Obesity Management

Adipose tissue as target organ in the treatment of hormone-dependent breast cancer: new therapeutic perspectives

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Summary

Breast cancer is the female malignant neoplasia with the highest incidence in the industrialized world. Despite many undeniable therapeutic successes obtained, breast cancer still remains, however, a major health issue. In the last few years, thanks to aromatase inhibitors, the hormone therapy for oestrogen-dependent breast cancer has evolved in terms of efficacy and tolerability; at the same time, it has enabled us to better define the role of oestrogens in the etiopathogenesis of this tumour. Weight increase and obesity have been identified as the most important risk and prognostic factors for breast cancer in postmenopausal women. Several hypotheses have been proposed to explain the association of obesity with postmenopausal breast cancer. A more recent hypothesis suggests that adipocytes and their autocrine (paracrine and endocrine actions) are at the centre of such an etiopathogenetic mechanism. A better understanding of the main mechanisms that link together menopause, body-weight increase and hormone-dependent breast cancer is paramount to enable the identification of key molecules involved in the development of breast carcinoma and suggest new therapeutic options. The present review will discuss important findings on the therapeutic aspects of adipose tissue and adipokines as a target for treatment of hormone-dependent breast cancer.

Keywords: Adipose tissue, breast cancer, leptin, obesity.

Introduction

Breast cancer is the female gender malignant neoplasia with the highest incidence in the industrialized world. Despite many undeniable therapeutic successes, breast cancer still remains, however, a major health issue. About 60% of breast carcinomas are hormone-dependent. Therefore, a specific antagonist to the oestrogen action or its deprivation must be considered as the most rational therapeutic approach for the prevention and treatment of hormone-dependent breast cancer.

Weight increase and obesity, subsequent to menopause, have been identified as the most important risk factor for breast cancer in postmenopausal women (1) (Fig. 1). Several hypotheses have been proposed to explain the association of obesity with postmenopausal breast cancer: (i) circulating oestrogen levels from peripheral aromatization of androgens in obese postmenopausal women are higher than in slim postmenopausal women; (ii) obesity results in higher circulating levels of insulin and insulin growth factor (IGF) and which are able to stimulate epithelial breast cell growth and neoplastic degeneration and (iii) a more recent hypothesis suggests that adipocytes and their autocrine (paracrine and endocrine actions) are at the centre of such an etiopathogenetic mechanism (2). Adipocytes, once considered solely as energy depot cells, are actually recognized...
as active endocrine cells that secrete cytokines, polypeptides and hormone-like molecules. Indeed, the most likely hypothesis is that all these mechanisms may concur to explain the association that links together menopause, the subsequent body-weight increase and hormone-dependent breast cancer.

Therefore, in postmenopausal women, the responsible mechanisms most likely involve increased oestrogen synthesis in adipose tissue, but in premenopausal women, the oestrogen levels secreted by the ovaries would greatly exceed extraglandular production and not be enhanced by adiposity. Here, non-steroidal hormones and growth factors, including insulin and the adipokines such as leptin, are likely to be involved (3).

Indeed, obesity is a recognized risk factor for breast cancer after menopause, whereas, in premenopausal women, there is an inverse relationship between body mass index (BMI) and risk (3,4).

However, it is to be noted that obesity is related to poor prognosis in breast cancer patients regardless of their menopausal status (3). It has been associated with larger tumour size, a higher incidence of lymph node metastases and high tumour grade as well as, of particular interest in the context of triple negative tumours, an increased risk of distant recurrence (5). Larger tumour size in obese women is the result of growth stimulation: they were more likely than tumours of the same size from non-obese women to have high Ki-67 antigen expression and high mitotic cell count as well as S-phase fraction (5).

This paper is a review of the current literature and aims to examine and discuss the mechanisms linking adiposity and breast cancer which contribute to an ideal environment for breast cancer development, particularly for hormone-positive tumours. The paper discusses the most important findings that demonstrate the correlation between obesity and breast cancer risk as well as the interactions between oestrogens and adipokines in hormone-dependent breast cancer. This mass of evidence suggests that in addition to conventional therapies, treatment options able to regulate adipokine levels and insulin-resistance may improve the care of obese patients with breast cancer.

### Oestrogens and menopause

The most compelling, yet indirect, evidence suggesting a role for oestrogen associated with obesity in breast cancer is that...
in postmenopausal women, circulating levels of oestrogen are strongly and linearly related to adiposity (6). Adipose tissue oestrogens biosynthesis is catalysed by the enzyme aromatase, a product of the CYP19 (aromatase) gene (7).

Besides the increased adipose mass, its specific body distribution can also contribute to breast tumorigenesis (4). The influence of adiposity on breast cancer risk and outcome applies specifically to upper body obesity; in spite of its limitations, in most studies in the literature it was a risk factor for postmenopausal women (8). Moreover, a central role is played by the adipose tissue that sustains the breast glandular tissue and includes a mix of mature adipocytes, undifferentiated fibroblasts and macrophages. Variations in fibroblast distribution may also regulate the local breast synthesis of oestrogen, thus influencing the tumour development (9). There are known adipose tissue-specific promoters of stromal cells aromatase such as the promoter I.4, which in turn are regulated by macrophagic cytokines and glucocorticoids (10).

There may be, however, an alternative mode of action for oestrogens, which can be determined in this scenario. The dense layer of fibroblasts that make up the capsule surrounding pre-malignant or cancerous breast lesions may have high levels of aromatase activity, thus enhancing oestrogens biosynthesis. As a result, the histological composition of breast tissue may favour the oestrogen-dependent growth and progression of breast cancer cells in a paracrine manner, in which the steroid spreads from its site of synthesis to interact with the oestrogen receptor (ERs) on nearby cancer cells. Moreover, some breast cancers possess themselves aromatase activity, and in the presence of ER+ breast cancer cells are able to stimulate tumour growth by an autocrine mechanism (11).

**Weight increase, insulin-resistance and risk of breast cancer**

Increase on BMI in postmenopausal women is associated not only with hyperestrogenism but also with hyperinsulinaemia, insulin-resistant type 2 diabetes and metabolic syndrome, which in turn are associated with a slight increase in the risk of hormone-dependent breast cancer (8). Under these metabolic conditions, tissues are not able to absorb, store and metabolize glucose efficiently and to prevent elevated glucose blood concentrations, the pancreas secretes increasing amounts of insulin (12) which in turn induces proliferation of ER+, but not ER−, breast cancer cell lines (13). Indeed, oestrogens and insulin may cooperate to promote cell-cycle progression (14) (Fig. 2).

Hyperinsulinaemia can also indirectly affect tumorigenesis by contributing to synthesis and activity of IGF-I and II. IGFs can act in an endocrine, paracrine or autocrine fashion to regulate cell growth, survival and differentiation, and it can also synergize with other growth factors such as oestrogens to enhance their mitogenic effect (15). Binding of IGF-IR to its ligand leads to its dimerization, activation of tyrosine kinase and phosphorylation of key substrates which in turn activate various intracellular pathways, including phosphoinositide 3-kinase and mitogen-activated protein kinase-signalling cascade (Fig. 2). Analysis of genetic polymorphism showed a significant correlation between the expression of specific insulin-related genes and increased risk of breast cancer in postmenopausal women exposed to oestrogens (16). Moreover, insulin and IGFs can activate ER transcriptional activity in breast cancer cell lines, even in the absence of oestrogens (17).

Given that obese postmenopausal women have more oestrogens, IGF-I and insulin than slim women, it is logical to conclude that the above-described crosstalk between the IGF pathways and oestrogen-mediated signalling may favour an increased risk of breast cancer to a greater extent in obese postmenopausal women (18).

It should be stressed that, as adipose tissue mass increases circulating concentrations of insulin and IGF-I, blood levels of sex hormone-binding globulin (SHBG) begin to diminish (19). As SHBG binds oestrogens with high affinity, its decrease results in an increased bioavailable fraction of circulating oestradiol. Accordingly, in postmenopausal women, blood levels of SHBG are inversely correlated with breast cancer risk (20). Additionally, SHBG may act directly on breast cancer cells to inhibit oestradiol-induced proliferation, and its loss in obese women could contribute to tumorigenesis (21).

**Adipocytes and breast cancer**

It has been clearly shown that the adipose tissue is a complex and metabolically active endocrine organ. Both the adipocytes as well as the non-adipocyte fraction of the adipose tissue synthesize and secrete several hormones which are known as ‘adipokines’ (22). Adipokines include leptin, tumour necrosis factor (TNF)-α, interleukin-6 (IL-6) and hepatocyte growth factors (HGF) which, apart from exerting their specific local biological effects, circulate in the plasma at concentrations positively correlated with BMI; one exception is adiponectin (ApN), which is inversely correlated with BMI (11).

Several in vitro and in vivo studies demonstrated that adipocytes can directly influence breast tumour growth (23,24). Two adipokines – leptin and ApN – have been recently studied for their influence on the breast cancer risk and tumour biology. Their metabolic effects as well as their biological activities on breast cancer cells are largely in opposition to each other (8). A third adipokine, the HGF, can have a positive effect on tumour development as a result of its specific angiogenic properties and capacity to promote neoplastic invasion. Different roles are played by IL-6, TNF-α and resistin (11).
Leptin

Leptin exerts its effects through binding to the leptin receptor (OB-R). Leptin is secreted by adipocytes proportionally to BMI as well as nutritional status and acts mainly upon the hypothalamus to regulate food intake and energy metabolism (25). It is also synthesized by pre-adipocytes, especially when these are stimulated in a paracrine way by the proinflammatory cytokines (TNF-α and IL-1β) secreted by the macrophages infiltrating the adipose tissue (26).

Circulating leptin levels rapidly decline under caloric restriction and weight loss. On the contrary, weight gain and the most common forms of obesity are characterized by high circulating leptin levels.

Evidence that obese women have a higher risk for breast cancer and that obesity is in turn characterized by high levels of circulating leptin has rapidly led to hypothesize a correlation between leptin and breast cancer risk. Indeed, in vitro leptin induces proliferation of normal and cancerous cells (27). Accordingly, both in humans and in rodents, high serum leptin concentrations during late pregnancy are associated with an intense increase in mammary epithelial growth and proliferation (28). Moreover, women with breast cancer have higher leptin plasma levels and mRNA expression in adipose tissue as compared with healthy subjects (29), and high plasma leptin concentrations has been associated with high tumour stage, grade and negative steroid hormone receptor status (30). However, the latter study, which has some limitation in design being cross-sectional, not following patients over time and unpowered for survival analysis, failed to demonstrate a clear-cut relationship between serum leptin levels and disease outcome. Therefore, the significance of leptin as prognostic factor for human breast cancer warrants carefully designed prospective studies (11).

The mechanism through which leptin promotes breast tumour growth is complex. Leptin is a mitogen for both normal and cancerous breast epithelial cells: when added to the culture, medium leptin stimulated the growth of ER-positive and -negative (31) human breast cancer cell
lines, and interactions between the adipokine and its receptor were shown to be essential for mammary carcinogenesis in relevant mouse models (32,33).

Recent studies have demonstrated that leptin is able to influence different second intracellular messengers involved in breast cancer cell proliferation and survival as well as in the regulation of aromatase expression, oestrogen synthesis and ER activation (34) (Fig. 2). There is also evidence that leptin directly up-regulates oestradiol/ER-α signalling in Michigan Cancer Foundation Line 7 (MCF-7) breast cancer cells even in the absence of its natural ligand (35).

Leptin gene expression occurs both in normal mammary tissue and in solid tumours (28). However, overexpression of leptin and its receptor, as determined by staining intensity, was observed in cancer cells but not in normal mammary epithelium. Interestingly, leptin and OB-R tumoural overexpression are negative prognostic factors, associated with the presence of distant metastases and lower survival rate in comparison with patients with OB-R-negative tumours (36). Indeed, leptin not only exerts stimulatory effects on breast cancer cell proliferation and invasion but also possesses angiogenic activity, both directly and by the induction of vascular endothelial growth factor (VEGF) expression, which in turn could be responsible for promoting blood-born distant metastases. Liu et al. reported that serum leptin concentrations were higher in patients with high-grade tumours and that polymorphism in the leptin receptor gene at codon 109 (LEPRO-109RR genotype) was more frequent in overweight patients. Among patients with the LEPRO-109RR phenotype, higher serum leptin concentrations were present in those with triple negative tumours (37).

Leptin interferes with insulin signalling and plasma levels of leptin directly correlate with the degree of insulin-resistance in breast cancer patients with type 2 diabetes (38). At the same time, serum leptin levels are not significantly different between premenopausal breast cancer patients and healthy women (39). This finding suggests that the biological effects of leptin do not influence mammary tumorigenesis in peri/premenopause but act as a specific factor in postmenopausal women because of the increased weight gain and hyperestrogenism. Indeed, it has been recently demonstrated that serum leptin levels significantly correlate with total body aromatization in postmenopausal breast cancer patients (40).

Adiponectin

The ApN is a 30 kDa polypeptide specifically secreted from adipocytes which circulates in serum in several different size isoforms (41). Binding of ApN to its receptors activates Adenosine Monophosphate (AMP)-activated protein kinase and peroxisome proliferator-activated receptor (PPAR)-γ metabolic pathways, leading to an increase in fatty acid oxidation, glucose uptake and a decreased rate of gluconeogenesis, thus enhancing insulin sensitivity (42). The physiologic functions of ApN are mainly endocrines, but it also exerts paracrine actions such as the inhibition of the leptin-induced production of TNF-α by macrophages (43).

The ApN biosynthesis is inhibited by the increase of fat concentrations in adipocytes. Therefore, its circulating levels are lower in obese or overweight patients and are inversely correlated with waist circumference and visceral fat, even more than with BMI. Low levels of ApN are associated with several metabolic diseases such as obesity and insulin-resistance in type 2 diabetes as well as inflammatory conditions (44). Conversely, ApN levels increase after weight reduction or treatment with insulin-sensitizing drugs such as thiazolidinedione agonists of PPAR-γ (45).

Studies confirm a significant inverse correlation between serum ApN levels, breast cancer risk and poor prognosis, independently from hormone receptor status (46). ApN inhibits the proliferation of several cell types and is a negative regulator of angiogenesis (47). It has been shown that ApN activates the PPAR-γ pathway, which in turn induces the transcription of several genes involved in the regulation of breast cancer cell proliferation (48). A possible explanation of the association between ApN levels and breast carcinoma risk is that the reduction of ApN may result in a decreased activation of PPAR signalling and low nuclear levels of BRCA1 with subsequent damage to DNA-repair mechanisms.

Hepatocyte growth factor

The adipocytes and the stromal cells of the adipose tissue are the main sources of HGF synthesis; therefore, it should be rightfully considered as an adipokine (49). Serum HGF levels positively correlate with BMI and decrease following body weight loss (50). The HGF exerts several functions that influence the development and metastatization of breast cancer. Stromal fibroblasts produce HGF, and their interaction with the breast epithelial cell is the basic requirement needed to enable HGF’s oncogenic, angiogenic and metastatic action. Serum HGF levels have been shown to significantly correlate with high-stage disease, ER-negative and poorly differentiated tumours (51).

Tumour necrosis factor-α

The TNF-α was the first inflammatory cytokine to be identified as a product of adipocytes (52). Both in experimental models and in humans, adipose tissue expression of TNF-α increases with obesity and is positively correlated with the amount of adipose tissue and degree of insulin-resistance (53).

The TNF-α in the adipose tissue acts in both an autocrine and paracrine way to influence a range of processes,
increased circulating TNF-α through the inhibition of the insulin receptor-signalling pathway in human MDA-MB-231 breast cancer cells (56). Moreover, it has been suggested that TNF-α plays a role in the development of insulin-resistance through the inhibition of the insulin receptor-signalling pathway (52). Thus, overweight subjects may have increased circulating TNF-α levels that could promote breast tumorigenesis through the induction of insulin-resistance and IL-6 and oestrogens biosynthesis.

**Interleukin-6**

The IL-6 is expressed and secreted by adipocytes and acts both locally and in a systemic way. IL-6 peripherally inhibits lipogenesis and ApN secretion, and it also centrally regulates body energy homeostasis. Both IL-6 plasma levels and its expression in the adipose tissue are high under obesity and insulin-resistance conditions. Moreover, circulating IL-6 levels are predictive of the development of type 2 diabetes and cardiovascular diseases (57).

The IL-6 seems to have an inhibitory action in the early-stage breast cancer, whereas high levels of IL-6 are associated with a poor prognosis in advanced and metastatic breast cancer (58). IL-6 induces cell migration through the activation of the mitogen-activated protein kinase pathway, acts as an anti-apoptotic factor, promotes the osteoclasts formation and inhibits the differentiation of dendritic cells, thus facilitating the metastatic process (59). Moreover, both in vitro and in vivo, IL-6 stimulates aromatase expression in the adipose tissue and in breast cancer cells, inducing oestrogens synthesis and contributing to breast cancer progression (60).

In a recent paper, Slattery et al. (61) suggested that IL-6 genotypes may influence breast cancer risk in conjunction with central adiposity in postmenopausal women. Indeed, IL-6 affects lipid and glucose metabolism and is a central factor in the aetiology of breast cancer. Polymorphisms in the IL-6 gene promoter have been related to circulating levels of C-reactive protein (62), different profiles of plasma IL-6 response to immunization (63), and increased association between high BMI and type 2 diabetes (64). Therefore, IL-6 may be associated with breast cancer through several mechanisms, including regulation of insulin, inflammation and oestrogen, all factors that may importantly influence breast cancer risk (65).

**Interactions between oestrogens and adipokines**

Despite the involvement of oestrogens in the aetiology and progression of breast cancer, about 30% of these tumours do not express the ER and thus are refractory to the anti-oestrogen therapy. Moreover, about 40% of breast tumours have ER but fail to respond to hormonal therapy. These findings warrant a careful assessment of the mechanism through which oestrogens carry out their actions and the implication of possible alternative or synergic mechanisms capable of regulating tumorigenesis and progression of breast carcinoma.

Catalano et al. (35) have demonstrated that leptin can activate the ER transcription in MCF-7 breast cancer cells independently from oestriadiol. Leptin induces the nuclear localization of ER through the stimulation of the synthesis of pS2, an oestrogen-inducible protein, which is expressed in the oestrogen-responsive breast tumour cells. By inducing the above-reported pathways, leptin can overcome the benefit deriving from oestrogen withdrawal obtained from aromatase inhibitors administration. Moreover, leptin can directly interfere with the anti-oestrogenic activity and therefore with the suppression of tumour cell proliferation associated with anti-oestrogen drugs (66). Additionally, a reciprocal functional dependency between leptin and the ER/ligand system has been found. Oestrogens induced a reversible increase in leptin mRNA expression and secretion from the adipose tissue (67). High intratumoural levels of leptin mRNA expression in ER-positive tumours are specifically involved in the growth stimulation of oestrogen-dependent breast cancer through an autocrine mechanism (68). Moreover, leptin in a paracrine way induced aromatase activity in stromal cells isolated from the subcutaneous and breast adipose tissue of premenopausal women (69). Miyoshi et al. (68) hypothesized that the paracrine regulation correlated between breast carcinoma cells and the surrounding adipose tissue is more important than the autocrine regulation. Additionally, Chen et al. (70) demonstrated that tumour surgical excision did not influence circulating leptin levels in patients with breast carcinoma. This finding is consistent with the hypothesis that the tumour is only a minor source of leptin, whereas the adipose tissue is the main contributor to its circulating levels.

Aromatase expression is also induced by other adipokines, namely IL-6 and TNF-α (55). In obesity, the infiltration of the adipose tissue by an increased number of TNF-α and IL-6 secreting macrophages can be responsible for the increase of the oestrogen synthesis from C19 steroids, thus contributing to an increased risk of breast cancer in postmenopausal obese women (71).

Moreover, it has been suggested (11) that the adipokines, which include leptin and VEGF as well as heparin-binding epidermal growth factor-like growth factor, exert a stimulatory effect also on ER-negative breast cancers, where oestrogen action is not a factor, by hormonal, paracrine and autocrine mechanisms.
Conclusion

Recent studies have tried to better understand the potential influence of each adipokine on the tumorigenesis of breast cancer. In fact, a better understanding of each adipokine function may be extremely important to enable further identification of key molecules involved in the development of breast carcinoma and to suggest new therapeutic options.

The discovery of leptin and the demonstration that its circulating concentrations positively correlate with BMI have been followed by attempts to link serum leptin levels to breast cancer risk. To date, however, conflicting results have been reported. This is mainly because leptin was assessed indiscriminately and not in specific populations of postmenopausal rather than premenopausal patients or in patients with ER-positive rather than ER-negative tumours. Moreover, the racial or ethnic composition of the study population may influence the breast cancer incidence and prognosis: e.g. African–American women have a greater risk of poor prognosis tumours than white American women (72).

It should be pointed out that the link between leptin and breast cancer goes through the well-known correlation of postmenopause, subsequent body weight gain, with the increase of aromatase activity and leptin levels also resulting from increased fat mass. Moreover, it is important to consider that leptin has direct and specific actions on the neoplastic cell. Therefore, the etiopathogenesis of breast cancer and the development of an aggressive, metastatic phenotype result from overstimulation of breast epithelium by oestrogen and direct or indirect effects of altered adipokine production on mammary tissue. In the first instance, leptin performs as a growth factor regardless of hormonal status and acts directly on its receptor present in the neoplastic cells. In the second instance, leptin levels reflect the total amount of fat mass, which can be directly correlated with aromatase activity and the subsequent amount of oestrogens.

These observations are of course meaningful only for that specific subgroup of patients where increase of adipose tissue, hormone dependency, oncogenesis, tumour growth and progression are strictly correlated. In this scenario, the direct proneoplastic action of leptin is associated with aromatase hyperactivity. In this context, a greater importance should be given to the use of aromatase inhibitors when BMI and the subsequent levels of leptin are a consideration. Paradoxically in obese women, we could be faced with an optimum action of the aromatase inhibitors in their capacity to suppress oestrogen synthesis, but such effect could be in part obfuscated by permanent high leptin levels capable of independently stimulating neoplastic progression.

In light of these considerations, anti-oestrogen and aromatase inhibitors therapy may have a different effectiveness for postmenopausal women with breast carcinoma with respect to BMI and leptin levels. In particular, leptin may compete with anti-oestrogens for the modulation of ER activity, and thus high serum levels of leptin in overweight breast cancer patients might counter the inhibitory effects of anti-oestrogenic therapy on cell proliferation and ER expression as well as transcription. In summary, the mass of evidence available so far seems to suggest that the increased leptin synthesis in postmenopausal overweight women may promote breast cancer growth by directly interacting with its specific receptor and by indirectly acting on the signalling pathways related to ER. Therefore, it is important to evaluate the appropriate pharmacological interventions needed to treat the metabolic disorders of the obese patients with breast cancer. Drugs such as oral hypoglycemic agents as well as those that act on IGF-IR could be effective in reducing the insulin-mediated tumour growth. In the same way, the use of ApN receptor agonists may provide a new therapeutic approach to reduce insulin-resistance and directly inhibit the proliferation of epithelial breast cells.

As the discovery of inflammation-signalling pathways regulated by IL-6 and TNF-α on breast tumour growth and disease outcome, several studies have investigated the use of aspirin and non-steroidal anti-inflammatory drugs in reducing breast cancer risk and prevention (73–75). It has been suggested that aspirin and other cyclooxygenase-2 inhibitors may reduce the risk of breast cancer by inhibiting aromatase activity (76). A recent study demonstrated that aspirin had the greatest reduction in risk in the presence of a high-risk IL-6 genotype and produced a more modest effect in the presence of the lower risk allele and when used together they attenuated the expected risk on a multiplicative way among postmenopausal women (65).

Recent studies have demonstrated that adipose tissue is particularly sensitive to angiogenesis inhibitors. Angiogenesis and adipogenesis processes are coordinated through a paracrine interaction between the development of new vessels and the differentiation of adipocytes. This process is mediated by VEGF but also involves leptin and its angiogenic properties (77).

Moreover, the evidence currently available in literature would seem to suggest that the expression of adipokines as well as that of oestrogens differ according to BMI changes and energy metabolic status. Indeed, different dietary patterns have been demonstrated to influence breast cancer risk (78): in particular, a food pattern characterized by high-fat food choices was significantly associated with increased risk of breast cancer. Additionally, dietary supplementation with omega-3 fatty acids has attracted considerable research attention for breast cancer prevention (79); it has been shown to increase adipocyte synthesis and plasma levels of ApN. Data from epidemiological studies suggest that physical activity is important in reducing risk

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of breast cancer in postmenopausal women (80). Moreover, weight reduction has been shown to reduce the breast cancer risk in obese/overweight postmenopausal women (81). Therefore, after primary treatment, safe weight loss via increased physical activity and healthful food choices should be encouraged for overweight or obese breast cancer survivors. Then, a careful assessment of the nutritional status and body composition is an indispensable requirement for a proper therapeutic approach for postmenopause breast carcinoma. The use of these new drugs associated with conventional hormone therapies and dietary/physical interventions could offer a new therapeutic approach for postmenopausal hormone-dependent breast carcinoma that develops in the context of adiposity (Fig. 3). More studies are, however, warranted to assess the feasibility of these new approaches.

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