

# Obesity, Inflammation, and Postmenopausal Breast Cancer: Therapeutic Implications

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Breast cancer is the female malignant neoplasia with the highest incidence in the industrialized world. Although early diagnosis has contributed to therapeutic success, breast cancer remains a major health issue. In the last few years the hormone therapy for estrogen-dependent breast cancer has evolved achieving significant clinical results; at the same time, it has enabled us to better define the role of estrogens 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. Specific obesity-associated factors, including leptin, insulin and inflammatory mediators, seem to influence breast cancer growth and prognosis independently of estrogens and at least in part by interacting with estrogen signalling at a cellular level. Therefore, a careful assessment of the nutritional status and body composition is paramount for a proper therapeutic approach for postmenopausal breast carcinoma. The use of antidiabetic and anti-inflammatory drugs associated with conventional hormone therapies and dietary/physical interventions could offer a new therapeutic approach for breast carcinoma that develops in the context of adiposity.

**KEYWORDS:** Obesity, breast cancer, postmenopausal women, inflammation, oxidative stress, metformin, aromatase inhibitors

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## 1. INTRODUCTION

Breast cancer is the most commonly occurring female cancer in the industrialized world. Although early diagnosis has contributed to therapeutic success, breast cancer remains a major health issue.

About 60% of breast carcinomas are hormone dependent. The hormonal changes in postmenopause, ascribable to a specific physical and metabolic remodelling, not only represent a greater risk for breast cancer, but also are to be considered indispensable for a more effective therapy [1]. Weight increase and obesity, subsequent to the menopause, have been identified as the most important risk and negative prognostic factors for breast cancer in postmenopausal women (Figure 1). Several studies pointed out that obese women exhibit at diagnosis an increase in lymph-nodes involvement and a higher propensity to distant metastases [2, 3].

According to this evidence, several hypotheses have been proposed to explain the association of obesity with postmenopausal breast cancer. The main one is that circulating estrogens from peripheral aromatization of androgens are higher in obese than in slim postmenopausal women. A second hypothesis is that obesity, being associated with metabolic syndrome, results in increased circulating levels of insulin and insulin-like growth factor (IGF), which, by acting as mitogens for epithelial breast cells, stimulate their growth and neoplastic degeneration. A third hypothesis suggests that adipocytes and their autocrine, paracrine, and endocrine actions are at the centre of such an etiopathogenetic mechanism (1). Adipocytes, until recently considered solely as an energy storage depot, are actually recognized as active endocrine cells producing hormones, growth factors, and cytokines. Indeed, the most likely hypothesis is that all these mechanisms may combine to explain the association which links together menopause, the subsequent body weight increase, and hormone-dependent breast cancer.

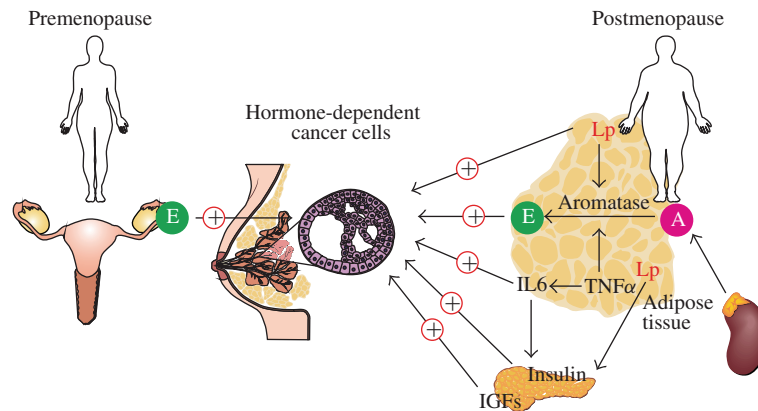
## 2. ADIPOSITY, ESTROGENS, AND BREAST CANCER

The most convincing, but indirect, evidence for a role of estrogen associated to obesity in postmenopausal breast cancer is that circulating levels of estrogens are strongly and linearly related to adiposity [4]. Endogenous estrogens biosynthesis after menopause is catalyzed almost exclusively by the aromatase enzyme in the adipose tissue. Beside the increased adipose mass, also fat distribution has been correlated with breast cancer risk and outcome: increased breast cancer risk and mortality have been associated with upper body obesity as defined by the waist-to-hip ratio, or suprailiac-to-thigh ratio [5].

Moreover, a central role is played by the adipose tissue that sustains and surrounds the breast glandular tissue and includes a mix of mature adipocytes, undifferentiated fibroblasts, and macrophages. Changes in fibroblasts distribution may regulate the local synthesis of estrogen, thus influencing the breast tumor development. It is important to bear in mind that the fibroblasts, as for quantity, tallies with that of adipocytes and that both components influence each other in their peculiar functional capacity. In fact, there are adipose tissue specific promoters of stromal cells aromatase, such as the promoter I.4, which, in turn, are regulated by macrophagic cytokines and glucocorticoids [6]. Furthermore, it seems that the increased aromatase expression in the adipose tissue of breast bearing carcinoma derives also from the activation of promoters II and I.3, which are regulated by unknown factors probably released by malignant epithelial cells: among these prostaglandin, (PG) E<sub>2</sub> seems to be a likely candidate [7]. Therefore, the histological composition of breast tissue may favour the estrogen-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 ERs on nearby cancer cells. Moreover, some breast cancers have themselves aromatase activity, and in the presence of ER+, breast cancer cells are able to stimulate tumour growth by an autocrine mechanism [8].

## 3. WEIGHT GAIN, INSULIN-RESISTANCE, AND BREAST CANCER RISK

Body mass index (BMI) increase in postmenopausal women is associated not only with hyperestrogenism, but also with hyperinsulinemia and insulin-resistant type-2 diabetes which, in turn, are associated with a



**FIGURE 1:** Different mechanisms of estrogen dependence for hormone-related breast cancer in pre- and postmenopausal women. In premenopausal women, the main site of synthesis of estrogen is the ovary. In postmenopausal women, adipose tissue is the main source of the circulating estrogens. Adipose tissue produces the enzymes aromatase; therefore, in obese women, there is an increased conversion of the androgens androstenedione and testosterone into the estrogens: oestrone and oestradiol, respectively, by aromatase. Moreover, obesity, being associated with metabolic syndrome, results in increasingly circulating levels of insulin and insulin-like growth factor, which, by acting as mitogens for epithelial breast cells, stimulate their neoplastic degeneration. Moreover, adipocytes produce several “adipokines” such as leptin and inflammatory cytokines which can influence aromatase activity and estrogen-dependent cell proliferation. IGF, insulin growth factor; IL, interleukin; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ ; Lp, leptin; E, estradiol; A, aromatase.

slight increase in postmenopausal breast cancer risk [9]. In particular, the increase of visceral adipose tissue has been associated with hyperinsulinemia, insulin-resistance, and dyslipidemia. Therefore, the involvement of adipose tissue in the pathogenesis of breast cancer is consistent with the identification of type-2 diabetes and metabolic syndrome as risk factors for this tumour. In clinically manifested type 2 diabetes and metabolic syndrome, tissues are not able to absorb, store, and metabolize glucose efficiently. Therefore, to prevent elevated glucose concentrations in the blood, the pancreas secrete increasing amounts of insulin in both the fed and fasted states. Hyperinsulinemia, even in the absence of diabetic symptoms, have been associated with an increase in breast cancer risk. Indeed, insulin exerts a direct mitogenic effect on breast cancer cells, which is limited to ER+ cancer cell lines. Moreover, insulin has a synergistic activity with estrogens in regulating c-Myc and cyclin D1 to promote cell-cycle progression [10].

Hyperinsulinemia can also affect indirectly tumorigenesis by contributing to the synthesis and activity of insulin-growth factor (IGF)-I and II. IGFs can act in an endocrine, paracrine, or autocrine fashion to regulate cell growth, survival, and differentiation and can synergize with other growth factors to enhance their mitogenic effect [11]. 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 estrogens. Approximately one half of primary breast cancers overexpresses the IGF-I receptor (IGF-IR), suggesting that these carcinomas have enhanced responses to the mitogenic and antiapoptotic effects of IGF-I [12]. Conversely, the inactivation of IGF-IR results in reduced mammary tumor growth and metastasis *in vivo* [13]. Binding of IGF-I to the specific receptor leads to the activation of various intracellular pathways, including phosphatidylinositol 3-kinase (PI 3-kinase) and mitogen-activated protein kinase (MAPK) signalling cascade. Both the PI 3-kinase and MAPK pathways are important for IGF-I-stimulated proliferation of MCF-7 human breast cancer cells and their inhibition abrogate IGFs' mitogenic effects [11]. Additionally, the insulin-IGF-I pathway interacts with estrogens to synergistically induce the mitogenic response in breast epithelial cells. The estradiol in the presence of IGF-I is able to induce the transcriptional activation of ER to levels higher than observed with the ligand alone, while loss of ER leads

to a decrease in IGF-I signalling and mitogenic activity [14]. Given that obese postmenopausal women have more estrogens, IGF-I, and insulin than slim women, it is logical to conclude that the above-described crosstalk between the IGF pathways and estrogen-mediated signalling may favour an increased risk of breast cancer to a greater extent in obese postmenopausal women.

Moreover, increased circulating concentrations of insulin and IGF-I cause a reduction in blood levels of sex hormone-binding globulin (SHBG) with a consequent elevation in the bioavailable fraction of circulating estradiol [15]. Accordingly, in postmenopausal women, blood levels of SHBG were inversely correlated with breast cancer risk [16]. Additionally, SHBG may act directly on breast cancer cells to inhibit estradiol-induced proliferation [17]. Thus, SHBG appears to be a regulator of estradiol action in breast cancer cells, acting as an antiproliferative factor, loss of which in obese women could contribute to tumorigenesis.

#### 4. ADIPOKINES AND BREAST CANCER

It has been clearly shown that the adipose tissue is a complex and metabolically active endocrine organ. Besides the storage and energy regulation function, the adipose tissue is equipped with the metabolic machinery that enables its communication with distant organs, including the central nervous system (CNS). Although the adipocytes synthesize and secrete several hormones, such as leptin and adiponectin, many proteins are produced by the nonadipocyte fraction of the adipose tissue, that is, fibroblasts and macrophages that infiltrate the adipose cell mass: all these factors are known as “adipokines” [18]. Indeed, adipokines including leptin, tumor necrosis factor-(TNF-) $\alpha$ , interleukin-6 (IL-6), and hepatocyte growth factors (HGFs), apart from exerting their specific local biological effects, circulate in the plasma at concentrations positively correlated with BMI; one exception is adiponectin, which is inversely correlated with BMI [8].

Several *in vitro* and *in vivo* studies demonstrated that adipocytes could directly influence breast tumour growth [19]. Recent experimental data [20] provide evidence that invasive cancer cells impact surrounding adipocytes; peritumoral adipocytes exhibit a modified phenotype and specific biological features sufficient to be named cancer-associated adipocytes; cancer-associated adipocytes modify the cancer cell characteristics/phenotype leading to a more aggressive behaviour. Adipocytes within a context of obesity, by the action of “adipokines”, participate in a highly complex cross talk with tumour cells to promote tumour progression.

Two adipokines, leptin and adiponectin, have been recently studied for their influence on the breast cancer risk and tumour biology. Their biological activities as their effects on breast neoplastic cells are largely in opposition to each other. 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. Among the adipose tissue-derived factors an emerging central role in the breast cancer pathogenesis and prognosis has been recently attributed to inflammatory mediators, that is, proinflammatory cytokines TNF- $\alpha$  and IL-6.

The exact interplay between these different adipokines is yet not well clarified; therefore, we will analyse them in detail discussing the most updated and useful findings in order to better explain their relationship and role in the pathogenesis of breast cancer.

##### 4.1. Leptin

Among adipokines, leptin plays a central role as irreplaceable prognostic and predictive factor. 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 [21]. It is also synthesised by preadipocytes, especially when these are stimulated in a paracrine way by the proinflammatory cytokines secreted by the macrophages infiltrating the adipose tissue [22]. Taking into account its numerous endocrine functions, leptin can be considered the prototype for all the adipose tissue-derived hormones. This has rapidly led

to hypothesise a correlation between its circulating levels and breast cancer risk. Women with breast cancer have higher leptin plasma levels and mRNA expression in adipose tissue as compared to healthy subjects, and the blood levels of estradiol increase concomitantly to those of leptin [23]. Then, a reciprocal functional dependency between leptin and the ER/ligand system is strongly conceivable. Indeed, estrogens induced a reversible increase in leptin mRNA expression and secretion from the adipose tissue [24] and high intratumoral levels of leptin in ER+ tumours are specifically involved in cancer growth stimulation through an autocrine mechanism [25]. However, Chen et al. [26] demonstrated that tumour surgical excision did not influence circulating leptin levels in patients with breast carcinoma. This is consistent with the idea that the tumour leptin production is only a minor source, whereas the adipose tissue is the main contributor to its circulating levels. Accordingly, serum leptin levels are not significantly different between premenopausal breast cancer patients and healthy women [27]. This result confirmed that leptin presumably does not influence mammary tumorigenesis in peri/premenopause but is a specific factor of postmenopause correlated with weight and hyperestrogenism. Indeed, it has been recently demonstrated that serum leptin levels significantly correlate with total body aromatase activity in postmenopausal breast cancer patients [28]. Goodwin et al. [29] observed an association also between high plasma leptin concentrations and negative steroid hormone receptor status. Then, the mechanism through which leptin promotes breast tumour growth is complex. Recent studies have demonstrated that leptin is able to influence different second intracellular messengers involved in breast cancer cell proliferation and survival, such as signal transducers and activators of transcription 3 (STAT3), transcription activator protein 1 (AP-1), extracellular signal regulated kinase-2 (ERK2) and MAPK. These mechanisms of signal transduction seem to be involved in the regulation of aromatase expression, estrogen synthesis, and ER activation. Furthermore, there is evidence that leptin can induce the direct activation of ER in MCF-7 breast cancer cells even in the absence of its natural ligand (E2) as well as upregulate the estradiol/ER $\alpha$  signalling in MCF-7 cells exposed to aromatizable androgen, and the latter signal is downregulated by the aromatase inhibitors [30]. Furthermore, leptin interferes with the insulin signalling, and plasma levels of leptin directly correlate with the degree of insulin resistance in patients with type-2 diabetes [31], whose association with breast carcinoma is well known. In a recently published paper, we demonstrated that in postmenopausal breast cancer patients, BMI, leptin, and interleukin-6 were significantly correlated with pathological tumour size (pT) and TNM stage. At multivariate regression analysis, BMI and leptin were independent predictive variables of pT and TNM stage. These results seem to suggest a twofold role of leptin in the etiopathogenesis of postmenopausal estrogen-positive breast cancer. Indeed, leptin reflects the total amount of fat mass, which correlates to aromatase activity and subsequent estrogens levels [32].

## 4.2. Adiponectin

Adiponectin (ApN) acts through its two receptors, AdipoR1 and AdipoR2, which are expressed widely in various tissues, including breast tissue. Binding of ApN to its receptors activates AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR)- $\gamma$  metabolic pathways, leading to an increase in fatty acid oxidation, glucose uptake, and a decreased rate of gluconeogenesis, thus enhancing insulin sensitivity. The physiologic functions of ApN are mainly endocrine, but it exerts also paracrine actions, such as the inhibition of the leptin-induced production of macrophage TNF- $\alpha$  [33]. ApN biosynthesis is inhibited by the increase of fat concentrations in adipocytes, and therefore, its circulating levels are lower in obese or overweight patients.

Studies confirm a significant inverse correlation between serum ApN levels, breast cancer risk, and poor prognosis, independently from hormone receptor status [34]. ApN inhibits the proliferation of several cell types and is a negative regulator of angiogenesis [35]. It has been shown that ApN, binding to its receptors, activates the PPAR- $\gamma$  pathway, which, in turn, induces the transcription of several genes involved in the regulation of cell proliferation and differentiation. Previous studies have demonstrated the importance of PPARs in the pathogenesis of breast cancer [36]. A plausible 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. Therefore, overweight subjects with low serum levels of ApN could also have an increased risk of developing tumours with an aggressive phenotype and enhanced neoangiogenesis.

### 4.3. Hepatocyte Growth Factor

The adipocytes and the stromal cells of the adipose tissue seem to be one of the main sources of HGF synthesis, and therefore, it should be rightfully considered as an adipokine. Serum HGF levels positively correlate with BMI and decrease following body weight loss [37]. The HGF exerts several functions which influence the development and metastatisation of breast cancer. Serum HGF levels have been demonstrated to significantly correlate with high stage, ER-, degree of differentiation, and presence of lymph node and distant metastases in patients with locally advanced breast cancer [38].

### 4.4. Tumor Necrosis Factor- $\alpha$

The TNF- $\alpha$  was the first inflammatory cytokine to be identified as a product of adipocytes. Within the adipose tissue, TNF- $\alpha$  is produced by adipocytes, stromavascular cells, and macrophages, and its expression is greater in subcutaneous than in visceral adipose tissue. Both in experimental models and in humans, adipose tissue expression of TNF- $\alpha$  increases with obesity and is positively correlated with the amount of adipose tissue [39]. The extent to which TNF- $\alpha$  produced by the adipose tissue is secreted in the circulation is unknown, even though a correlation between TNF- $\alpha$  levels and obesity indices has been reported. TNF- $\alpha$  in the adipose tissue acts both in an autocrine and paracrine way to influence a range of processes, including apoptosis and synthesis of other cytokines and adipokines. Interestingly, TNF- $\alpha$  regulates IL-6 synthesis and aromatase expression in the adipose tissue, thus stimulating estrogen production [40]. Moreover, it has been suggested that TNF- $\alpha$  plays a role in the development of insulin-resistance through the inhibition of the insulin receptor-signalling pathway [41]. Thus, overweight subjects may have increased circulating TNF- $\alpha$  levels that could promote breast tumorigenesis through the induction of insulin-resistance and IL-6 and estrogens biosynthesis.

### 4.5. Interleukin-6 (IL-6)

IL-6 is a known inflammatory cytokine secreted by activated macrophage and involved in several functions of the immune response that exerts also various metabolic and endocrine activities. It has been demonstrated that IL-6 increases following menopause in healthy women [42], also it is released by adipocytes, and, by acting both locally and in a systemic fashion, it could disrupt the synthesis of estrogens. Both IL-6 plasma levels and its expression in the adipose tissue are high under obesity and insulin-resistance conditions [43]. Slattery et al. [44] found a significant interaction between high waist-to-hip ratio, a specific IL-6 genotype, and an increased risk of breast cancer, thus suggesting that IL-6 genotypes may influence breast cancer risk in conjunction with central adiposity in postmenopausal women. Moreover, a recent paper showed that the association between a specific IL-6 promoter haplotype and worse outcomes in breast cancer patients was limited to those patients with ER+ tumours, thus providing further support for the hypothesis that IL-6 exerts its effect on breast cancer cells at least in part through hormonal pathways [45]. In fact, IL-6 acts as a regulator of estrogen synthesis and aromatase expression and activity both in the adipose tissue and in malignant breast tissue, contributing to breast cancer progression [46]. A recent *in vitro* paper demonstrated that adipocytes isolated from breast tumour samples overexpressed IL-6 and that higher levels of this cytokine were associated with the tumours of larger size and with lymph-node involvement [20]. Therefore, IL-6 seems to play a key role in the acquired proinvasive feature of tumour cells. Furthermore, IL-6 induces cell migration through the activation of the MAPK pathway, acts as an antiapoptotic factor, promotes the osteoclasts formation, and inhibits the differentiation of dendritic cells, thus facilitating the metastatic process.

In conclusion, IL-6 may be associated with breast cancer through several mechanisms, including regulation of insulin, inflammation, and estrogen, all factors that may significantly influence the evolution of this disease [47]. In fact, proinflammatory cytokines could facilitate tumour growth and metastasis by altering tumour cell biology and activating stromal cells, tumour-associated macrophages and fibroblasts [48]. Moreover, systemic chronic inflammation mediated by IL-6 may increase the risk of breast cancer recurrence and affect its prognosis [49].

## 5. OXIDATIVE STRESS

Obesity, as a result of metabolic and inflammatory changes, is commonly associated with increased oxidative stress, the latter characterized by high levels of reactive oxygen species (ROS) [50]. These highly reactive free radicals created by incomplete reduction of oxygen result in molecules of singlet oxygen and superoxide. Unless these free radicals are neutralized by antioxidant cell protective mechanisms, they can cause damage to lipids, proteins, and nucleic acids. ROS could also lead to progressive genetic instability, tumour progression, and metastasis in triggering the P13 K/Akt pathway that, in turn, is activated by some of the obesity-associated cytokines and growth factors and mutagenic changes [51].

Increased oxidative stress in accumulated fat has recently been identified as an important pathologic mechanism in insulin resistance and metabolic syndrome. In turn, energy balance changes have marked effects on ROS levels in obese subjects: dietary energy restriction brings acute reduction in ROS, whereas overfeeding increases levels of ROS [52]. Accordingly, it has been demonstrated that common single-nucleotide polymorphisms (SNPs) in candidate genes related to oxidative stress was associated with postmenopausal breast cancer risk [53].

Indeed, there is evidence that oxidative stress is involved in breast carcinogenesis. Production of ROS and nitric oxide (NO) species in cancer-associated fibroblasts is sufficient to induce genomic instability in adjacent cancer cells, via a bystander effect, potentially increasing their aggressive behaviour. Breast cancer cells use “oxidative stress” in adjacent fibroblasts as an “engine” to fuel their own survival via the stromal production of nutrients. Therefore, treatment with antioxidants (such as N-acetyl-cysteine, metformin, and quercetin) or NO inhibitors seems to be sufficient to reverse many of the cancer-associated fibroblast phenotypes [54].

## 6. THERAPEUTIC PERSPECTIVES

Antiestrogens, such as tamoxifen, were the first drugs developed for the treatment of hormone-dependent breast cancer. The third-generation aromatase inhibitors have been shown to be superior to tamoxifen in terms of reducing recurrence risk and are recommended for the treatment of postmenopausal women with hormone receptor-positive breast cancer, both in the metastatic and adjuvant and neoadjuvant setting. Importantly, as the reduction in the risk of distant metastases often precedes improvements in overall survival, these results may translate into a significant survival benefit with longer follow-up.

Despite the involvement of estrogens in the aetiology and progression of breast cancer, about 30% of these tumours do not express the ER, and then, they are refractory to the antiestrogen 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 estrogens carry out their actions and the implication of possible alternative or synergic mechanisms capable of regulating tumorigenesis and progression of breast carcinoma.

Recent studies were trying 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 the further identification of key molecules involved in the development of breast carcinoma and to suggest new therapeutic options.

The identification 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, these studies have reported conflicting results. This is mainly because leptin was assessed indiscriminately and not in specific populations of postmenopausal rather than premenopausal patients or in patients with ER+ rather than ER– tumors. Indeed, it should be pointed out that the link between leptin and breast cancer goes through the well-known correlation of postmenopause and subsequent body weight gain, with the increase of aromatase activity and leptin levels also resulting from increased fat mass. Moreover, it is important to underline that leptin seems to have direct and specific actions on the neoplastic cell. Therefore, the role of leptin in the etiopathogenesis of breast cancer and its development would thus seem to be twofold: (1) direct and (2) indirect. 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 to the aromatase activity and the subsequent amount of estrogens [1].

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 to aromatase hyperactivity. In this respect, great importance would be assigned to the use of aromatase inhibitors in the function of the BMI and the subsequent levels of leptin. Paradoxically, in obese women, we could be faced with an optimum action of the aromatase inhibitors in their capacity to suppress estrogen synthesis, but such effect could be in part counteracted by permanent high leptin levels capable of independently perform a specific stimulus of the neoplastic proliferation.

In the light of these considerations, antiestrogen and aromatase inhibitors therapy may have a different effectiveness for postmenopausal women with breast carcinoma in respect of BMI and leptin levels. A recently published exploratory analysis from the ATAC trial [55] showed that postmenopausal ER-positive breast cancer patients with a high BMI ( $\text{BMI} > 35 \text{ kg/m}^2$ ) at baseline had a significantly higher rate of breast cancer recurrence compared to those women with a low BMI ( $\text{BMI} < 23 \text{ kg/m}^2$ ) and significantly more distant recurrences. In detail, recurrence rates in the anastrozole group were lower than those in the tamoxifen group at all BMI levels although the benefit of anastrozole was greater in thinner women ( $\text{BMI} > 30 \text{ kg/m}^2$  versus  $\text{BMI} < 28 \text{ kg/m}^2$ ). One possible explanation for these findings is (as authors stated in the paper) that higher estrogen levels resulting from a high BMI may lead to incomplete inhibition with anastrozole. It seems that there are overweight/obese women whose extraglandular aromatisation from adipose tissue cannot be fully suppressed by the standard treatment dose of 1 mg/day of anastrozole. Therefore, women with a high BMI might need higher dosages to achieve the fully antitumor efficacy of this drug. To test this hypothesis, a thorough assessment of BMI-related efficacy of aromatase inhibitors in randomised trials in both adjuvant and metastatic setting is warranted. Therefore, the evaluation in properly designed and adequately powered clinical trials of the potential benefit of adjusting dose of aromatase inhibitors by body weight will be critical in determining whether outcomes for overweight and obese breast cancer patients can be improved.

Moreover, as discussed in the present paper, other obesity-associated factors, including insulin, adipokines (i.e., leptin), and inflammatory mediators, may influence breast cancer growth and prognosis independently of estrogens and at least in part by interacting with estrogen signalling at a cellular level. In particular, leptin competes with antiestrogens for the modulation of ER activity, and thus, high serum levels of leptin in overweight breast cancer patients might contrast the inhibitory effects of antiestrogenic therapy on cell proliferation and ER expression and transcription. Leptin, with its capacity to increase the activation of estrogen receptors, may reduce or even overcome the antiproliferative effects induced by antiestrogen in breast carcinoma cells [56]. 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 assess the use of drugs which act on the several altered pathways correlated to obesity.



### 6.1. Antidiabetic Drugs: Metformin

Drugs such as oral hypoglycaemic agents as well as those which act on IGF-IR could be effective in reducing the insulin-mediated tumour cells growth. In the same way the adiponectin receptor agonists could offer a new therapeutic approach to improve insulin-resistance and directly inhibit the proliferation of epithelial breast cells.

The concurrence of clinical and epidemiologic evidence linking hyperinsulinemia, insulin resistance, and diabetes to poor breast cancer outcomes has been recently coupled with enhanced understanding of molecular effects of metformin and its potential role in malignancy [57]. It is well known that insulin can promote tumorigenesis both by a direct effect on epithelial tissues or indirectly affecting the levels of other modulators, such as IGFs, sex hormones, and adipokines. The insulin/IGF-I signalling pathway is activated when nutrients are available; *vice versa*, another alternative way is activated when cells are starved of energy through the AMPK pathway as a sensor of cellular energy balance [58]. Therefore, AMPK is the central cellular energy sensor which responds to increases in the adenosine monophosphate/adenosine triphosphate ratio. Physiological conditions of nutrient deprivation activate AMPK, leading to inhibition of energy-consuming processes (gluconeogenesis, protein and fatty acid synthesis, and cholesterol biosynthesis) and the stimulation of processes that generate energy (glycolysis and fatty acid beta oxidation), resulting in restoration of the adenosine triphosphate supply [59]. One of the major growth regulatory pathways controlled by AMPK is the mammalian target of rapamycin (mTOR) pathway and its downstream substrates, such as the ribosomal S6 kinase (S6K1). This pathway regulates protein translation of cell growth regulators such as cyclin D, hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ), and MYC. All these factors control key cell processes such as cycle progression, growth, and angiogenesis [60].

Consequently, IGF signalling concurs to normal cell growth, but it is also a known mediator of the malignant phenotype. IGF-I receptor ligand binding leads to autophosphorylation of tyrosines at its kinase domain; this induces the phosphorylation of tyrosines and serines to form binding sites for insulin receptor substrates (IRSs) and Src and subsequent activation of signalling via the phosphatidylinositol-3-kinase (PI3 K)/Akt/mTOR and RAS/RAF/mitogen-activated protein kinase (MAPK) pathways. It is relevant that mTOR activity is in part regulated by cellular energy levels and nutrients as well as oxygen and growth factors. When mTOR is deregulated, it leads to increased cell growth and proliferation. Therefore, on the basis of the above reports, insulin, both directly and indirectly, promotes lipid, protein, and glycogen synthesis, whereas AMPK inhibits these biosynthetic pathways [60].

Exciting preclinical studies have demonstrated that the antidiabetic drug metformin can inhibit the growth of cancer, including breast cancer cells [61]. Also, population studies increasingly suggest that metformin decreases the incidence of cancer and cancer-related mortality in diabetic patients [62, 63]. More recently, a retrospective study in breast cancer patients who received neoadjuvant chemotherapy showed that diabetic patients receiving metformin during their neoadjuvant chemotherapy had a higher pathological complete response rate than diabetic patients not receiving metformin (24% versus 8%,  $P = 0.007$ ) [64]. The primary actions of metformin are the inhibition of hepatic glucose production and the reduction of insulin resistance in peripheral tissue leading to enhanced glucose uptake and utilisation in skeletal muscle. This reduces the levels of circulating glucose and decreases the plasma insulin levels improving long-term glycemic control and reducing the incidence of diabetes-related complications. The antineoplastic effects of metformin, in particular in breast cancer, are supported by a specific biological rationale involving important factors associated with breast cancer growth and prognosis.

At cell-signalling level, several mechanisms of metformin action have been proposed; the most important relates to the activation of AMPK [65]. In patients with type 2 diabetes mellitus, the activation of AMPK by metformin results in partial reversal of metabolic disturbances such as hyperglycaemia, hyperinsulinemia, and insulin resistance and their mitogenic effects. Therefore, metformin inhibits the growth of various types of cancer cells both *in vitro* and *in vivo* [61] through the activation of AMPK. Activation of AMPK by metformin results in phosphorylation and stabilisation of tuberous sclerosis complex, which integrates regulatory inputs including oxygen-dependent signals and growth factor-dependent signalling pathways such as the PI3 K and the MAPK. Activation of AMPK by metformin can phosphorylate and

activate the tumour suppressor p53 leading to the inhibition of cell division and the induction of apoptosis in cells that encounter low nutrient conditions [66]. This mechanism can lead to apoptosis in p53-proficient cells and induce re-expression of functional p53 in cells with low levels of wild-type p53 [67]. However, p53 expression in adipose tissue is involved in the development of insulin resistance, and therefore, metformin-induced p53 expression may be expected to increase insulin resistance [68].

However, the majority of the growth inhibitory effects of metformin are mediated through the inhibition of mTOR signalling: mTOR phosphorylates downstream mediators leading to the regulation of cell-cycle progression, cell growth, and angiogenesis. Also, metformin-induced reduction of HER-2 protein expression in human breast cancer cells is mediated by inhibition of mTOR [69]. Other reported mechanisms of action for metformin include reduced insulin-like growth factor, insulin-mediated signalling, the inhibition of angiogenesis, and the induction of cell-cycle arrest and apoptosis. Metformin may also have antiproliferative effects both by reversing hyperinsulinaemia and also by indirectly lowering IGF-I levels through effects on insulin and insulin-binding proteins levels [70].

The inhibition of angiogenesis is another proposed mechanism of metformin's effect. Metformin attenuates angiogenic stimuli in the serum of polycystic ovarian syndrome patients with insulin resistance and decreases levels of vascular endothelial growth factor (VEGF) in obese diabetic patients. In addition, in vitro studies have shown the inhibition of angiogenesis and inflammation by metformin through inhibition of mediators such as HIF-1 $\alpha$ , tumour necrosis factor alpha, plasminogen activator inhibitor-1 antigen, and von Willerbrand factor, possibly through the inhibition of mTOR signalling. Therefore, there is a strong preclinical rationale for a potentially beneficial effect of metformin in breast cancer outcomes [71].

## 6.2. Anti-Inflammatory Drugs

Since inflammation-signalling pathways, through the action of some mediators such as IL-6 and TNF- $\alpha$ , may influence breast tumour growth and disease outcome, several studies have investigated associations between aspirin and nonsteroidal anti-inflammatory drugs and breast cancer risk [72]. A recent study demonstrated that aspirin had the greatest reduction in risk in the presence of a high-risk IL-6 genotype and a more modest effect in the presence of the lower-risk allele and concluded that the joint effect of IL-6 genotype and aspirin use attenuated the expected risk in a multiplicative way among postmenopausal women [73].

Aspirin and other NSAIDs are widely used for the treatment of minor injuries and headaches, degenerative joint diseases such as rheumatoid arthritis, and as prophylaxis against cardiovascular diseases. NSAIDs inhibit the activity of COX leading to the inhibition of synthesis of prostaglandins (PGs) that cause inflammation, swelling, pain, and fever. Some NSAIDs are more potent against COX-1 (e.g., aspirin); others have greater affinity for COX-2.

Increasing evidence from in vitro and animal models as well as human epidemiological studies suggests that aspirin and other NSAIDs may prevent the occurrence of cancers of epithelial origin [74]. In particular, daily intake of NSAIDs, primarily aspirin, produced risk reductions of 39% for breast cancer [75]: these chemopreventive effects were apparent after 5 or more years of NSAID use and were stronger with longer duration. These observations have collectively initiated a wide variety of investigations to determine the mechanisms by which aspirin and other NSAIDs reduce the risk or progression of cancers.

In detail, research on human cell lines and animal models indicates a role for COX-2 in breast carcinogenesis, thus suggesting that selective COX-2 (sCOX-2) inhibitors and NSAIDs may prevent the growth of mammary tumours. In fact, COX-2 is overexpressed in approximately 40% of human breast tumours, and it is induced in response to stimuli such as cytokines [76].

NSAIDs may exert a protective effect against breast cancer, apart from by inhibiting COX-2, by reducing the level of prostaglandins, estrogens, and/or prolactin [77, 78]. Furthermore, studies in the literature suggest that in different cancer cells, aspirin induces the upregulation of their mitochondrial proapoptotic proteins, such as Bax and Bak, and the downregulation of antiapoptotic proteins such as Bcl-2 and Bcl-xl [79] as well as increases mitochondrial membrane permeability and the release of cytochrome c, leading to the activation of caspases and cell apoptosis [80]. One of the most widely accepted mechanisms

for the anticancer effect of NSAIDs is the reduced PG synthesis through acetylation and inhibition of COX. However, NSAIDs have growth inhibitory effects also against cancer cell lines that do not express COX-1 or -2 and against mouse embryo fibroblasts that are null for both enzymes [81]. These observations suggest that COX-independent pathways may also contribute to the anticancer effects of NSAIDs. Although the effects of aspirin on COX have been well studied, little is known as to whether it induces acetylation of cellular proteins, particularly those that regulate apoptosis, which may also contribute to its anticancer effects. Alfonso et al. demonstrated that the ability of aspirin to induce apoptosis involves acetylation of the tumour suppressor protein p53 [82], leading to the modulation of its target genes, p21CIP1, a protein involved in cell cycle arrest, and Bax, a mitochondrial pro-apoptotic protein.

Another possible mechanism by which the COX/PGE<sub>2</sub> cascade promotes breast cancer is via increasing estrogen production. It is known that PGE<sub>2</sub> upregulates aromatase activity leading to increased estrogen synthesis, and recently, *vice versa* dose-dependent decreases of aromatase activity were observed in breast cancer cells following treatment with NSAIDs, a COX-1 selective inhibitor, and COX-2 selective inhibitors [83]. Indeed, laboratory results have shown that estradiol production is decreased in breast cells exposed to the selective COX-2 inhibitor celecoxib [84]. Although the above-mentioned pathway through which NSAIDs may decrease the development of breast cancer has been previously highlighted, the association between NSAID use and circulating estradiol in women is currently unknown. Therefore, a recent cross-sectional investigation demonstrated that NSAID use was associated with lower circulating estradiol levels in a population of postmenopausal women not taking menopausal hormone therapy [85], thus suggesting a potential mechanism through which NSAIDs exert their protective effects on breast cancer.

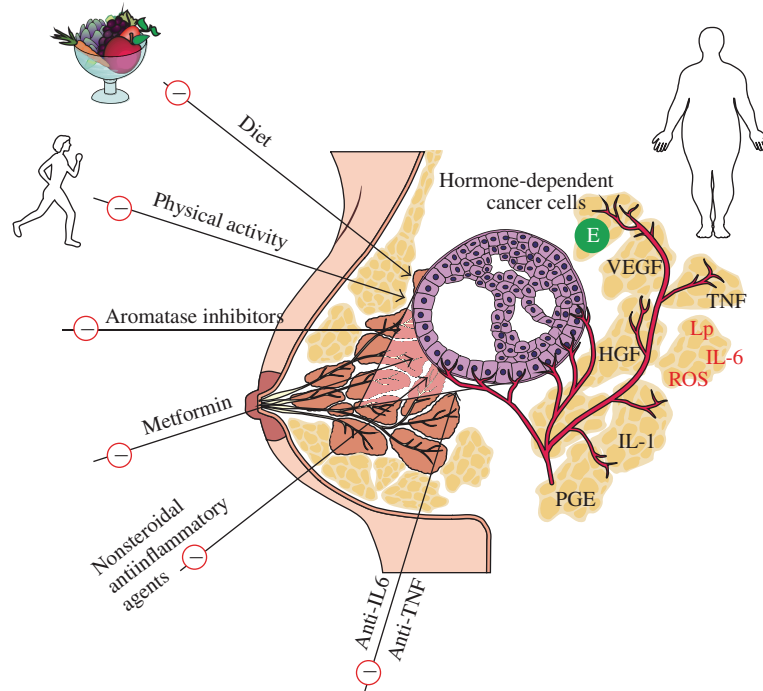
To date, however, results of epidemiological studies of NSAIDs and breast cancer risk have been uncertain. In fact, some cohort studies [86, 87] have found a reduced risk of breast cancer associated with aspirin use. On the other hand, others [88, 89] have failed to find any association or have even suggested an increased risk. Few meta-analyses of this association have been performed, and all have methodological limitations. None was exhaustive, and none assessed heterogeneity in an in-depth manner. However, recently, an exhaustive meta-analysis on NSAID use and risk of breast cancer was carried out following the MOOSE guidelines for meta-analyses of observational studies and provided evidence that NSAID use is associated with reduced risk for breast cancer. The authors included COX-2-nonselective inhibitors (a group that contains aspirin and ibuprofen as the most widely used drugs) as well as the more recent COX-2-selective inhibitors with the aim to provide a more definitive answer about a possible inverse correlation between the use of these drugs and the risk for breast cancer [90].

## 7. CONCLUSIONS

The evidence currently available in the literature would seem to suggest that the expression of adipokines as well as that of estrogens differ according to BMI changes and energy metabolic status. Therefore, a careful assessment of the nutritional status and body composition is paramount for a proper therapeutic approach for postmenopausal breast carcinoma. The use of antidiabetic and anti-inflammatory drugs associated with conventional hormone therapies and dietary/physical interventions could offer a new therapeutic approach for breast carcinoma that develops in the context of adiposity (Figure 2).

Different dietary patterns were demonstrated to influence breast cancer risk [91]: in particular, a food pattern characterized by high-fat food choices was significantly associated with increased risk of breast cancer. Moreover, data from epidemiological studies suggest that physical activity is important in reducing the risk of breast cancer in postmenopausal women [73]. Indeed, these approaches target the upstream factors, that is, adiposity and physical inactivity, which drive chronic inflammation linked to breast carcinogenesis and prognosis.

To date, however, only few randomized clinical trials have investigated the associations of diet, physical activity, or weight with prognosis among women diagnosed with breast cancer [92]. An analysis of lifestyle and survival in the control arm of the Women's Healthy Eating and Living Study (WHEL) trial found that the combination of consuming five or more daily servings of vegetables and fruits and



**FIGURE 2:** Potential therapeutic approaches for postmenopausal hormone-dependent breast carcinoma which develops in the context of adiposity. Adipokines-, insulin-, inflammation-, and angiogenesis-signalling pathways influence the development of hormone-dependent breast carcinoma and might represent new targets of treatment in combination with conventional hormone therapies. COX-2, cyclooxygenase-2; E, estradiol; HGF, hepatocyte growth factor; IGF, insulin growth factor; IL, interleukin; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

accumulating  $\geq 540$  metabolic equivalent tasks-minutes/wk (equivalent to walking 30 minutes 6 days/wk), was associated with a significant survival advantage (HR, 0.56; 95% CI, 0.31 to 0.98). These findings were similar in obese and nonobese women and were stronger in those with estrogen receptor-positive tumours. Behaviour changes associated with increased physical activity have also been shown to moderately decrease cancer incidence, slow down cancer progression in model systems, and improve cancer survival by multiple mechanisms, including improved insulin resistance resulting in lower insulin levels, reduced circulating bioactive hormone concentrations resulting in increased steroid hormone binding proteins, and reduced inflammatory cytokines. Recent publications have reported on associations between physical activity and prognosis among breast cancer survivors. In 2,987 women from the Nurses' Health Study diagnosed with stage I to III breast cancer between 1984 and 1998 and followed until death or 2002, the relative risk of death from breast cancer for activity equivalents of walking was 0.80 for 1 to 3 hours/wk, 0.50 for 3 to 5 hours/wk, 0.56 for 5 to 8 hours/wk, and 0.60 for  $\geq 8$  hours/wk, compared with inactive women. In a cohort of 688 women diagnosed with local or regional breast cancer between 1995 and 1998 and observed until death or 2004, the HR for total deaths for women expending the energy equivalent of 2 to 3 hours/wk of brisk walking at 2 years after diagnosis was 0.33 (95% CI, 0.15 to 0.73,  $P$  for trend 0.046) compared with inactive women. In a cohort of 1,970 early-stage patients with breast cancer identified primarily through a health maintenance organization, a protective association between physical activity and all-cause mortality remained in multivariable analyses (HR, 0.66; 95% CI, 0.42 to 1.03;  $P$  for trend = 0.04).

Future studies that exploit emerging ways to target energy balance-responsive pathways through combinations of lifestyle (particularly diet and physical activity) and pharmacologic approaches will



facilitate the translation of this research into effective cancer prevention and targeted effective therapeutic strategies in humans.

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