0.58 (95% CI: 0.48–0.68)	Higher leptin levels in breast cancer patients *Subgroup analysis:* Higher leptin levels in breast cancer patients independently of menopausal status
Resistin				
Gui Y et al. The association between obesity related adipokines and risk of breast cancer: a meta-analysis. Oncotarget 2017; 8:75389–99.	23 case-control studies and 3 cross-sectional studies	3787 breast cancer patients and 5231 healthy controls	SMD: 1.70 (95% CI: 1.10, 2.30; $P < 0.001$)	Higher resistin levels were associated with breast cancer No significant association between resistin levels and menopausal status

Table 1 (continued)

Meta-analysis (study)	Number of studies	Number of participants	Study outcomes	Comments
Visfatin (eNampt)				
Gui Y et al. The association between obesity related adipokines and risk of breast cancer: a meta-analysis. Oncotarget 2017; 8:75389–99.	23 case-control studies and 3 cross-sectional studies	3787 breast cancer patients and 5231 healthy controls	SMD: 1.06 (95% CI: 0.20, 1.93; $P = 0.02$)	Higher visfatin levels were associated with breast cancer No analysis including ER or menopausal status
Lipocalin 2 (LCN2)				
Wang Y et al.. Neutrophil gelatinase-associated lipocalin protein as a biomarker in the diagnosis of breast cancer: A meta-analysis. Biomed Rep 2013;1:479-83	4 case-control, single-center trials	332 breast cancer patients/142 controls	Sensitivity: 64% (95% CI: 0.59–0.69), Specificity: 87% (95% CI: 0.81–0.92), PLR: 5.63 (95% CI: 3.63–8.74), NLR: 0.32 (95% CI: 0.14–0.71), Diagnostic OR: 18.02 (95% CI: 9.84–32.98)	ROC curve analysis (AUC:0.9008) showed that LCN2 is a potential biomarker for the diagnosis of breast cancer
Osteopontin (OPN)				
Hao C et al. Prognostic Value of Osteopontin Splice Variant-c Expression in Breast Cancers: A Meta-Analysis. Biomed Res Int 2016; 2016: 7310694.	10 survival-analysis studies	1567 breast cancer patients	HR: 2.22 (95% CI: 1.23–4.00; $P = 0.008$) HR: 2.14 (95% CI: 1.51–3.04; $P < 0.0001$)	High level of OPN expression indicated a poor outcome in the overall survival High level of OPN splice variant-c expression appeared to be more significantly associated with poor survival OPN and OPN-c can be considered as prognostic markers for breast cancer
Xu YY et al. Prognostic value of osteopontin expression in breast cancer: A meta-analysis. Mol Clin Oncol 2015; 3:357-62.	8 studies examining the association of OPN with clinicopathological characteristics and/or overall survival in BC	1559 breast cancer patients	pooled OR: 2.026 (95% CI: 1.199–3.425; $P = 0.008$) HR; 3.69 (95% CI: 1.45–9.42; $P = 0.000$) HR = 2.40 (95% CI: 1.27–4.56; $P = 0.007$)	OPN expression was positively associated with lymph node metastasis OPN expression was positively associated with overall survival and disease-free survival OPN overexpression is a positive prognostic biomarker in breast cancer

AUC area under the curve, *ER* estrogen receptor, *HR* hazard ratio, *NLR* negative likelihood ratio, *OR* odds ratio, *PLR* positive likelihood ratio, *ROC* receiver operator characteristic, *SMD* standardized mean difference, *SRR* summary relative risk

Table 2 Main mechanisms of actions of adipokines in breast cancer

Adipokine	Physiologic function	Actions in BC tumorigenesis	Mechanism of action/cell signaling
Adiponectin	↓inflammation, insulin sensitizer, regulates lipid metabolism	↓proliferation, ↓migration, ↑apoptosis, ↓bioavailability of several growth factors ER-negative BC: ↓growth, proliferation, and invasion	LKB1/AMPK, mTOR, NF-κB, JNK, STAT3, cyclin D1
Leptin	actions in the brain: satiety signaling, counterbalances ghrelin, ↑GH and TRH, ↑IGF-1 binding capacity, LH secretion and sex steroid levels regulation, puberty regulation, actions in the periphery: ↓lipid storage in non-adipose tissues, ↑glucose consumption and oxidation, glycogen synthesis, and lactate production in skeletal muscle, ↓hepatic gluconeogenesis, ↓glucose, galactose, amino acid absorption, and ↑fructose and butyrate absorption in small intestine	anti-apoptotic, pro-inflammatory, ↑angiogenesis, upregulation of aromatase, activation of ERα, suppression of p53 in ER-positive cells	JAK/STAT3, MAPK, PI3K/Akt, ERK1/2, AMPK pathways, and IRS activation
Resistin	↑insulin resistance, ↑inflammation	↑cell proliferation, migration and adhesion, promotion of EMT and stemness	MAPK, PI3K, NF-κB pathways, phosphorylation of the ezrin, radixin, and moesin (ERM) complex
Visfatin	NAD biosynthesis, intracellular metabolism, cell growth	pro-inflammatory, ↑cell proliferation, ↑inflammation, ↓apoptosis, immunosuppression, ↑angiogenesis	MAPK, ERK 1/2, NF-kB, STAT3, PI3K-Akt, SIRT1, and p53 deacetylation
Apelin	regulation of insulin secretion and sensitivity, blood pressure, and fluid homeostasis	lymphangiogenesis, tumor neoangiogenesis, promotion of cell proliferation and invasion	ERK1/2, PI3K/Akt pathways
Chemerin	implication in adipogenesis, immunity, and metabolic activity	tumor and antitumor effects, recruitment of NK cells, and T cells in the tumor microenvironment, possible promotion of angiogenesis, inflammation, and matrix metalloproteinase activity	MAPK, ERK pathways
Irisin	modulation of the adipose phenotype, energy expenditure and systemic metabolism	antitumor effect, suppressive effect on number, migration and viability of BC cells, induction of apoptosis	suppression of NF-κB activity
Lipocalin 2	transportation of small hydrophobic molecules and immune response	promotion of epithelial-to-mesenchymal transition, cell migration and invasion, VEGF production and angiogenesis	PI3K/Akt/NF-κB and HIF-1a/ERK pathways, formation of the MMP9/LCN2 complex
Oncostatin M	inflammation, hematopoiesis, and bone formation	promotion of BC progression and metastasis, increase in circulating tumor cells, mesenchymal and stem cell–like differentiation, estrogen receptor downregulation	JAK/STAT3, MAPK, PI3K pathways
Osteopontin	biomineralization, inflammation, bone remodeling	↑angiogenesis, metastasis, suppression of apoptosis	integrin-mediated pathways

Akt v-Akt murine thymoma viral oncogene homolog, *AMPK* 5′ AMP-activated protein kinase, *ER* estrogen receptor, *ERK 1/2* extracellular signal-regulated kinase 1/2, *HIF-1α* hypoxia-inducible factor-1a, *IGF* insulin-like growth factor, *IRS* insulin receptor substrate, *JAK* Janus kinase, *JNK* Jun N-terminal kinase, *LCN2* lipocalin 2, *LKB1* else known as STK11(serine/threonine kinase 11), *MAPK* mitogen-activated protein kinase, *MMP* matrix metalloproteinase, *mTOR* mammalian target of rapamycin, *NF-κB* nuclear factor-κB, *NK* natural killer, *PI3K* phosphoinositide-3-kinase, *SIRT1* sirtuin 1, *STAT* signal transducer and activator of transcription, *VEGF* vascular endothelial growth factor

for postmenopausal women [70]. Overall, based on meta-analyses examining the relation of serum adiponectin and BC, a common pattern emerges: when all women are included in the analysis, elevated adiponectin is associated with reduced BC risk but this association is more pronounced in postmenopausal women. More larger prospective studies are required to delineate the potentially mediating role of adiponectin in BC.

Leptin and Breast Cancer

Leptin, a 16-kDa polypeptide produced mainly from the adipose tissue, was discovered by Friedman and colleagues in 1994 [71]. It is the product of the *Ob* gene and after its secretion, it circulates in a free and a bound form [72]. Leptin affects its target tissues through the leptin receptor (LEPR), a single transmembrane protein that is ubiquitously expressed [71]. Leptin secretion is in proportion to the adipose tissue mass and serves as a message of satiety and energy adequacy suppressing appetite [73]. LEPR can affect multiple intracellular pathways including Janus kinase/signal transducer and activator of transcription (JAK/STAT3), mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase/v-Akt murine thymoma viral oncogene homolog (PI3K/Akt), extracellular signal-regulated kinase 1/ 2 (ERK1/2), 5′ AMP-activated protein kinase (AMPK), and insulin receptor substrate (IRS) [73, 74].

In the context of cancer, JAK2 activates STAT3 and 5 promoting the expression of genes crucial to tumorigenesis, affecting cell proliferation, invasion, angiogenesis, and inflammation [46]. In addition, leptin upregulates the expression of anti-apoptotic proteins, inflammatory markers (tumor necrosis factor-α/TNF-a, IL-6), angiogenic factors (VEGF), and the hypoxia-inducible factor-1a (HIF-1a) [75, 76]. The ERK signaling promotes the activation of transcription factors that induce cell division [77]. Moreover, after JAK2 stimulation, PI3K and Akt are activated affecting glucose metabolism, cell growth, proliferation, and apoptosis [78].

The oncogenic mechanism of leptin in breast tissue involves the stimulation of JAK/STAT3 and PI3K pathways [79]. Leptin can inhibit apoptosis of BC cells favoring the expression of anti-apoptotic genes (*bcl-xL*, *bax*) and induce angiogenesis by stimulation of VEGF production [80]. Leptin displays an interesting relationship with estrogen signaling. Leptin can potentiate estrogen signaling through three mechanisms: (1) upregulation of aromatase, (2) direct activation of ERα, and (3) suppression of p53 [81–83]. In vivo, leptin administration was found to double tumor size after 13 weeks when compared with estradiol treatment [84]. A study that assessed the possible synergistic effect of estrogen and leptin in BC development revealed that ER signaling promotes leptin-induced autophagy that in turn contributes to BC growth [85].

In vivo studies have shown that elimination of peripheral tissue leptin signaling with concurrent preservation of leptin receptor signaling can decrease BC development and progression [86]. When leptin signaling was inhibited in mammary tumor virus-Wnt-1 mice (MMTV-Wnt-1), tumor growth was reduced and BC stem cell (CSC) population was suppressed [87]. Moreover, Western diet–induced obese rats exhibited increased BC incidence and aggressiveness as well as upregulated leptin and LEPR expression and signaling [88].

Interestingly, recent evidence has shown that leptin can render BC cells less susceptible to treatment with tamoxifen, an effect probably mediated by induction of the membrane tyrosine kinase HER2 receptor expression [89]. Moreover, leptin may promote CSC proliferation, migration, and angiogenesis through a complex signaling combination between Notch, IL-1, and leptin, termed NILCO [90, 91]. Chang and colleagues have demonstrated that leptin can further promote the formation of breast CSC by epigenetic downregulation of miR-200c [88]. Additionally, leptin signaling may activate fatty acid b-oxidation (FAO), through upregulation of carnitine palmitoyltransferase 1B (CPT1B), inducing BC stemness and resistance to chemotherapy, phenomena reversed by FAO and/or leptin signaling inhibition [92]. Leptin is considered a mediator molecule between stromal cells and tumor microenvironment.

Clinical data have confirmed the correlation of serum leptin and BC. The most recent meta-analysis investigating the relationship of leptin levels with BC concluded that BC patients exhibited higher serum leptin levels. Subgroup analysis for BMI and menopausal status revealed that the association was significant only in overweight and obese postmenopausal women [93•]. In another meta-analysis, Niu and colleagues have demonstrated that serum leptin levels were escalating from healthy controls to benign breast tumor, local BC, and lymph node–positive BC subgroups [94].

Resistin and Breast Cancer

Resistin is an adipokine of 12.5 kDa that is secreted by mononuclear cells and adipocytes [95]. Discovered in 2001, it was regarded as the mediator between obesity and diabetes (the name "resistin" stems from the property of insulin resistance amplification) [96]. Resistin exerts its effects through binding to Toll-like receptor 4 (TLR4), resulting in activation of the PI3K, p38, MAPK, and NF-kB pathways [97].

High levels of resistin have been associated with many disease states, such as visceral obesity, coronary artery disease, lung disease, various malignancies, and critical illness [9••].

Resistin may trigger tumorigenesis via inflammation (PI3K and NF-kB pathways), immune cell extravasation (MAPK pathway), expression of cardinal molecules for adhesion of cancerous cells (NF-κB pathway), and promotion of survival

and invasiveness of tumor cells (PI3K and MAPK pathways) [9••].

In the context of BC, researchers using MCF-7 BC cell lines discovered that resistin enhances the metastatic potential of BC cells by promotion of epithelial-to-mesenchymal transition (EMT) and stemness, and these effects were largely attributed to adenylyl cyclase–associated protein 1 (CAP1) [98]. In line with this, resistin was shown to promote metastasis in MDA-MB-231 human BC cells through phosphorylation of the ezrin, radixin, and moesin (ERM) complex [99].

Interestingly, two groups have indicated that resistin may confer chemoresistance properties to BC cells [100, 101]. One group proposed that the stimulation of AMPK/mTOR/ULK1 and c-Jun N-terminal kinase (JNK) signaling induces autophagy bypassing doxorubicin-induced apoptosis [100], whereas another found that chemoresistance was mediated through STAT3 activation [101].

Clinical data linking resistin to BC have been heterogeneous with some studies highlighting its association with postmenopausal BC [33, 35, 102]. Independent groups have found that elevated resistin expression in BC tissue is associated with adverse clinical and pathological characteristics as well as poor patient survival [35, 103].

In a recent meta-analysis of 13 studies, resistin levels were associated with an increased incidence of obesity-related cancers (breast, endometrial, and colorectal cancer) but despite its association with BC, resistin levels were found to be of limited diagnostic and predictive value [104]. Another very recent meta-analysis which evaluated the association of several adipokines with BC has shown significantly higher resistin in BC patients without a significant association between resistin levels and menopausal status [25••].

Visfatin/Nampt and Breast Cancer

Visfatin, also known as Nampt or pre-B cell colony–enhancing factor (PBEF), is a 52-kDa protein, that is produced by the *NAMPT* gene. It exhibits a multi-faceted role acting concurrently as an enzyme, adipokine, and a growth factor [105, 106]. Nampt exists in two forms, the intracellular-iNampt and the extracellular-eNampt [42]. iNampt participates in NAD biosynthesis that functions as an important electron carrier, and exerts a crucial function in cell metabolism. eNampt is excreted by a multitude of tissues such as adipose, liver, and heart, and the mechanism of excretion is thought to be cell lysis [107]. eNampt has been implicated in several diseases including diabetes, obesity, aging, atherosclerosis, cardiac hypertrophy, and autoimmune diseases [9••].

With respect to cancer development, visfatin displays pro-inflammatory, proliferative, anti-apoptotic, and pro-angiogenic effects [108]. It has been shown to promote inflammatory processes through the activation of NF-kB and induce cell proliferation through the upregulation of Notch-1, cyclin D1, cyclin-dependent kinase 2, MAPK, ERK-1/2, and p38 signaling pathways [109–111]. eNampt may also function in an endocrine manner contributing through its immunosuppressive properties to the surviving strategies of cancer that take advantage of immune evasion [112]. Serum eNampt is elevated in many cancers, and is generally correlated with worse prognosis and aggressive behavior [9••].

Preclinical and clinical studies have implicated visfatin/Nampt in BC pathogenesis. In MCF-7 BC cells, eNampt mediated the upregulation of SIRT1 and p53 deacetylation, contributing to BC progression [113]. These mechanisms were confirmed in BC cell lines where eNampt induced BC cell proliferation and suppressed apoptosis through AKT/PI3K and ERK/MAPK activation [114].

Higher visfatin expression in BC tissue correlated with more malignant tumor behavior as well as poor patient survival [115], tumor size, ER negativity, progesterone receptor (PR) negativity, and decreased recurrence rate after hormone therapy [115]. Visfatin expression alone was associated with poor disease-free and overall survival, and this association was more pronounced in combination with ER- and PR-negative status [115]. Another group has confirmed the association of visfatin with tumor aggressiveness, but also tried to elucidate the underlying mechanism. They found that phosphorylation of c-Abl and STAT3 in breast tumor tissues was associated with high serum visfatin levels. Inhibiting c-Abl and STAT3 reversed eNampt-induced cell viability and metastatic potential [116].

Several studies have indicated that serum visfatin levels are elevated in BC [34, 36, 37]. Interestingly, serum visfatin levels when integrated in a multi-factorial ROC analysis may predict BC progression [117]. A recent meta-analysis has shown that higher visfatin levels were associated with cancer risk [118] while another meta-analysis of BC patients revealed that mean concentration of visfatin was higher in BC patients than controls without taking into account menopausal status [25••].

Novel Adipokines and Breast Cancer

Apelin, a 9-kDa peptide identified in 1998 and encoded by the *APLN* gene, is the endogenous ligand of the G-protein-coupled receptor APJ and exerts its action through the activation of the ERK and PI3K/Akt pathways [119]. Increased apelin levels are found in mammary gland and its secretion in the milk is abundant. Apelin possesses various metabolic functions, such as regulation of insulin secretion and sensitivity, blood pressure, and fluid homeostasis while it plays a role in lymphangiogenesis and neoangiogenesis [120–122]. Notably, in MCF-7 BC cells, apelin induced cell proliferation and invasion via the ERK1/2 pathway [123], whereas it activated tumor neoangiogenesis in TS/A mammary carcinoma cells [124], demonstrating potent angiogenic properties. Several immunohistochemical studies have shown higher

apelin expression in human BC [125, 126], while Salman et al. found increased circulating serum levels of apelin in postmenopausal BC patients compared with controls and a significant reduction after treatment with an aromatase inhibitor [127]. Moreover, recent data have revealed a strong association of apelin with lymph node metastasis and TNM staging in BC showing that this adipokine can be used as an independent prognostic factor for BC [125].

Chemerin is a 14-kDa protein which acts through binding to G-protein-coupled receptors and plays a multifunctional role in adipogenesis, immunity, and metabolic activity [128, 129]. Its implication in cancer is conflicting as it can trigger tumorigenesis by promoting angiogenesis, inflammation, and matrix metalloproteinase (MMP) activity, whilst it also exhibits antitumor properties depending on its concentration [130, 131]. Chemerin's main receptor, ChemR23, is found in breast tissue. Chemerin expression is downregulated in BC samples compared with normal controls and seems to be correlated with poor survival outcome [132]. However, it has been shown that induction of chemerin overexpression in the EMT6 BC model suppressed tumor growth by recruiting immune cells into the tumor microenvironment [133•]. There is conflicting evidence regarding the clinical utility of chemerin as a prognostic factor in BC. El-Sagheer et al. showed that chemerin expression in breast tissue correlated with poor prognosis and unfavorable clinical and pathological parameters [132]. However, in another study, serum chemerin levels were not associated with BC stage, as there was no difference in patients with metastatic and non-metastatic BC [134].

Encoded by the *FNDC5* gene, *irisin* is a newly discovered adipo-myokine that is involved in the browning of white adipose tissue regulating energy expenditure and systemic metabolism [135–137]. This 12-kDa protein is predominantly secreted from skeletal muscle but immunohistochemical studies have also revealed local production in various central and peripheral tissues [138, 139]. The antitumor effect of irisin has been shown in a recent in vitro study where a considerable tumor suppressive result was noted on the number, migration, and viability of malignant BC cell lines, with the induction of cell apoptosis and the suppression of NF-κB activity [140]. Few clinicoepidemiologic studies have examined circulating irisin in BC. Serum concentration of irisin in patients with BC was significantly lower than in healthy participants and was correlated with tumor stage [141]. In line with the previous findings, lower serum levels of irisin were observed in BC patients with spinal metastasis than BC patients without spinal metastasis, where irisin emerged as an independent prognostic factor in BC after adjustment for age and BMI [142].

Lipocalin 2 (Lcn2), also known as neutrophil gelatinase–associated lipocalin (NGAL), is a 25-kDa secretory peptide, member of the lipocalin family which is involved in transportation of small hydrophobic molecules and immune response [143]. Lcn2 was recently recognized as an adipokine that is also secreted from adipose tissue of both mice and humans. Upregulated expression levels of Lcn2 have been reported in tissue, serum, and urine of BC patients [144••]. A growing body of evidence from in vitro and in vivo studies have shown that Lcn2-tumorigenic and metastatic potential is induced via the promotion of EMT, cell migration and invasion, VEGF production, and angiogenesis [145–148]. The mechanisms explaining and supporting the Lcn2-oncogenic and metastatic potential comprise the activation of multiple signal pathways, including PI3K/Akt/NF-κB, HIF-1a/ERK, and the protective formation of the MMP-9/Lcn2 complex [144••]. Of note, Lcn2 silencing or inhibition in BC cells or mouse models destabilizes MMP-9/Lcn2 complex, reduces MMP-9 activity, cell migration, and invasion, decreases VEGF and angiogenesis, and may lessen tumor progression [144••]. A meta-analysis of four single-centered trials has highlighted the diagnostic potential of Lcn2 in BC [149]. Additionally, various studies have shown that Lcn2 correlated with histological grade, BC relapse, metastasis, and poor prognosis, including estrogen receptor (ER)– negative status [147, 150–154], suggesting that Lcn2 may serve as a promising noninvasive diagnostic and prognostic biomarker in BC.

Oncostatin M (OSM), a 24-kDa protein identified in 1986 and encoded by the *OSM* gene, is a pleiotropic cytokine that belongs to the IL-6 family being involved in inflammation, hematopoiesis, and bone formation [155, 156]. OSM interacts with the gp130 complex with either OSM receptor type I (known as LIFR) or OSM receptor II (known as OSMR), stimulating several signaling pathways such as JAK/STAT3 and PI3K [157, 158]. In vitro studies have shown that OSM expression correlated not only with tumor progression in BC cell lines via a JAK/STAT3-dependent mechanism [159], but also with phenotypic changes associated with mesenchymal and stem cell–like differentiation via the PI3K pathway upregulation [160]. The ability of OSM to facilitate metastasis in BC has also been shown in a mouse BC model where OSM potentiated pre-intravasation events, increased circulating tumor cells, and promoted lung metastasis [161]. Moreover, recent accumulating clinical and experimental evidence have associated elevated expression of OSM with decreased BC survival and a worse clinical outcome mediated by estrogen receptor downregulation [162–164], suggesting a potential role of OSM in BC prognosis.

Osteopontin (OPN), also called bone sialoprotein 1, is a 44-kDa cytokine-like, calcium binding, and multifunctional protein involved in biomineralization, inflammation, and tissue remodeling [165, 166]. OPN interacts with a plethora of cell surface receptors, including several integrins and CD44 [167]. Particularly in BC, OPN has been shown to preferentially bind to specific integrins, such as $\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta e$, and $\alpha v\beta 5$ receptors which are associated with different signaling pathways, resulting in an increase in cell adhesion, migration, and invasion [168–170]. Elevated OPN expression in tissue,

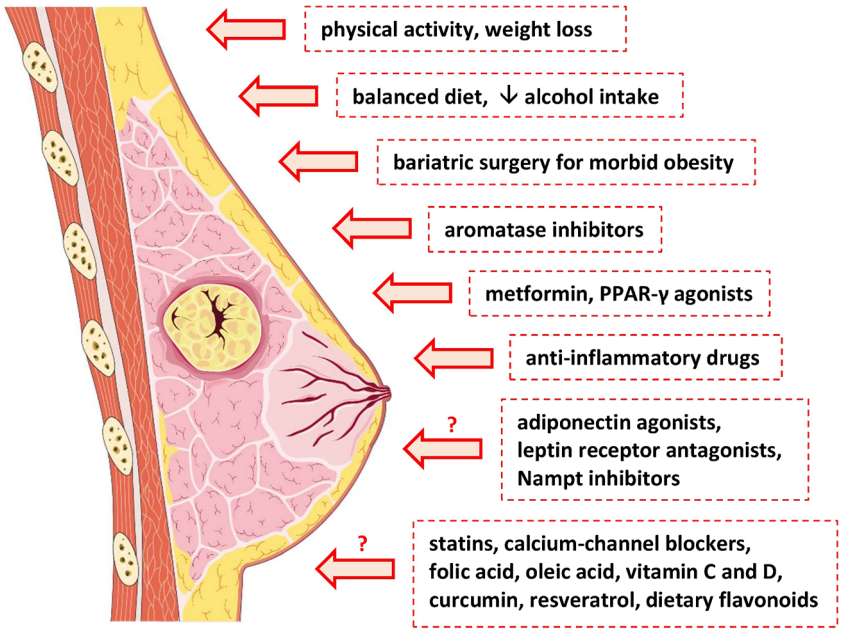

Fig. 2 Potential therapeutic strategies in postmenopausal breast cancer. Nampt, nicotinamide phosphoribosyltransferase; PPAR-γ, peroxisome proliferator–activated receptors-γ. (Image of breast cancer tissue is derived from the free medical site http://smart.servier.com/ by Servier licensed under a Creative Commons Attribution 3.0 Unported License)

plasma, or serum in BC has been found in many studies, with higher OPN concentrations being associated with higher tumor grade [171–174], while a number of studies have demonstrated that OPN may be correlated with BC progression and metastasis [175–177]. Interestingly, OPN downregulation via the miR-181c inhibited cell proliferation and enhanced chemosensitivity in resistant BC cells [178•]. A growing body of evidence has highlighted the prognostic value of OPN in BC, as shown in a recent meta-analysis where high OPN and particularly OPN splice variant-c levels were correlated with poor survival [179]. Moreover, in another meta-analysis, OPN overexpression was positively associated with lymph node metastasis as well as overall and disease-free survival in BC [180].

Implications in Public Health and Therapeutics

A small but considerable percentage of BC cases could be preventable through maintaining a healthy weight, adopting a diet with fruits, nuts, vegetables, whole grains, and olive oil, reducing unhealthy diet (consumption of sugar, trans-fats and saturated fats, refined grains, red and processed meat), increasing physical exercise, and decreasing alcohol intake [3, 181, 182]. Figure 2 presents potential therapeutic strategies in postmenopausal BC, which is associated with obesity. The American Society of Clinical Oncology has highlighted that obesity is one of the most cardinal preventable lifestyle risk factor for cancer mortality [183]. Based on IARC and WCRF/AICR reports, physical activity may decrease both postmenopausal and premenopausal (vigorous activity) BC risk and BC mortality [13••, 182, 184] through modulation of insulin resistance, chronic inflammation, and circulation of sex steroid hormones and adipokines. In the SHAPE study of postmenopausal women with BC, a significant reduction of circulating leptin was observed with a physical activity program yielding a weight decrease of more than 5% [185].

Intentional weight loss is related with a significant decrease in the risk of postmenopausal BC [186] contributing to a better life expectancy [187]. Ongoing, large, weight loss intervention randomized trials will explore the effects on BC outcomes [13••]. However, the current state of knowledge corroborates the daily incorporation of weight loss intervention in the management of BC. Regarding all-cause mortality in BC patients, a beneficial effect of the Mediterranean diet was observed but no positive effect from other diets such as low-carbohydrate, ketogenic, or vegetarian/vegan diets was found [188]. Based on two very recent meta-analyses, bariatric surgery for morbidly obese women has been shown to reduce the incidence of BC [189, 190]. Due to underpowered and heterogenous studies, limited follow-up, and difficulty in identifying proper controls, larger RCTs are needed to explore the effect of bariatric surgery on BC incidence and outcomes.

In the setting of obesity, which is considered a systemic endocrine dysfunction characterized by chronic inflammation, adipokines exert independent and joint effects on activation of major intracellular signal networks implicated in cell proliferation, growth, survival, invasion, and metastasis [9••]. Circulating levels of adipokines could be modifiable by weight loss, adoption of a balanced diet, and physical activity [30, 42, 95]. Although many adipokines are not only adipocyte-derived, they are responsive to adiposity alterations. Bariatric surgery, which is related to BC risk reduction via

regulation of the adipokine profile, may increase levels of adiponectin and decrease levels of leptin, resistin, visfatin/eNampt, and chemerin [191–193].

Glycemic control may restore adipokine levels [194]. Antidiabetic drugs such as metformin or PPAR-γ agonists that elevate adiponectin and decrease resistin and visfatin concentrations in both humans and mice may be at the forefront of therapeutic strategies for BC [195]. Besides its role as an activator of AMP-kinase, metformin potentiates non-AMPK-dependent protective networks such as decreases in leptin, insulin signaling, IGF-1, and inflammatory pathways and increases in adiponectin [195]. Although data regarding metformin and BC incidence and mortality are inconclusive showing, however, a tendency of protective effects on BC particularly in HR-positive and diabetic patients [40, 195–197], recent meta-analyses have indicated significant reductions in leptin and other metabolic parameters (hsCRP, glucose, insulin, BMI) in BC patients receiving metformin [196, 198]. More RCTs are awaited to determine the role of metformin in BC risk decrease and prognosis in diabetic and non-diabetic patients as well as an adjuvant therapy in BC reversing chemotherapy resistance [199]. On the other hand, in vitro and in vivo studies have shown that PPAR-γ agonists as well as high-affinity PPAR-γ agonists, which upregulate adiponectin expression and decrease inflammatory cytokines, have the potential to suppress the proliferation and invasion of BC cells through the inhibition of leptin signaling [40, 200]. Nevertheless, PPAR-γ agonists do not seem to affect BC risk when employed as a single agent or in combination with hormone therapy or chemotherapy [40, 201].

Whilst some preclinical and epidemiologic studies have suggested a protective role for statins, aspirin, and other non-steroidal anti-inflammatory drugs in BC (particularly postmenopausal and HR-positive tumors) risk and mortality, other studies did not support these findings, and further large-scale evidence from RCTs is required [202–207]. Although calcium channel blockers, folic acid, oleic acid, and vitamin C and D supplementation could significantly restore adipokine levels [9••, 42, 208], controversy exists between the potential association of those agents with BC risk and progression [209–213]. Some phytochemicals such as curcumin and resveratrol as well as dietary flavonoids such as catechin and genistein, which may regulate mRNA and protein levels of adiponectin, resistin, and visfatin [42], have been reported to present anti-neoplastic and chemoprevention effects on BC in experimental studies [214, 215].

Several adipokine-oriented therapeutic approaches have been developed and used in preclinical studies for BC with promising results. Antagonists of the leptin receptor that can suppress leptin signaling as well as adiponectin agonists mimicking adiponectin action have been shown to inhibit the proliferation of BC cells [216, 217]. Indeed, pegylated leptin receptor antagonist 2 as well as other leptin receptor antagonists based on mutants of the full leptin protein or leptin peptide fragments have decreased the proliferation and angiogenesis of ER-positive or ER-negative BC cells in xenograft mice models [216–218]. Peptide-based adiponectin receptor agonists such as ADP-355, which is an adiponectin mimetic binding to both AdipoR1 and AdipoR2, have been reported to suppress the growth of BC cell lines and orthotopic xenograft BC models [219]. Nampt inhibitors, which limit NAD production in BC cells, have demonstrated significant in vitro and in vivo antitumor efficacy in an orthotopic MDA-MB-231 triple negative BC xenograft tumor model [220]. Therefore, continued research is necessary to explore whether adipokines may be potential therapeutic targets for both BC and obesity. The research of the role of novel adipokines merits further attention in future studies in obesity and BC.

Adipokines could be useful diagnostic, prognostic, and predictive biomarkers, reflecting BC advanced stage, adverse prognosis, and inflammatory state. However, large-scale prospective and longitudinal studies are required to investigate the diagnostic, prognostic, and predictive utility of adipokines as BC biomarkers and to exclude a potential "epiphenomenon" effect of adipokines variation in the context of BC systemic inflammatory response [9••]. Additional challenges encompass the lack of standardization of adipokine immunoassay procedures and the development of reliable, "user friendly," and practical automated laboratory technique such as multiplexing technology to explore the physiologic and pathophysiological relevance of adipokines in BC and their clinical utility. To investigate the potential relationship of adipokines and BC risk, adequately powered Mendelian randomization studies using genetic determinants of adipokines derived from genome-wide associations studies are necessary because they circumvent confounding of lifestyle variables and reverse causation improving causal inference in the association of obesity-related biomarkers with cancer risk [221].

Conclusions

In summary, this review shows evidence for an association between adipokines and BC. High throughput technologies such as proteomics and metabolomics will discover novel adipokines. Further evidence from basic and translational research is necessary to delineate the ontological role of adipokines and their interplay in BC pathogenesis. More studies are needed to explore the epigenetic regulation of adipokine genes and to map out their receptors and critical signaling pathways. More large-scale clinical and longitudinal studies are awaited to assess their clinical utility in BC prognosis and follow-up. Finally, novel more effective and safer adipokine-centered therapeutic strategies could pave the way for targeted oncotherapy.

Compliance with Ethical Standards

Conflict of Interest Gerasimos Socrates Christodoulatos, Nikolaos Spyrou, Jona Kadillari, Sotiria Psallida, and Maria Dalamaga declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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