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 tumor. 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 signaling 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 l.3, which are regulated by unknown factors probably released by malignant epithelial cells: among these prostaglandin, (PG) E2 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-α, tumour necrosis factor-α; Lp, leptin; E, estradiol; A, aromatase.
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-)α, 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-α and IL-6.

The exact interplay between these different adipokines is yet nor 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 involve 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/ERα signalling in the 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. 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)-γ 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-α [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-γ 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-α

The TNF-α was the first inflammatory cytokine to be identified as a product of adipocytes. Within the
adipose tissue, TNF-α 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-α increases with obesity and is positively correlated with the amount of
adipose tissue [39]. The extent to which TNF-α produced by the adipose tissue is secreted in the circulation
is unknown, even though a correlation between TNF-α levels and obesity indices has been reported. TNF-α
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-α regulates IL-6 synthesis
and aromatase expression in the adipose tissue, thus stimulating estrogen production [40]. 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 [41]. 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 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 PI3 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 (BMI > 35 kg/m²) at baseline had a significantly higher rate of breast cancer recurrence compared to those women with a low BMI (BMI < 23 kg/m²) 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 (BMI > 30 kg/m² versus BMI < 28 kg/m²). 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 1α (HIF1α), 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, hyper-insulinemia, 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-1α, 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-α, 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/PGE2 cascade promotes breast cancer is via increasing estrogen production. It is known that PGE2 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
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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REFERENCES

[1] A. MacCiò, C. Madeddu, and G. Mantovani, “Adipose tissue as target organ in the treatment of hormone-dependent breast cancer: new therapeutic perspectives,” Obesity Reviews, vol. 10, no. 6, pp. 660–670, 2009.
[2] B. Dirat, L. Bochet, G. Escourrou, P. Valet, and C. Muller, “Unraveling the obesity and breast cancer links: a role for cancer-associated adipocytes?” Endocrine Development, vol. 19, pp. 45–52, 2010.
[3] A. R. Carmichael, “Obesity and prognosis of breast cancer,” Obesity Reviews, vol. 7, no. 4, pp. 333–340, 2006.
[4] D. P. Rose, D. Komninou, and G. D. Stephenson, “Obesity, adipocytokines, and insulin resistance in breast cancer,” Obesity Reviews, vol. 5, no. 3, pp. 153–165, 2004.
[5] M. J. Borugian, S. B. Sheps, C. Kim-Sing et al., “Waist-to-hip ratio and breast cancer mortality,” American Journal of Epidemiology, vol. 158, no. 10, pp. 963–968, 2003.
[6] Y. Zhao, J. E. Nichols, S. E. Bulun, C. R. Mendelson, and E. R. Simpson, “Aromatase P450 gene expression in human adipose tissue. Role of a Jak/STAT pathway in regulation of the adipose-specific promoter,” Journal of Biological Chemistry, vol. 270, no. 27, pp. 16449–16457, 1995.
[7] Y. Zhao, V. R. Agarwal, C. R. Mendelson, and E. R. Simpson, “Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene,” Endocrinology, vol. 137, no. 12, pp. 5739–5742, 1996.
[8] L. Vona-Davis and D. P. Rose, “Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression,” Endocrine-Related Cancer, vol. 14, no. 2, pp. 189–206, 2007.
[9] L. Vona-Davis, M. Howard-McNatt, and D. P. Rose, “Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer,” Obesity Reviews, vol. 8, no. 5, pp. 395–408, 2007.
[10] A. Mawson, A. Lai, J. S. Carroll, C. M. Sergio, C. J. Mitchell, and B. Sarcevic, “Estrogen and insulin/IGF-1 cooperatively stimulate cell cycle progression in MCF-7 breast cancer cells through differential regulation of c-Myc and cyclin D1,” Molecular and Cellular Endocrinology, vol. 229, no. 1-2, pp. 161–173, 2005.
[11] D. Sachdev and D. Yee, “The IGF system and breast cancer,” Endocrine-Related Cancer, vol. 8, no. 3, pp. 197–209, 2001.
[12] M. L. Slattery, C. Sweeney, R. Wolff et al., “Genetic variation in IGF1, IGFBP3, IRS1, IRS2 and risk of breast cancer in women living in Southwestern United States,” Breast Cancer Research and Treatment, vol. 104, no. 2, pp. 197–209, 2007.
[13] D. Sachdev, J. S. Hartell, A. V. Lee, X. Zhang, and D. Yee, “A dominant negative type I insulin-like growth factor receptor inhibits metastasis of human cancer cells,” Journal of Biological Chemistry, vol. 279, no. 6, pp. 5017–5024, 2004.
[14] D. Yee and A. V. Lee, “Crosstalk between the insulin-like growth factors and estrogens in breast cancer,” Journal of Mammary Gland Biology and Neoplasia, vol. 5, no. 1, pp. 107–115, 2000.
[15] A. McTiernan, K. B. Rajan, S. S. Tworoger et al., “Adiposity and sex hormones in postmenopausal breast cancer survivors,” Journal of Clinical Oncology, vol. 21, no. 10, pp. 1961–1966, 2003.
[16] T. J. Key, “Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies,” Journal of the National Cancer Institute, vol. 94, no. 8, pp. 606–616, 2002.
[17] M. G. Catalano, R. Frairia, G. Boccuzzi, and N. Fortunati, “Sex hormone-binding globulin antagonizes the anti-apoptotic effect of estradiol in breast cancer cells,” Molecular and Cellular Endocrinology, vol. 230, no. 1-2, pp. 31–37, 2005.
[18] E. E. Kershaw and J. S. Flier, “Adipose tissue as an endocrine organ,” Journal of Clinical Endocrinology and Metabolism, vol. 89, no. 6, pp. 2548–2556, 2004.
[19] P. Iyengar, T. P. Combs, S. J. Shah et al., “Adipocyte-secreted factors synergistically promote mammary tumorigenesis through induction of anti-apoptotic transcriptional programs and proto-oncogene stabilization,” *Oncogene*, vol. 22, no. 41, pp. 6408–6423, 2003.

[20] B. Dirat, L. Bochet, M. Dabek et al., “Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion,” *Cancer Research*, vol. 71, no. 7, pp. 2455–2465, 2011.

[21] R. S. Ahima, D. Prabakaran, C. Mantzoros et al., “Role of leptin in the neuroendocrine response to fasting,” *Nature*, vol. 382, no. 6588, pp. 250–252, 1996.

[22] P. J. Simons, P. S. Van Den Pangaart, C. P. A. A. Van Roomen, J. M. F. G. Aerts, and L. Boon, “Cytokine-mediated modulation of leptin and adiponectin secretion during in vitro adipogenesis: evidence that tumor necrosis factor-α- and interleukin-1β-treated human preadipocytes are potent leptin producers,” *Cytokine*, vol. 32, no. 2, pp. 94–103, 2005.

[23] L. Tessitore, B. Vizio, D. Pesola et al., “Adipocyte expression and circulating levels of leptin increase in both gynaecological and breast cancer patients,” *International Journal of Oncology*, vol. 24, no. 6, pp. 1529–1535, 2004.

[24] F. Machinal-Quelin, M. N. Dieudonné, R. Pecquery, M. C. Leneveu, and Y. Giudicelli, “Direct in vitro effects of androgens and estrogens on ob gene expression and leptin secretion in human adipose tissue,” *Endocrine*, vol. 18, no. 2, pp. 179–184, 2005.

[25] Y. Miyoshi, T. Funahashi, S. Tanaka et al., “High expression of leptin receptor mRNA in breast cancer tissue predicts poor prognosis for patients with high, but not low, serum leptin levels,” *International Journal of Cancer*, vol. 118, no. 6, pp. 1414–1419, 2006.

[26] D. C. Chen, Y. F. Chung, Y. T. Yeh et al., “Serum adiponectin and leptin levels in Taiwanese breast cancer patients,” *Cancer Letters*, vol. 237, no. 1, pp. 109–114, 2006.

[27] C. S. Mantzoros, K. Bolhke, S. Moschos, and D. W. Cramer, “Leptin in relation to carcinoma in situ of the breast: a study of premenopausal cases and controls,” *International Journal of Cancer*, vol. 80, no. 4, pp. 523–526, 1999.

[28] J. Geisler, B. Haynes, D. Ekse, M. Dowsett, and P. E. Lønning, “Total body aromatization in postmenopausal breast cancer patients is strongly correlated to plasma leptin levels,” *Journal of Steroid Biochemistry and Molecular Biology*, vol. 104, no. 1-2, pp. 27–34, 2007.

[29] P. J. Goodwin, M. Ennis, I. G. Fantus et al., “Is leptin a mediator of adverse prognostic effects of obesity in breast cancer?” *Journal of Clinical Oncology*, vol. 23, no. 25, pp. 6037–6042, 2005.

[30] N. Yin, D. Wang, H. Zhang et al., “Molecular mechanisms involved in the growth stimulation of breast cancer cells by leptin,” *Cancer Research*, vol. 64, no. 16, pp. 5870–5875, 2004.

[31] S. Fischer, M. Hanefeld, S. M. Haffner et al., “Insulin-resistant patients with type 2 diabetes mellitus have higher serum leptin levels independently of body fat mass,” *Acta Diabetologica*, vol. 39, no. 3, pp. 105–110, 2002.

[32] A. MacCio, C. Madeddu, G. Gramignano et al., “Correlation of body mass index and leptin with tumor size and stage of disease in hormone-dependent postmenopausal breast cancer: preliminary results and therapeutic implications,” *Journal of Molecular Medicine*, vol. 88, no. 7, pp. 677–686, 2010.

[33] Y. Matsuzawa, “Adiponectin: identification, physiology and clinical relevance in metabolic and vascular disease,” *Atherosclerosis Supplements*, vol. 6, no. 2, pp. 7–14, 2005.

[34] A. Schönfeld, J. Schölmich, and C. Buechler, “Mechanisms of disease: adipokines and breast cancer—endocrine and paracrine mechanisms that connect adiposity and breast cancer,” *Nature Clinical Practice Endocrinology and Metabolism*, vol. 3, no. 4, pp. 345–354, 2007.

[35] E. Bräkenhielm, N. Veitonmäki, R. Cao et al., “Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 8, pp. 2476–2481, 2004.

[36] M. Pignatelli, C. Cocca, A. Santos, and A. Perez-Castillo, “Enhancement of BRCA1 gene expression by the peroxisome proliferator-activated receptor γ in the MCF-7 breast cancer cell line,” *Oncogene*, vol. 22, no. 35, pp. 5446–5450, 2003.

[37] J. Rehman, R. V. Considine, J. E. Bovenkerk et al., “Obesity is associated with increased levels of circulating hepatocyte growth factor,” *Journal of the American College of Cardiology*, vol. 41, no. 8, pp. 1408–1413, 2003.

[38] S. M. Sheen-Chen, Y. W. Liu, H. L. Eng, and F. F. Chou, “Serum levels of hepatocyte growth factor in patients with breast cancer,” *Cancer Epidemiology Biomarkers and Prevention*, vol. 14, no. 3, pp. 715–717, 2005.
[39] H. Ruan and H. F. Lodish, “Insulin resistance in adipose tissue: Direct and indirect effects of tumor necrosis factor-α,” *Cytokine and Growth Factor Reviews*, vol. 14, no. 5, pp. 447–455, 2003.

[40] A. Purohit, S. P. Newman, and M. J. Reed, “The role of cytokines in regulating estrogen synthesis: implications for the etiology of breast cancer,” *Breast Cancer Research*, vol. 4, no. 2, pp. 65–69, 2002.

[41] G. S. Hotamisligil, N. S. Shargill, and B. M. Spiegelman, “Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance,” *Science*, vol. 259, no. 5091, pp. 87–91, 1993.

[42] J. E. Morley and R. N. Baumgartner, “Cytokine-related aging process,” *Journals of Gerontology. Series A*, vol. 59, no. 9, pp. 924–929, 2004.

[43] B. Vozarova, C. Weyer, K. Hanson, P. A. Tataranni, C. Bogardus, and R. E. Pratley, “Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion,” *Obesity Research*, vol. 9, no. 7, pp. 414–417, 2001.

[44] M. L. Slattery, K. Curtin, C. Sweeney et al., “Modifying effects of IL-6 polymorphisms on body size-associated breast cancer risk.” *Obesity*, vol. 16, no. 2, pp. 339–347, 2008.

[45] A. DeMichele, R. Gray, M. Horn et al., “Host genetic variants in the interleukin-6 promoter predict poor outcome in patients with estrogen receptor-positive, node-positive breast cancer,” *Cancer Research*, vol. 69, no. 10, pp. 4184–4191, 2009.

[46] A. Purohit, M. W. Ghilchik, L. Duncan et al., “Aromatase activity and interleukin-6 production by normal and malignant breast tissues,” *Journal of Clinical Endocrinology and Metabolism*, vol. 80, no. 10, pp. 3052–3058, 1995.

[47] S. W. Cole, “Chronic inflammation and breast cancer recurrence,” *Journal of Clinical Oncology*, vol. 27, no. 21, pp. 3418–3419, 2009.

[48] B. L. Pierce, R. Ballard-Barbash, L. Bernstein et al., “Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients,” *Journal of Clinical Oncology*, vol. 27, no. 21, pp. 3437–3444, 2009.

[49] P. Seibold, R. Heim, P. Schmezer et al., “Polymorphisms in oxidative stress-related genes and postmenopausal breast cancer risk.” *International Journal of Cancer*, vol. 129, no. 6, pp. 1467–1476, 2011.

[50] D. G. Hardie, “AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy,” *Nature Reviews Molecular Cell Biology*, vol. 8, no. 10, pp. 777–807, 2007.
[61] I. N. Alimova, B. Liu, Z. Fan et al., “Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro,” Cell Cycle, vol. 8, no. 6, pp. 909–915, 2009.

[62] J. M. M. Evans, L. A. Donnelly, A. M. Emslie-Smith, D. R. Alessi, and A. D. Morris, “Metformin and reduced risk of cancer in diabetic patients,” British Medical Journal, vol. 330, no. 7503, pp. 1304–1305, 2005.

[63] S. L. Bowker, S. R. Majumdar, P. Veugelers, and J. A. Johnson, “Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin,” Diabetes Care, vol. 29, no. 2, pp. 254–258, 2006.

[64] S. Jiralerspong, S. L. Palla, S. H. Giordano et al., “Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer,” Journal of Clinical Oncology, vol. 27, no. 20, pp. 3297–3302, 2009.

[65] G. Zhou, R. Myers, Y. Li et al., “Role of AMP-activated protein kinase in mechanism of metformin action,” Journal of Clinical Investigation, vol. 108, no. 8, pp. 1167–1174, 2001.

[66] C. C. Thoreen and D. M. Sabatini, “AMPK and p53 help cells through lean times,” Cell Metabolism, vol. 1, no. 5, pp. 287–288, 2005.

[67] T. Minamino, M. Orimo, I. Shimizu et al., “A crucial role for adipose tissue p53 in the regulation of insulin resistance,” Nature Medicine, vol. 15, no. 9, pp. 1082–1087, 2009.

[68] A. Vazquez-Martin, C. Oliveras-Ferraros, and J. A. Menendez, “The antidiabetic drug metformin suppresses HER2 (erbB-2) oncprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells,” Cell Cycle, vol. 8, no. 1, pp. 88–96, 2009.

[69] P. Goodwin, K. Pritchard, M. Ennis, M. Clemons, M. Graham, and I. G. Fantus, “Insulin-lowering effects of metformin in women with early breast cancer,” Clinical Breast Cancer, vol. 8, no. 6, pp. 501–505, 2008.

[70] A. M. Gonzalez-Angulo and F. Meric-Bernstam, “Metformin: a therapeutic opportunity in breast cancer,” Clinical Cancer Research, vol. 16, no. 6, pp. 1695–1700, 2010.

[71] L. R. Howe and S. M. Lippman, “Modulation of breast cancer risk by nonsteroidal anti-inflammatory drugs,” Journal of the National Cancer Institute, vol. 100, no. 20, pp. 1420–1423, 2008.

[72] M. L. Slattery, S. Edwards, M. A. Murtaugh et al., “Physical activity and breast cancer risk among women in the southwestern United States,” Annals of Epidemiology, vol. 17, no. 5, pp. 342–353, 2007.

[73] R. E. Harris, J. Beebe-Donk, H. Doss, and D. Burr Doss, “Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade,” Oncology reports, vol. 13, no. 4, pp. 559–583, 2005.

[74] L. R. Howe, “Inflammation and breast cancer. Cyclooxygenase/prostaglandin signaling and breast cancer,” Breast Cancer Research, vol. 9, no. 4, pp. 252–266, 2007.

[75] S. S. Tworoger, A. H. Eliassen, P. Sluss, and S. E. Hankinson, “Nonsteroidal anti-inflammatory drug use and serum total estradiol in postmenopausal women,” Cancer Epidemiology Biomarkers and Prevention, vol. 17, no. 3, pp. 680–687, 2008.

[76] S. S. Tworoger, A. H. Eliassen, P. Sluss, and S. E. Hankinson, “A prospective study of plasma prolactin concentrations and risk of premenopausal and postmenopausal breast cancer,” Journal of Clinical Oncology, vol. 25, no. 12, pp. 1482–1488, 2007.

[77] K. C. Zimmermann, N. J. Waterhouse, J. C. Goldstein, M. Schuler, and D. R. Green, “Aspirin induces apoptosis through release of cytochrome c from mitochondria,” Neoplasia, vol. 2, no. 6, pp. 505–513, 2000.

[78] X. Zhang, S. G. Morham, R. Langenbach, and D. A. Young, “Malignant transformation and antineoplastic actions of nonsteroidal antiinflammatory drugs (NSAIDs) on cyclooxygenase-null embryo fibroblasts,” Journal of Experimental Medicine, vol. 190, no. 4, pp. 451–459, 1999.
[82] L. F. Alfonso, K. S. Srivenugopal, T. V. Arumugam, T. J. Abbruscato, J. A. Weidanz, and G. J. Bhat, “Aspirin inhibits camptothecin-induced p21CIP1 levels and potentiates apoptosis in human breast cancer cells,” *International Journal of Oncology*, vol. 34, no. 3, pp. 597–608, 2009.

[83] R. W. Brueggemeier, B. Su, Y. Sugimoto, E. S. Díaz-Cruz, and D. D. Davis, “Aromatase and COX in breast cancer: enzyme inhibitors and beyond,” *Journal of Steroid Biochemistry and Molecular Biology*, vol. 106, no. 1–5, pp. 16–23, 2007.

[84] R. N. DuBois, “Aspirin and breast cancer prevention: the estrogen connection,” *Journal of the American Medical Association*, vol. 291, no. 20, pp. 2488–2489, 2004.

[85] G. L. Gierach, J. V. Lacey Jr., A. Schatzkin et al., “Nonsteroidal anti-inflammatory drugs and breast cancer risk in the National Institutes of Health-AARP Diet and Health Study,” *Breast Cancer Research*, vol. 10, no. 2, article R38, 2008.

[86] R. E. Harris, S. Kasbari, and W. B. Farrar, “Prospective study of nonsteroidal anti-inflammatory drugs and breast cancer,” *Oncology Reports*, vol. 6, no. 1, pp. 71–73, 1998.

[87] T. W. Johnson, K. E. Anderson, D. Lazovich, and A. R. Folsom, “Association of aspirin and nonsteroidal anti-inflammatory drug use with breast cancer,” *Cancer Epidemiology Biomarkers and Prevention*, vol. 11, no. 12, pp. 1586–1591, 2002.

[88] S. F. Marshall, L. Bernstein, H. Anton-Culver et al., “Nonsteroidal anti-inflammatory drug use and breast cancer risk by stage and hormone receptor status,” *Journal of the National Cancer Institute*, vol. 97, no. 11, pp. 805–812, 2005.

[89] E. J. Jacobs, M. J. Thun, E. B. Bain, C. Rodriguez, S. J. Henley, and E. E. Calle, “A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence,” *Journal of the National Cancer Institute*, vol. 99, no. 8, pp. 608–615, 2007.

[90] B. Takkouche, C. Regueira-Méndez, and M. Etminan, “Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis,” *Journal of the National Cancer Institute*, vol. 100, no. 20, pp. 1439–1447, 2008.

[91] M. A. Murtaugh, C. Sweeney, A. R. Giuliano et al., “Diet patterns and breast cancer risk in Hispanic and non-Hispanic white women: the Four-Corners Breast Cancer Study,” *American Journal of Clinical Nutrition*, vol. 87, no. 4, pp. 978–984, 2008.

[92] A. McTiernan, M. Irwin, and V. Vongruenigen, “Weight, physical activity, diet, and prognosis in breast and gynecologic cancers,” *Journal of Clinical Oncology*, vol. 28, no. 26, pp. 4074–4080, 2010.

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