Obesity, chronic breast inflammation and carcinogenesis: Molecular pathways and clinical implications (Review)

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Abstract. Obesity is a global epidemic strongly associated with increased breast cancer (BC) risk and mortality, particularly in postmenopausal women. Obesity-induced chronic breast inflammation drives carcinogenesis via dysregulated adipokine signaling (leptin and adiponectin), insulin resistance, hyperinsulinemia and pro-inflammatory cytokines (TNF-α and IL-6). These factors activate oncogenic pathways (NF-κB and PI3K/AKT/mTOR pathways), which promote DNA damage, cell proliferation and immunosuppression. Clinically, obesity is associated with advanced tumor presentation, reduced treatment efficacy and poorer survival compared with those of normal-weight patients with BC. Despite progress, the molecular interactions between obesity-related inflammation and BC remain incompletely understood, and diagnostic/prognostic tools for obese patients require refinement. The present review synthesizes current evidence on obesity-BC mechanisms and their clinical translation to inform prevention and precision oncology strategies.

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1. Introduction

Obesity prevalence continues to rise globally, with >1.9 billion adults classified as overweight and >650 million classified as obese, according to the latest World Health Organization reports (1). Obesity is a key risk factor for numerous chronic diseases, including type 2 diabetes mellitus (2), cardiovascular diseases (3) and osteoarthritis (4). Obesity leads to insulin resistance, which can progress to type 2 diabetes (2). The excess fat tissue alters metabolic processes, increasing the production of pro-inflammatory cytokines and free fatty acids, which in turn impair insulin signaling (2). Obesity also elevates the risk of cardiovascular diseases. The excess adipose tissue increases the workload of the heart, raises the blood pressure and contributes to the buildup of plaque in the arteries (3). Furthermore, obesity is linked to a higher incidence of osteoarthritis, as the excess weight puts additional stress on joints, causing cartilage degradation and inflammation (4). The global economic burden of obesity is enormous, with healthcare costs related to obesity-related diseases increasing in both developed and developing nations (5).

BC stands out as a leading cause of cancer-related mortality among women globally. In 2020 alone, there were ~2.3 million new cases diagnosed, accounting for a significant proportion of all cancer cases (6). The impact of BC extends beyond physical health, affecting psychological wellbeing and the quality of life (6). The diagnosis of BC often leads to heightened anxiety, depression and body image issues (7). Conventional treatments, including surgery, chemotherapy and radiation therapy, while effective in numerous cases, are associated with a range of side effects. These can include lymphedema, fatigue, nausea, hair loss and, in some instances, long-term organ damage (8). The economic costs of BC treatment are also substantial, including direct medical expenses as well as indirect costs due to lost productivity (9). Despite advances in early detection and treatment, certain subtypes of BC, such as triple-negative BC (TNBC), remain particularly aggressive and challenging to treat, with limited targeted therapies available (10).

Recent research has begun to unravel the complex relationship among obesity, chronic breast inflammation and BC development (11). Epidemiological studies have established a clear association between obesity and an increased risk of BC, particularly in postmenopausal women (11,12). The mechanisms underlying this link are multifaceted. Adipose tissue in the breast is not inert; it actively secretes a variety of inflammatory mediators. These include cytokines such as IL-6 and TNF-α, which create a pro-inflammatory microenvironment (13). Chronic inflammation is now recognized as a key driver of carcinogenesis. Persistent low-grade inflammation leads to DNA damage through the production of reactive oxygen species (ROS) and nitrogen species (13). Inflammatory cells also secrete growth factors and angiogenic factors, promoting cell proliferation and the formation of new blood vessels to supply growing tumors (13). Emerging evidence suggests that specific signaling pathways, such as the NF-κB pathway, are activated in obese breast tissue (14). This pathway regulates the expression of genes involved in cell survival, proliferation and immune responses (14). Cyclooxygenase-2 (COX-2) upregulation in obese breast tissue results in increased prostaglandin E2 levels, which suppress apoptosis and induce DNA damage (15). Furthermore, the PI3K/AKT/mTOR pathway is often dysregulated in obesity-related BC (16). This pathway is critical for the regulation of cell proliferation and metabolism, and its activation can lead to uncontrolled cell proliferation and resistance to cell death (16).

The present review aims to comprehensively explore the molecular mechanisms that connect obesity, chronic breast inflammation and breast carcinogenesis. By delving into the latest research findings from PubMed-listed studies (https://pubmed.ncbi.nlm.nih.gov/), the present review aims to provide a detailed understanding of how obesity-induced inflammation contributes to the development and progression of BC. The search strategy employed the following key words and Boolean operators: ('obesity' OR 'adiposity') AND ('chronic inflammation' OR 'breast inflammation') AND ('breast cancer' OR 'breast carcinogenesis') AND ('molecular mechanisms' OR 'signaling pathways'). Articles published in English between 2013 and 2025 were included, with priority given to meta-analyses, systematic reviews and high-impact original research. The clinical implications of these molecular insights are also discussed, focusing on novel diagnostic approaches, biomarkers for early detection and risk assessment, and innovative prevention and treatment strategies tailored to the obese population. Furthermore, the present review aims to identify gaps in the current knowledge and propose future research directions, such as long-term intervention studies and the exploration of personalized medicine approaches based on the obese inflammatory phenotype in patients with BC. The ultimate goal is to enhance the prevention, early detection and treatment of BC in the context of the obesity epidemic, improving outcomes for this vulnerable patient population and reducing the global burden of BC.

2. Obesity and BC epidemiology

Obesity represents a significant global health challenge and is a well-established modifiable risk factor for postmenopausal BC, while its association with premenopausal BC risk appears more complex (17-19). Furthermore, a substantial body of evidence has demonstrated that obesity adversely impacts prognosis and treatment outcomes across various BC subtypes, contributing to cancer-related mortality (20-22). This section synthesizes key epidemiological findings on the relationships among obesity, BC risk, prognosis and treatment response (Table SI).

Obesity as a risk factor for BC development. Numerous large-scale epidemiological studies have demonstrated that an elevated BMI increases the risk of developing postmenopausal BC (19,23) (Table SI). A secondary analysis of the Women's Health Initiative (WHI) observational study revealed a clear positive association between higher BMI and increased risk of invasive postmenopausal BC (18). Crucially, Ladoire *et al* (21) demonstrated that even among postmenopausal women with a normal BMI, higher levels of body fat were independently associated with an increased BC risk, suggesting that adiposity itself, beyond BMI classification, is a critical factor. The risk appears to be further amplified by metabolic dysfunction. Agnoli *et al* (12) found that metabolic syndrome, a cluster of conditions often associated with obesity (including hypertension, dyslipidemia, insulin resistance and central adiposity), conferred an elevated risk of BC in postmenopausal women compared with that of those without metabolic syndrome. The underlying mechanisms linking obesity to carcinogenesis involve chronic low-grade inflammation and oxidative stress (24). Dias *et al* (24), in a nested case-control study within the Malmö Diet and Cancer Cohort, provided evidence that systemic low-grade inflammation and oxidative stress biomarkers were associated with an increased risk of invasive postmenopausal BC, suggesting that these inflammatory and oxidative processes may mechanistically link obesity to breast carcinogenesis by promoting genomic instability and epithelial cell proliferation. Kabat *et al* (19) further investigated metabolic phenotypes, suggesting that specific obesity-related metabolic disturbances contribute to BC risk beyond overall adiposity. Recent data from the WHI reported by Chlebowski *et al* (25) reinforced these findings, revealing higher BC incidence and mortality rates among postmenopausal women with obesity or metabolic syndrome compared with those without these conditions. The relationship between obesity and premenopausal BC risk appears inconsistent, with some studies suggesting a lower risk in women with a higher BMI, possibly due to hormonal modulation (19,23).

Impact of obesity on BC prognosis and outcomes. Beyond increasing BC incidence, obesity is strongly linked to poorer prognosis in women diagnosed with BC compared with that of non-obese counterparts, affecting disease-free survival (DFS) and overall survival (OS) (21,25-27) (Table SI). Ladoire *et al* (21), in a pooled analysis of two large French randomized trials, reported that obese women (BMI ≥30 kg/m^2) with node-positive BC had worse DFS and OS compared with non-obese patients. This adverse prognostic effect was particularly pronounced in hormone receptor-positive (HoR^+) disease. Analysis of the CALGB 9741 trial by Ligibel *et al* (22) confirmed that a higher BMI was associated with increased recurrence and mortality risks in women with node-positive BC, especially within the luminal A subtype as defined by the PAM50 gene expression assay. Widschwendter *et al* (26), analyzing the SUCCESS A trial focusing on high-risk early BC (EBC), also found that obesity was an independent negative prognostic factor for DFS, OS and distant DFS. Gennari *et al* (27) reported that obese patients with high-risk EBC treated with adjuvant chemotherapy had shorter DFS and OS times compared with normal-weight patients. Biganzoli *et al* (28) observed distinct recurrence dynamics based on baseline BMI, with obese patients showing a persistently elevated recurrence risk over time compared with non-obese patients.

However, the prognostic impact appears to vary by BC subtype. While consistently negative in HoR^+ disease, some studies suggest a potentially less detrimental or even neutral effect in $HER2^+$ BC or TNBC (26,29). Widschwendter *et al* (26) noted that the negative impact of obesity was significant in HoR^+ disease but not in TNBC within their cohort. Studies continue to explore these nuances. Lammers *et al* (29) specifically investigated HoR^+ BC, confirming that a higher BMI was associated with worse prognosis in this HoR^+ patient subgroup (n=3,521; 78% of the study cohort). Furthermore, obesity may influence tumor biology and dissemination; Tzschaschel *et al* (30) found an association between obesity and increased detection of circulating tumor cells in patients with EBC, potentially indicating a mechanism for worse outcomes. Tangalakis *et al* (31) suggested that obesity might not significantly influence the management or outcomes of advanced BC in elderly patients, highlighting the context-dependency of the effects of obesity.

Obesity is generally linked to worse prognosis in HoR^+ BC; however, its impact on TNBC remains debated (32-35). A secondary analysis of the SUCCESS-A trial indicated that BMI ≥30 kg/m^2 did not significantly influence DFS or OS in the TNBC subgroup [n=769; hazard ratio (HR), 1.12; 95% CI, 0.82-1.53] (32). Conversely, metabolomics studies have identified obesity-associated lipid-peroxidation products, particularly 4-hydroxy-2-nonenal (4-HNE), as activators of the nuclear factor erythroid 2-related factor 2 (Nrf2) cytoprotective axis in TNBC cells, promoting doxorubicin and carboplatin resistance (33-35). Integration of these contradictory data suggests that the prognostic neutrality of obesity in early TNBC cohorts may not extend to tumors with high 4-HNE/Nrf2 signaling, a hypothesis requiring prospective validation.

Obesity, treatment response and interventions. Obesity can modulate the efficacy of BC therapies and influence treatment-related side effects (36). Studies in the neoadjuvant and adjuvant settings suggest differential responses based on BMI (35-37). Di Cosimo *et al* (36), in an exploratory analysis of the NeoALTTO trial, observed that obese patients with $HER2^+$ BC had lower rates of pathological complete response following dual HER2-targeted therapy plus chemotherapy compared with normal-weight patients. An analysis of the ALTTO trial by Martel *et al* (37) also indicated that a higher BMI was associated with worse outcomes in patients with $HER2^+$ EBC treated with adjuvant trastuzumab-based therapy, particularly in terms of DFS. Similarly, sub-analysis of the APHINITY trial (pertuzumab and trastuzumab) by Dauccia *et al* (38) revealed that a higher BMI was associated with an increased risk of invasive DFS (IDFS) events in $HER2^+$ EBC, specifically among node-positive patients, consistent with the subgroup analysis of patients with $HER2^-$ early BC with node-positive disease, showing an increased risk of IDFS events with higher BMI.

Weight gain during treatment is another concern. Sedjo *et al* (39) documented significant weight gain among overweight and obese BC survivors prior to enrolling in a weight-loss intervention study. Mutschler *et al* (40) demonstrated that weight gain during adjuvant chemotherapy was an independent negative prognostic factor for DFS in patients with high-risk EBC. Conversely, intentional weight loss may improve outcomes (41,42). Goodwin *et al* (41) conducted the LISA trial, a randomized study showing that a telephone-based weight loss intervention was feasible and effective in reducing weight among postmenopausal women receiving adjuvant letrozole for BC. While LISA was not powered for survival endpoints, it established the principle of intervention feasibility. Babatunde *et al* (42) demonstrated that a dietary and physical activity intervention successfully reduced chronic inflammation markers in obese African-American women, a group at heightened risk of obesity-related BC. The impact of obesity extends to survivorship issues; Inglis *et al* (43) linked excess body weight in BC survivors to increased cancer-related fatigue, systemic inflammation and adverse serum lipid profiles. Furthermore, Kiecolt-Glaser *et al* (44) demonstrated that obesity, alongside chemotherapy, was associated with lower primary vaccine responses (reduced anti-typhoid Vi IgG titers) in BC survivors, underscoring obesity-related immune suppression. Analyses have also explored how obesity might influence specific treatments. Poggio *et al* (45), analyzing the GIM2 trial, reported that the benefit of dose-dense adjuvant chemotherapy on disease-free survival did not differ significantly between obese (BMI ≥30 kg/m^2) and non-obese patients with early BC (P=0.17), indicating no evidence for schedule-specific BMI-dependent efficacy in that cohort. Meanwhile, Biganzoli *et al* (46), examining the SOLE trial, observed that obese patients receiving extended letrozole had a shorter disease-free survival than non-obese patients, indicating BMI-related prognostic divergence during prolonged endocrine therapy. Macis *et al* (47) explored adiponectin as a potential mediator of the obesity-BC risk relationship.

In conclusion, epidemiological evidence robustly establishes obesity as a risk factor for postmenopausal BC development and a negative prognostic factor impacting survival outcomes across various BC subtypes, particularly HoR^+ disease (Table SI). Obesity also influences treatment efficacy, potentially contributing to reduced response rates in neoadjuvant settings and worse survival outcomes in adjuvant settings, while also exacerbating treatment-related toxicities and survivorship issues (41,42). These findings underscore the critical importance of addressing obesity within comprehensive BC prevention and management strategies. Further research is required to fully elucidate subtype-specific effects and optimize weight management interventions to improve BC outcomes (47).

3. Molecular mechanisms linking obesity to BC

Adipose expansion in obesity orchestrates a protumorigenic milieu: Hypertrophic adipocytes release excess leptin and reduced adiponectin, skewing signaling toward Janus kinase 2 (JAK2)/STAT3 and PI3K/AKT/mTOR activation,

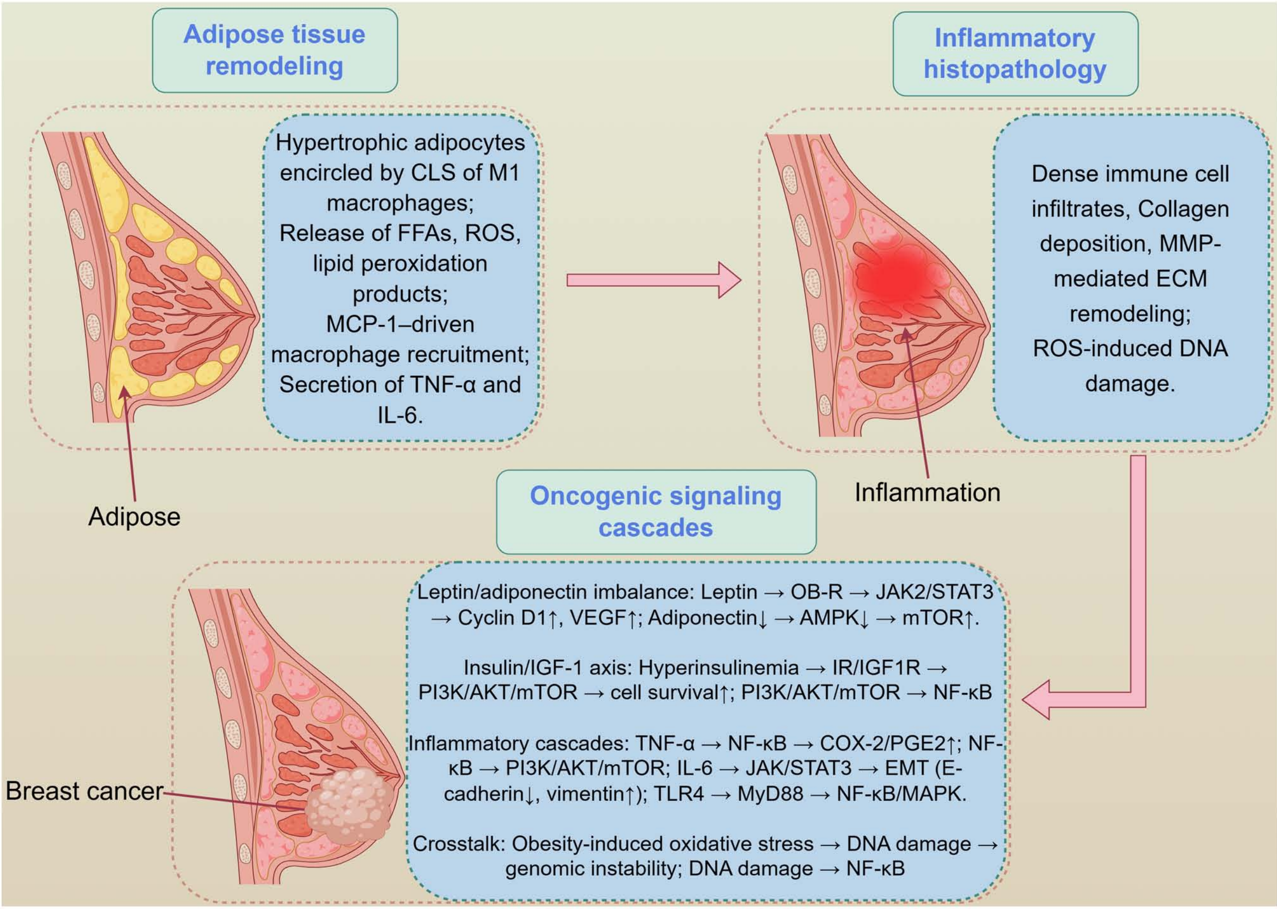

Figure 1. Obesity-induced molecular events and chronic breast inflammation. By Figdraw (https://www.figdraw.com/static/index.html#/; 2.0 version; ID: RSAYO3b3b5). AMPK, AMP-activated protein kinase; CLS, crown-like structures; COX-2, cyclooxygenase-2; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FFA, free fatty acids; IGF-1, insulin-like growth factor-1; IGF1R, IGF-1 receptor; IR, insulin receptor; JAK2, Janus kinase 2; MCP-1, monocyte chemoattractant protein-1; MyD88, myeloid differentiation primary response 88; PGE2, prostaglandin E2; ROS, reactive oxygen species; TLR4, toll-like receptor 4.

while insulin resistance-driven hyperinsulinemia amplifies insulin-like growth factor-1 (IGF-1)-mediated mitogenesis (48-50). Concurrently, dying adipocytes recruit M1 macrophages that form crown-like structures (CLS) and secrete IL-6 and TNF-α, sustaining NF-κB and MAPK loops, which promote DNA damage, epithelial-mesenchymal transition (EMT) and angiogenesis (51,52). These intertwined adipokine, metabolic and inflammatory circuits, including leptin-STAT3, insulin-PI3K/AKT/mTOR and TNF-α/IL-6-driven NF-κB activation, are schematically shown in Fig. 1 (48-52), which illustrates obesity-induced breast tissue inflammation, CLS formation and downstream protumorigenic signaling cascades.

Adipokines and their roles

Leptin. The levels of leptin, predominantly produced by adipose tissue, are elevated in obese individuals (48). Leptin binds to its receptor OB-R, which is expressed in various tissues, including breast tissue (48). The activation of leptin signaling pathways promotes BC development and progression through the JAK-STAT and PI3K-Akt pathways. Specifically, leptin activates JAK2, leading to STAT3 phosphorylation and nuclear translocation, which promotes cell proliferation and angiogenesis (48,49). Leptin also activates the PI3K-Akt pathway, reducing apoptosis and stimulating mTOR-dependent cell proliferation (50).

In breast epithelial cells, insulin receptor substrate 1/2 (IRS-1/2) phosphorylation constitutes a shared regulatory node that integrates leptin-activated JAK2/STAT3 signaling with the insulin resistance-driven PI3K/AKT/mTOR axis (53). Leptin induces JAK2-dependent phosphorylation of IRS-1 on Tyr608 and Ser307, which impairs insulin-receptor signaling and promotes compensatory hyperinsulinemia (53). Conversely, chronic hyperinsulinemia leads to phosphorylation of IRS-1/2 on additional serine residues (Ser612 and Ser636) via mTOR/ribosomal protein S6 kinase B1 feedback loops, further amplifying PI3K/AKT/mTOR activity (54). This bidirectional crosstalk creates a feed-forward circuit in which leptin-driven JAK2/STAT3 signaling exacerbates insulin resistance, and hyperinsulinemia in turn heightens leptin sensitivity, jointly accelerating breast epithelial proliferation (55).

Adiponectin. Adiponectin, another important adipokine secreted by adipose tissue, has antitumor properties (56). Adiponectin binds to its receptors adiponectin receptor (AdipoR)1 and AdipoR2 on the surface of cells, including breast cells, and activates the AMP-activated protein kinase (AMPK) pathway (56). AMPK is an energy-sensing enzyme that regulates cellular metabolism. Activation of AMPK by adiponectin leads to a series of downstream effects that inhibit cell proliferation and promote apoptosis (57). Conversely, gene-expression profiling has revealed increased adiponectin signaling in aggressive Claudin-low and mesenchymal-type BCs, indicating that adiponectin function may be context-dependent rather than adiponectin being universally protective (58). However, adiponectin levels are decreased in obesity, impairing these protective effects and potentially contributing to BC development (59).

Insulin resistance and hyperinsulinemia. Obesity is closely associated with insulin resistance, characterized by reduced cellular responsiveness to insulin (60). This condition is driven by hypertrophic adipose tissue that secretes pro-inflammatory cytokines such as TNF-α and IL-6, thereby promoting chronic inflammation (60). These cytokines interfere with insulin signaling by activating the NF-κB pathway, leading to the expression of suppressor of cytokine signaling proteins that inhibit IRS signaling (61). Additionally, lipotoxicity from excess free fatty acids generates diacylglycerols and ceramides, which activate protein kinase C isoforms and impair insulin receptor (IR) and IRS function through serine phosphorylation (62). Oxidative stress further exacerbates insulin resistance by damaging insulin signaling components (62).

Insulin resistance leads to hyperinsulinemia, which can affect breast cells (63). Insulin binds to IRs on breast cells, activating the PI3K-Akt-mTOR pathway (63). This promotes cell proliferation and survival by stimulating protein and lipid synthesis and inhibiting apoptosis (63). Hyperinsulinemia also enhances the activity of the IGF pathway. Insulin can bind to IGF-1 receptors with lower affinity, but high insulin levels can amplify growth-promoting signals through crosstalk between insulin and IGF pathways (64). These activated pathways synergistically promote cell proliferation, survival and transformation, increasing the BC risk (64).

Inflammatory mediators from adipose tissue. In summary, obesity drives BC development and progression through molecular mechanisms such as adipokine dysregulation (for example, elevated leptin levels and reduced adiponectin levels), insulin resistance and compensatory hyperinsulinemia, and chronic inflammation mediated by cytokines such as IL-6 and TNF-α (19,63). Understanding these mechanisms is crucial for developing targeted prevention and treatment strategies for BC in obese individuals.

TNF-α and IL-6 levels are markedly elevated in obese mammary fat (65,66). TNF-α promotes cell survival via PI3K/Akt-dependent upregulation of Bcl-2 (65) and induces COX-2 transcription (66). IL-6 triggers JAK/STAT3 phosphorylation, driving VEGF secretion and EMT (51). Conversely, local delivery or adipocyte-derived IL-4/IL-13 can polarize macrophages toward an anti-inflammatory M2 phenotype, which downregulates TNF-α and IL-6, and attenuates NF-κB signaling, and thereby limits obesity-driven epithelial proliferation (51,52). The canonical NF-κB and MAPK cascades activated by these cytokines are described in the section on molecular pathways in chronic breast inflammation, where they are examined specifically within the chronically inflamed breast microenvironment.

Role of non-coding RNAs in obesity-related BC. Emerging evidence has highlighted the critical role of non-coding RNAs, particularly long non-coding RNAs (lncRNAs), in mediating obesity-driven breast inflammation and carcinogenesis (67,68). The lncRNA HOX transcript antisense RNA (HOTAIR) is upregulated in breast adipose tissue of obese individuals and promotes tumor progression by recruiting chromatin-modifying complexes that silence tumor suppressor genes (67). In obese mouse models, HOTAIR overexpression is associated with enhanced NF-κB and STAT3 signaling, driving pro-inflammatory cytokine production and macrophage polarization towards an M2 tumor-promoting phenotype (68).

Pre-clinical proof-of-concept studies have indicate that antisense oligonucleotides (ASOs) targeting the obesity-upregulated lncRNA HOTAIR can blunt tumor growth in murine BC models (58,69). Gupta *et al* (69) first demonstrated that HOTAIR recruits polycomb repressive complex 2 to silence metastasis-suppressor loci; when HOTAIR was knocked down with 2'-O-methyl gapmer ASOs (25 mg kg^{-1}; intraperitoneal; twice weekly for 3 weeks), orthotopic 4T1 mammary tumors grew 45% more slowly and exhibited a 60% reduction in pulmonary metastatic foci ($P<0.01$) compared with those of control mice treated with scrambled antisense oligonucleotides. In high-fat diet-induced obese MMTV-PyMT mice, the same regimen decreased mammary tumor multiplicity and lowered IL-6 and TNF-α protein levels in peritumoral adipose tissue, indicating that HOTAIR blockade can simultaneously restrain tumor progression and dampen obesity-driven inflammation (58). RNA sequencing (RNA-seq) of liver and kidney samples collected at necropsy revealed no significant off-target transcriptomic perturbations, and serum chemistry profiles remained within normal limits, suggesting an acceptable acute-toxicity window (32). While these data are confined to rodent systems and lack chronic-dosing or formal immunogenicity analyses, they provide the first direct evidence that pharmacological inhibition of HOTAIR can reverse obesity-promoted mammary tumorigenesis and adipose inflammation, providing a mechanistic rationale for future Good Laboratory Practice toxicology and dose-finding studies (32).

RNA-seq analysis of mammary tissue from ASO-treated obese mice revealed minimal off-target transcriptomic perturbations beyond the intended HOTAIR network, with no significant toxicity in liver or kidney function tests (70). To further assess systemic safety, RNA-seq was also performed on liver and kidney tissues collected at necropsy; these datasets showed no significant off-target gene expression changes compared with scrambled-ASO controls, supporting the specificity of the HOTAIR-targeting approach (70). However, comprehensive organ-specific toxicity studies and assessments of immune activation (for example, complement activation) remain pending, highlighting the need for rigorous safety evaluations before clinical translation (71).

Obesity-mediated tumor immune microenvironment (TIME) remodeling. In addition to myeloid-derived suppressor cell (MDSC) expansion via leptin/IL-6-JAK/STAT3 signaling, obesity directly enforces T-cell exhaustion in breast tissue (72). Single-cell RNA-seq of mammary tumors from high-fat diet-fed MMTV-PyMT mice revealed a 2.3-fold increase in programmed cell death protein 1 (PD-1)$^+$ T-cell immunoglobulin and mucin-domain containing-3$^+$ CD8$^+$ T cells vs. lean controls, accompanied by reduced granzyme-B secretion ($P<0.01$) (72). Analogously, peripheral blood of obese post-menopausal women (BMI ≥35 kg m^{-2}) harbored significantly higher exhausted T cell frequencies (PD-1$^+$ cytotoxic T-lymphocyte associated protein 4$^+$) that were correlated with elevated serum leptin levels ($r=0.62$; $P=0.003$) (73). These findings demonstrate that obesity promotes the expansion of immunosuppressive myeloid cells and concurrently impairs cytotoxic T-cell function, thereby facilitating immune escape during early breast carcinogenesis.

4. Chronic breast inflammation and BC

Obesity-driven CLS formation, macrophage infiltration and sustained TNF-α/IL release establish a protumorigenic breast microenvironment (66,74,75). Histological immune clustering, oxidative DNA damage and extracellular matrix remodeling converge on NF-κB and MAPK activation, accelerating carcinogenesis (as schematically outlined in Fig. 1, which integrates these obesity-driven inflammatory and molecular events into a unified protumorigenic framework).

Definition and characteristics of chronic breast inflammation

Histological features. Chronic breast inflammation is characterized by immune cell infiltrates, including macrophages and lymphocytes, often forming clusters around adipocytes or within the stromal compartments (74). This condition is associated with fibrosis and tissue remodeling, leading to the deposition of extracellular matrix components such as collagen and the activation of fibroblasts. These changes alter breast tissue architecture, with activated fibroblasts depositing extracellular matrix proteins such as collagen, thereby forming fibrotic bands and replacing normal glandular tissue with dense fibrous tissue (76). Proteolytic enzymes such as MMPs are also activated, facilitating cell migration and potentially promoting cancer cell dissemination (77).

Causes of chronic breast inflammation in the context of obesity. Obesity contributes to chronic breast inflammation through several mechanisms. Adipocyte death is a key factor. In obese individuals, the increased size of adipocytes can lead to hypoxia and cell death. The dead adipocytes trigger an inflammatory response, with infiltration of macrophages and the formation of CLS around dead adipocytes (78). These CLS are composed of macrophages encircling a necrotic core of dead adipocytes and are associated with the secretion of pro-inflammatory cytokines (78). Additionally, lipid peroxidation and oxidative stress serve significant roles in amplifying local inflammation and promoting DNA damage within the obese breast tissue microenvironment (66). The excessive accumulation of lipids in obese breast tissue can lead to the generation of ROS and lipid peroxidation products. These oxidative stress-related molecules can damage cellular components, including DNA, proteins and lipids, and activate inflammatory signaling pathways, further exacerbating the inflammatory response in the breast tissue (79).

Molecular pathways in chronic breast inflammation-induced carcinogenesis

NF-κB pathway activation. The NF-κB pathway is a central player in the inflammatory response and is frequently activated in chronic breast inflammation (75). Inflammatory mediators, such as TNF-α and IL-1β, which are produced by immune cells in the inflamed breast tissue, can activate the NF-κB pathway (75). Upon activation, NF-κB translocates to the nucleus and regulates the transcription of numerous genes involved in cell survival, proliferation and inflammation. For example, NF-κB activation leads to the increased expression of anti-apoptotic proteins such as Bcl-2 and Bcl-XL, promoting cell survival. NF-κB activation also upregulates cyclin D1 and other cell cycle-promoting genes, driving cell proliferation (75). Furthermore, NF-κB induces the production of pro-inflammatory cytokines and chemokines, creating a self-sustaining inflammatory loop that contributes to the development of a tumor-promoting microenvironment (75).

MAPK pathway activation. The MAPK pathway is another critical signaling pathway involved in chronic breast inflammation-induced carcinogenesis (80). There are several types of MAPK pathways, including the ERK, JNK and p38 kinase pathways. In chronic breast inflammation, these pathways can be activated by various stimuli, such as growth factors, cytokines and oxidative stress (80). For instance, ERK activation can be triggered by growth factors released from inflammatory cells, leading to the phosphorylation and activation of transcription factors such as Elk-1 and c-Fos, which promote cell proliferation and differentiation (81). JNK and p38 pathways are often activated in response to stress signals, including oxidative stress and inflammatory cytokines. Their activation results in the phosphorylation of transcription factors such as c-Jun and activating transcription factor-2, which regulate the expression of genes involved in cell survival, apoptosis and inflammation (82). The activation of MAPK pathways can lead to changes in breast cell behavior, such as increased proliferation, migration and invasion, which are hallmarks of cancer development (80-82).

Toll-like receptor (TLR) signaling. TLRs are pattern recognition receptors that serve a crucial role in the innate immune response (83). During chronic breast inflammation, TLRs in breast tissue can be activated by various endogenous ligands released from damaged cells or by pathogens (83). For example, TLR4 can be activated by saturated fatty acids, the levels of which are elevated in the breast tissue of obese individuals (83). Once activated, TLRs initiate downstream signaling cascades, such as the MyD88-dependent pathway, leading to the activation of NF-κB and MAPK pathways. This results in the production of pro-inflammatory cytokines and chemokines, amplifying the inflammatory response in the breast tissue (83). The chronic activation of TLR signaling can create a prolonged inflammatory state, which contributes to DNA damage, genomic instability and the promotion of carcinogenesis (84). Additionally, TLR signaling can also influence the TIME by modulating the function and recruitment of immune cells, potentially facilitating tumor immune evasion and progression (85).

In summary, chronic breast inflammation, particularly in the context of obesity, contributes to breast carcinogenesis through various molecular pathways, including the NF-κB, MAPK and TLR signaling pathways. These pathways drive

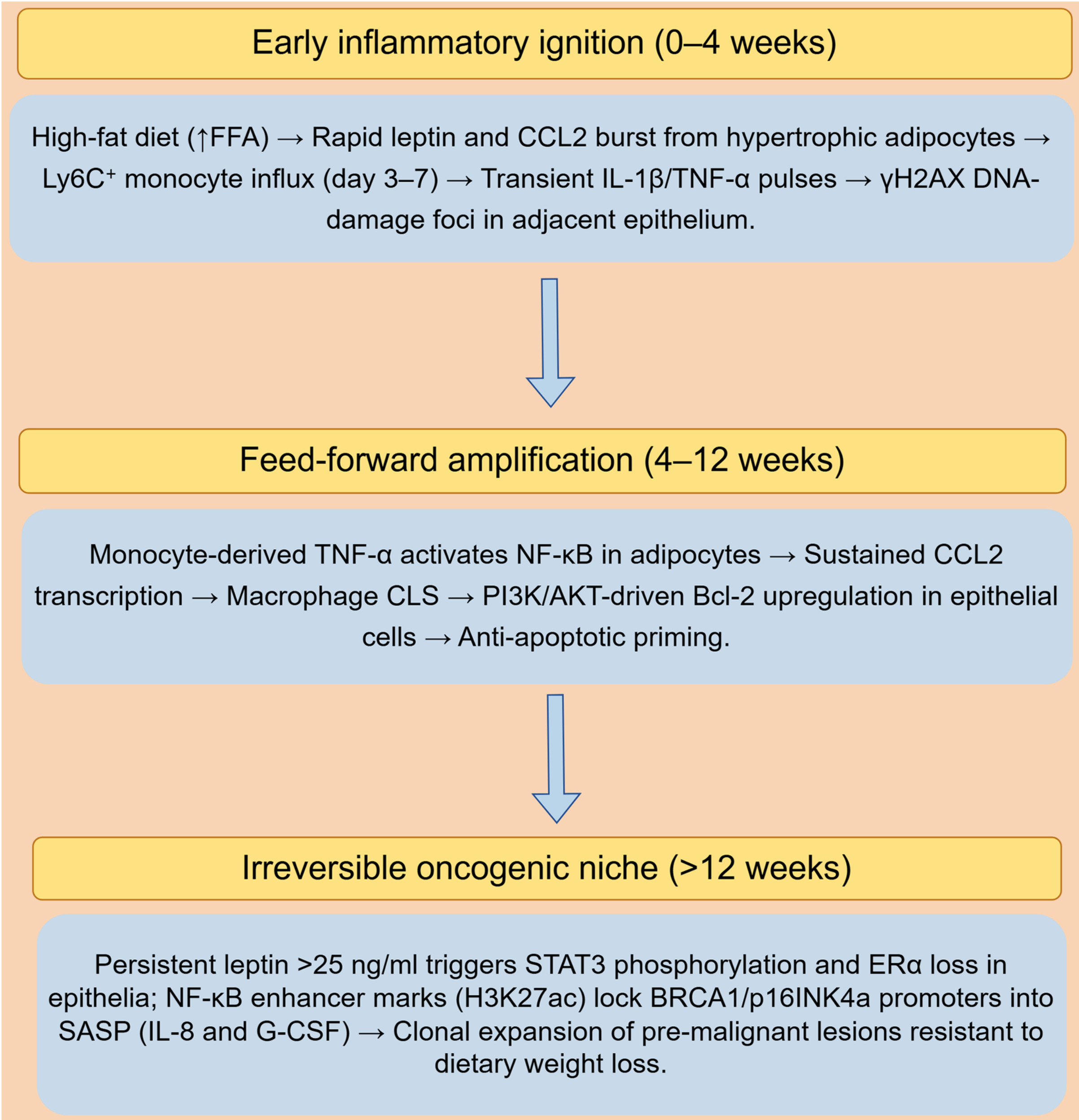

Figure 2. Time-resolved crosstalk in the obese breast microenvironment during early carcinogenesis. By Figdraw (https://www.figdraw.com/static/index.html#/; 2.0 version; ID: UAAWW758ae). The depicted adipocyte-immune interactions and epigenetic reprogramming events are primarily derived from high-fat diet-fed, ovariectomized (postmenopausal) murine mammary tissue models and *ex vivo* explants from obese postmenopausal women. γH2AX, phosphorylated histone H2AX; CCL2, C-C motif chemokine ligand 2; CLS, crown-like structures; ERα, estrogen receptor α; FFA, free fatty acids; G-CSF, granulocyte-colony stimulating factor; H3K27ac, histone H3 lysine 27 acetylation; Ly6C, lymphocyte antigen 6C; SASP, senescence-associated secretory phenotype.

the development of a tumor-promoting microenvironment, characterized by increased cell survival, proliferation and inflammation, thereby increasing the risk of BC. Understanding these mechanisms provides insights into potential therapeutic targets for the prevention and treatment of BC in individuals with chronic breast inflammation.

5. Interplay between obesity-related factors and chronic breast inflammation in carcinogenesis

Dynamic, time-resolved crosstalk among adipocytes, immune cells and epithelia converts obesity-associated inflammation from a reversible stress into an irreversible oncogenic driver (86). This section delineates the sequential ignition, amplification and commitment phases that precede malignant transformation, emphasizing dynamic feed-forward loops, circadian regulation and epigenetic memory. Rather than merely outlining isolated signaling events, it integrates temporal and contextual dynamics to provide a more mechanistic understanding of obesity-driven breast carcinogenesis (Fig. 2). Notably, the time-resolved sequence summarized in Fig. 2 is derived exclusively from ovariectomized (postmenopausal) MMTV-PyMT mice and short-term explants of breast adipose tissue from obese postmenopausal women (23,87,88).

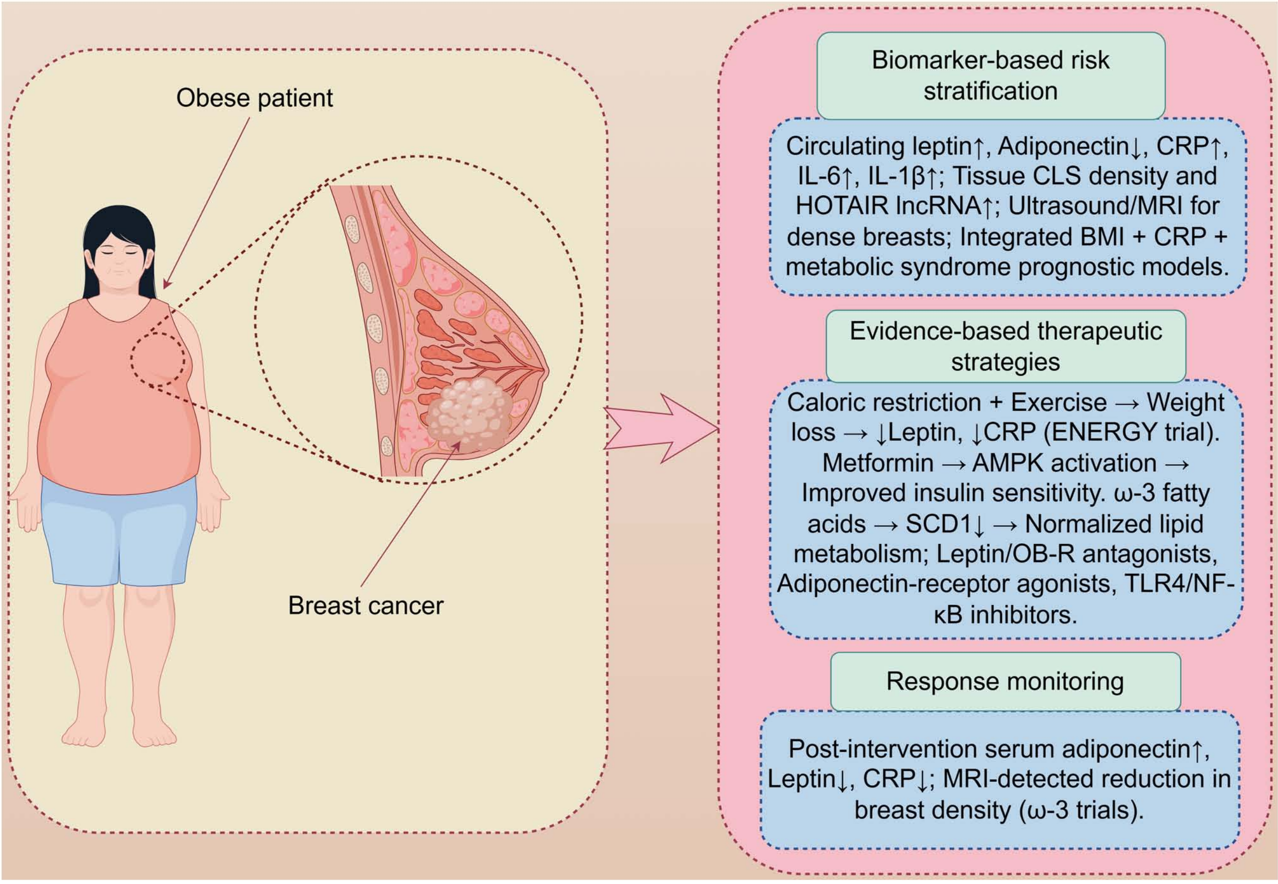

Figure 3. Clinical translation: Risk stratification, intervention and monitoring in obese patients with breast cancer. By Figdraw (https://www.figdraw.com/static/index.html#/; 2.0 version; ID: POWPUb1704). AMPK, AMP-activated protein kinase; CLS, crown-like structures; HOTAIR, HOX transcript antisense RNA; lncRNA, long non-coding RNA; SCD1, stearoyl-CoA desaturase-1; TLR4, toll-like receptor 4.

Early inflammatory ignition (0-4 weeks). High-fat feeding in MMTV-PyMT mice rapidly (within 7 days) elevates mammary C-C motif chemokine ligand 2 (CCL2) and leptin secretion, leading to lymphocyte antigen 6C-positive monocyte influx that precedes CLS formation (87). Single-cell RNA-seq time-courses reveal that these monocytes transiently express IL-1β and TNF-α at day 7, coinciding with phosphorylated histone H2AX DNA-damage foci in adjacent epithelial cells (86). In human breast tissue explants from obese women (BMI ≥30 kg/m^2), a similar early cytokine switch (IL-1β to IL-6) has been observed within 6 days *ex vivo*, supporting the translational relevance (23).

Feed-forward amplification (4-12 weeks). During this amplification phase, NF-κB activation in adipocytes further amplifies CCL2 transcription, establishing a self-sustaining macrophage retention loop (88). Simultaneously, monocyte-derived TNF-α activates NF-κB in adipocytes, further reinforcing this feed-forward inflammatory cycle (88). Concomitant PI3K/AKT signaling in epithelial cells upregulates anti-apoptotic Bcl-2, rendering cells resistant to physiological clearance (65). This feed-forward circuit is unique to the obese state; in lean controls, macrophage numbers plateau after day 7 and do not sustain NF-κB activity (86).

Irreversible oncogenic niche transition (>12 weeks). After chronicity, transient NF-κB pulses are replaced by stable enhancer histone marks (histone H3 lysine 27 acetylation) at BRCA1 and p16^{INK4a} promoters, locking cells into a senescence-associated secretory phenotype that continuously secretes IL-8 and granulocyte-colony stimulating factor (88). Obesity-specific miR-155 elevation persists even upon *in vitro* adipocyte dedifferentiation, indicating a cell-autonomous memory transferable to epithelial cells via exosomal cargo (89). Multiphoton intravital microscopy demonstrates that CD68$^+$ macrophages form periductal niches that expand clonally once circulating leptin exceeds 25 ng ml^{-1}; epithelial cells within these niches exhibit STAT3 phosphorylation and loss of estrogen receptor α expression, changes that do not regress after 8 weeks of dietary weight loss (90), signifying an irreversible commitment to oncogenesis.

6. Clinical implications

Composite models combining elevated leptin, CRP and IL-6 levels, and MRI-detected breast density outperform single-parameter risk prediction (91-93). Lifestyle caloric restriction, metformin-mediated AMPK activation and high-dose ω-3 fatty acids reduce systemic inflammation and tumor-promoting signaling; therapeutic monitoring via serial assessment of these biomarker trajectories can track intervention efficacy and disease progression (Fig. 3). Fig. 3 illustrates an integrated clinical approach for obese patients with BC, encompassing risk stratification using composite biomarkers and imaging, targeted interventions including lifestyle modifications and pharmacotherapy, and continuous monitoring of biomarker dynamics to optimize outcomes (91,94,95).

Diagnosis

Biomarkers for the prediction of BC risk in obese patients with chronic breast inflammation. In obese patients with chronic breast inflammation, several biomarkers show promise in predicting BC risk. Adipokines are a key focus. Leptin, the levels of which are elevated in obesity, is linked to BC risk, and promotes cell proliferation and inhibits apoptosis via pathways such as the JAK-STAT and PI3K-Akt pathways (96). Conversely, adiponectin levels are reduced in obesity, and adiponectin has anti-inflammatory and anti-proliferative effects. Lower adiponectin levels are associated with an increased risk of BC (97).

Inflammatory markers are also crucial. CRP, a marker of systemic inflammation, is positively associated with BC risk in obese postmenopausal women (91). Elevated CRP levels are linked to shorter DFS (91). Similarly, IL-6, IL-1β and TNF-α are upregulated in obese breast tissue. These cytokines induce DNA damage through ROS production and promote a tumor-supportive microenvironment (92).

Imaging techniques for the detection of BC in obese individuals. Obesity poses challenges for traditional mammography. The increased breast density and volume can obscure tumors, reducing the sensitivity of mammography (98). Alternative imaging modalities are being explored (98). Ultrasound is useful for distinguishing between cystic and solid masses. Ultrasound offers real-time imaging and avoids radiation exposure. However, its sensitivity decreases for smaller tumors (99). MRI shows higher sensitivity than traditional mammography in detecting BC in obese patients. MRI provides detailed soft tissue contrast and can identify multiple tumors. Despite its advantages, MRI is costly and may yield false-positive results, requiring further confirmation (93).

Prognosis

Impact of obesity and chronic breast inflammation on BC prognosis. Obesity impacts BC prognosis. Obese patients with BC often have poorer OS rates compared with normal-weight patients. They tend to present with higher tumor grades, larger tumor sizes and increased lymph node involvement (100). Obesity-related inflammation promotes tumor progression and metastasis (101). Additionally, compared with their non-obese counterparts, obese patients are more likely to develop resistance to endocrine therapy and chemotherapy (102).

Molecular mechanisms related to obesity and inflammation influence prognosis. The chronic inflammatory state in obese patients leads to elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α. These cytokines activate signaling pathways that promote cell proliferation, inhibit apoptosis and enhance angiogenesis (52). The dysregulated adipokines leptin and adiponectin also contribute to a poorer prognosis in obese patients compared with their non-obese counterparts by creating a tumor-supportive microenvironment (52). Furthermore, obesity-associated insulin resistance and elevated IGF-1 levels are linked to increased tumor recurrence and mortality (103).

Prognostic models incorporating obesity-related and inflammatory factors. Prognostic models that integrate obesity-related and inflammatory factors are being developed to better predict BC outcomes. These models incorporate clinical data such as BMI, waist circumference and metabolic markers (94). They also include levels of inflammatory cytokines such as CRP, IL-6 and TNF-α. Laforest *et al* (95) have shown that combination of these factors improves the accuracy of prognosis prediction. For instance, a model incorporating BMI and CRP levels, along with components of metabolic syndrome such as waist circumference, hypertension, dyslipidemia and insulin resistance, demonstrated better predictive performance for disease recurrence and survival compared with models using single factors (93). However, validation across diverse patient populations is needed to ensure reliability and applicability. Further research is ongoing to refine these models and enhance their clinical utility (91).

7. Therapeutic strategies for obesity management in BC

The established link between obesity and adverse BC outcomes necessitates evidence-based therapeutic strategies targeting weight management and metabolic dysregulation (104). This section synthesizes clinical evidence on interventions spanning lifestyle modifications, pharmacotherapy and molecularly targeted approaches, emphasizing their mechanistic foundations and clinical applicability (Table SII).

Lifestyle interventions: Cornerstone of weight management. Lifestyle interventions combining dietary modification and physical activity constitute the most extensively studied therapeutic approach. The landmark ENERGY trial demonstrated that a structured 12-month behavioral intervention (caloric restriction + 225 min/week moderate exercise) achieved marked weight reduction (mean loss, 6.0% body weight) in overweight/obese BC survivors, translating to clinically relevant improvements in physical function and quality of life (105,106). Furthermore, this trial established the feasibility of sustained weight management in cancer survivors, a population often challenged by treatment-related fatigue and metabolic alterations. Subsequent research refined these approaches for specific subgroups: Culturally adapted interventions for African American survivors yielded a weight loss of 6.1% vs. 1.8% in controls ($P<0.001$) (107), while telemedicine-based programs effectively addressed barriers for rural populations, maintaining a weight loss of 7.3% at 18 months (108). Exercise regimens require optimization; Courneya *et al* (109) established a dose-response relationship, showing that 300 min/week of aerobic exercise significantly improved quality of life vs. 150 min/week in postmenopausal survivors ($P<0.05$).

Pharmacological and metabolic interventions. Pharmacological strategies target obesity-associated metabolic pathways to enhance treatment efficacy. Yam *et al* (110) conducted a phase II trial combining metformin (500 mg twice daily), everolimus (5 mg/day) and exemestane in obese metastatic HoR^+ patients, demonstrating a 48% clinical benefit rate and median progression-free survival of 5.6 months. This synergistic approach concurrently inhibited mTOR signaling and estrogen synthesis, counteracting obesity-induced pathway activation. Similarly, metformin monotherapy shows promise; Patterson *et al* (111) designed the first randomized controlled trial (RCT) examining metformin + weight loss in survivors, with preliminary data suggesting enhanced insulin sensitivity. Complementarily, nutritional pharmacology leverages specific nutrients to modulate molecular pathways: High-dose ω-3 fatty acids (3.6 g/day) reduced breast density by 6.2% [Sandhu *et al* (112); P=0.03], and improved leptin/adiponectin ratios in high-risk women (113). Mechanistically, Manni *et al* (114) identified ω-3-mediated suppression of stearoyl-CoA desaturase-1 (reduction of 38%; P=0.008), a key enzyme in lipid metabolism promoting tumorigenesis in obesity.

Targeting molecular mediators and biomarkers. Emerging strategies focus on obesity-related molecular mediators as therapeutic targets and response biomarkers. Bowers *et al* (88) demonstrated that caloric restriction reversed obesity-induced pro-tumorigenic genomic signatures in triple-negative models, suppressing tumor growth by 67% (P<0.001) through epigenetic modulation. Clinically, molecular biomarkers facilitate intervention personalization: Macis *et al* (47) established adiponectin as a mediator of 19% of the obesity-BC risk association (P=0.02), suggesting its utility for monitoring intervention efficacy. Concurrently, interventions modulate inflammatory cascades; combined exercise and weight loss in the WISER Survivor trial significantly reduced CRP (-12.3%; P=0.03) and insulin resistance (homeostatic model assessment of insulin resistance reduced by 18.5%; P=0.01) (90,115). Furthermore, recent translational work has revealed that weight loss alters cancer-related proteins: Bull *et al* (116) identified 14 serum proteins (including leptin and IL-6) modulated by weight loss, providing mechanistic insights for BC applications.

Therapeutic strategies for obesity in BC span lifestyle, pharmacological and molecular interventions, collectively targeting metabolic dysregulation, inflammation and tumor-promoting pathways. While lifestyle modifications remain foundational, emerging biomarker-driven approaches enable personalization. Crucially, overcoming implementation barriers requires culturally adapted, accessible programs integrated into standard oncology care. As evidenced by the reversal of obesity-induced genomic alterations reported by Bowers *et al* (88), these strategies hold promise not only for improving outcomes but potentially disrupting the obesity-BC pathogenetic axis.

Emerging evidence suggests that obesity modulates the TIME in TNBC, influencing the response to immune checkpoint inhibitors (ICIs) (72). In obese TNBC models, leptin and IL-6 promote the expansion and recruitment of MDSCs via JAK/STAT3 signaling, which dampens cytotoxic T-cell activity and contributes to immunotherapy resistance (72). For instance, Pingili *et al* (72) demonstrated that diet-induced obesity increased MDSC infiltration and reduced PD-1 inhibitor efficacy in TNBC murine models, an effect reversible upon MDSC depletion or leptin signaling blockade. Clinically, a retrospective analysis has indicated that obese patients with TNBC may exhibit lower objective response rates to anti-PD-1/programmed death-ligand 1 (PD-L1) therapies compared with non-obese counterparts (117), although some studies have reported a paradoxical 'obesity benefit' in other cancer types, underscoring context-dependent effects (72,73). These findings highlight the need to consider obesity-associated immune dysregulation, particularly MDSC-mediated suppression, when designing immunotherapy trials for TNBC.

Limitations of current obesity-targeted therapies in BC management. Despite mechanistic evidence supporting obesity-targeted interventions (88), clinical translation faces significant limitations. First, most lifestyle trials (such as the ENERGY and LISA trials) are underpowered for survival endpoints, with follow-up ≤5 years, precluding definitive conclusions on long-term oncologic benefits (88,105,106). Second, pharmacologic approaches exhibit constrained efficacy: Metformin monotherapy failed to improve IDFS in the National Cancer Institute of Canada (NCIC) MA.32 trial (HR, 1.01; 95% CI, 0.84-1.21; n=3,649), despite preclinical AMPK activation (118). Everolimus-based regimens suffer from dose-limiting toxicities (mucositis, 63% grade ≥3), restricting applicability in obese populations with pre-existing metabolic syndrome (110). Third, biomarker-driven stratification remains rudimentary: While adiponectin mediates 19% of the obesity-BC risk association (47), to the best of our knowledge, no trial has prospectively selected or stratified patient cohorts based on adipokine signatures, leading to heterogeneous responses. Fourth, trials disproportionately enroll postmenopausal HoR^+ patients [≥70% in the ENERGY trial (105)], leaving TNBC and premenopausal obesity-associated BC understudied. Finally, weight-loss interventions exhibit poor durability: 40% of participants in the WISER Survivor trial regained ≥5% body weight within 18 months post-intervention (90), undermining sustained anti-inflammatory effects. These gaps necessitate adaptive trial designs integrating real-time metabolomic profiling and minimal residual disease monitoring to circumvent empirical therapy limitations.

Although lifestyle modification remains the cornerstone, the pooled adherence across four RCTs in BC survivors was only 54% at 12 months and fell to 34% by 36 months (105-108). Pharmacologic approaches face uncertainty regarding long-term safety: The NCIC MA.32 trial showed no excess adverse events with metformin after a median follow-up of 6.3 years (118); however, to the best of our knowledge, liraglutide or tirzepatide have not been prospectively evaluated in BC survivors for durations exceeding 2 years, and their chronic gastrointestinal and pancreatic safety profiles remain undefined. Likewise, dose-limiting mucositis (grade ≥3 rate, 63%) restricted everolimus exposure in the metformin-everolimus-exemestane phase-II study (110), underscoring the need for rigorous toxicity surveillance.

The impact of obesity on immunotherapy response also remains underexplored in clinical trials. While preclinical data implicate MDSCs and adipokine signaling in ICI resistance (117), to the best of our knowledge, no prospective studies have stratified patients with TNBC by obesity status or MDSC levels when evaluating PD-1/PD-L1 inhibitors at present. This represents a significant translational gap, as combinatorial strategies targeting MDSCs or leptin may enhance immunotherapy efficacy in obese patients with TNBC (117).

Bariatric surgery and BC risk. Cohort data provide robust evidence for a protective effect of bariatric surgery against postmenopausal BC, with studies showing a 32-42% reduction in long-term incidence among obese women following surgical weight loss (119,120). In the Swedish Obese Subjects study, 1,116 women who underwent bariatric surgery (mainly vertical-banded gastroplasty or gastric bypass) exhibited a 32% reduction in post-menopausal BC incidence compared with matched non-surgical controls (adjusted HR, 0.68; 95% CI, 0.48-0.96; median follow-up, 21.3 years) (119). Similarly, analysis of the US Kaiser Permanente database (n=22,198) demonstrated a 42% lower BC risk after Roux-en-Y gastric bypass (HR, 0.58; 95% CI, 0.42-0.79) that became apparent 5 years post-procedure and persisted beyond 15 years post-procedure (120). Mechanistically, surgery-induced weight loss rapidly decreases circulating leptin, CRP and IL-6 levels, while restoring adiponectin levels, collectively reversing the obesity-driven chronic inflammatory milieu implicated in mammary carcinogenesis (121).

8. Future directions

Despite significant progress, the molecular mechanisms linking obesity, chronic breast inflammation and carcinogenesis remain unclear. The interplay among signaling pathways, including the NF-κB, MAPK and TLR signaling pathways, is complex and context-dependent (92). For example, further research is needed to elucidate how these pathways synergistically or antagonistically drive cancer initiation and progression in different stages of obesity and inflammation (52,94). Specifically, studies should focus on the temporal dynamics of these pathways and their interactions with adipokines and inflammatory mediators.

The role of novel factors such as exosomes and extracellular vesicles in mediating crosstalk among adipose tissue, immune cells and breast epithelial cells has only recently gained attention (122). Future research should explore the detailed mechanisms by which these vesicles transfer oncogenic signals and modulate the tumor microenvironment (122). For instance, exosomes derived from obese adipose tissue have been shown to promote BC progression by transferring miRNAs and proteins that enhance cell proliferation and migration (122).

Long-term follow-up studies on obese patients with chronic breast inflammation are lacking. Large-scale, longitudinal studies are required to better understand the long-term impact of obesity and chronic inflammation on BC risk and progression (122). These studies should account for ethnic and sex differences, as preliminary evidence suggests variations in obesity-related cancer risk across different populations (123).

Personalized medicine offers a promising avenue for improving outcomes in obese patients at risk of BC. Advances in genomic and proteomic technologies enable the identification of individual molecular profiles related to obesity and chronic inflammation (124). Future research could focus on developing biomarker panels that predict cancer risk and treatment response. By integrating genetic, epigenetic and transcriptomic data, therapies can be tailored to the unique profile of an individual, potentially improving efficacy and reducing adverse effects (91).

The identification of novel therapeutic targets through advanced omics technologies is another frontier. Metabolomics can reveal altered metabolic pathways in obesity and cancer, pointing to potential targets for metabolic modulation (125). Integration of untargeted plasma metabolomics with single-cell RNA-seq now enables obesity subtyping: Simultaneous profiling of serum kynurenine/4-HNE levels and mammary-tissue scRNA-seq delineated an 'inflammatory-proliferative' obese subtype (IL-6^{high} macrophages + leptin^{high} adipocytes), which exhibited a 2.1-fold higher BC risk compared with a 'metabolically quiescent' subtype (AdipoQ^{high}; AMPK-activated) in postmenopausal women (n=34; metabolome-transcriptome correlation r=0.62; P<0.01) (125). Such metabolomics-plus-single-cell strategies refine risk prediction beyond BMI and nominate subtype-specific molecular targets (for example, enzymes in the kynurenine pathway such as indoleamine 2,3-dioxygenase 1) for precision prevention trials in obese cohorts using pharmacological inhibitors (125). Transcriptomics and proteomics can uncover previously unknown signaling nodes or protein interactions that are critical in the inflammatory-carcinogenic process. For example, lncRNAs and circular RNAs, which have been implicated in regulating gene expression in cancer, may serve as diagnostic biomarkers or therapeutic targets (71).

The gut microbiota has emerged as a critical player in systemic inflammation and metabolism (126). In obesity, dysbiosis of the gut microbiota contributes to chronic inflammation and metabolic dysfunction (126). Previous studies have suggested that gut microbial metabolites, including short-chain fatty acids and secondary bile acids, could influence BC risk and progression (127,128). Future research could explore how modulating the gut microbiota through prebiotics, probiotics or fecal microbiota transplantation affects BC outcomes in obese individuals. Specifically, obesity-associated enrichment of deoxycholic acid (DCA), a secondary bile acid generated by bacterial 7α-dehydroxylation, activates the farnesoid X receptor (FXR)/NF-κB axis in breast adipose tissue and increases oxidative DNA damage, thereby accelerating tumor initiation (127). In high-fat diet-fed mice, elevated fecal DCA levels are associated with larger mammary tumor volume and higher incidence of pulmonary metastases, an effect that can be reversed by oral administration of a bile-acid sequestrant or by genetic ablation of the FXR receptor (128). Understanding the molecular mechanisms underlying gut microbiota-breast crosstalk, such as through the production of inflammatory mediators or the modulation of host metabolism, may open up novel avenues for prevention and treatment of obesity-related BC (126,127). To accelerate mechanistic discovery and therapeutic testing, obesity-driven breast carcinogenesis research should incorporate next-generation animal and culture models that faithfully replicate the inflamed obese microenvironment.

Despite robust and accumulating preclinical evidence demonstrating that obesity fuels breast carcinogenesis through chronic inflammation, adipokine dysregulation and immune microenvironment remodeling (13,51,65,72,88), several translational gaps persist that hinder clinical implementation: i) At present, no phase I trial has been registered that specifically depletes or reprograms adipose-tissue macrophages (for example, via colony-stimulating factor 1 receptor or C-C motif chemokine receptor 2 inhibitors) in obese patients with BC, although mouse data show marked tumor growth delay when CLS macrophages are eliminated (79,88); ii) biomarker-adaptive trials that incorporate circulating leptin, adiponectin and MRI-determined breast density as eligibility criteria have not yet been conducted, limiting the ability to achieve precision enrollment in obesity-related BC studies (105,106); iii) long-term oncological endpoints (>5 years) are rarely captured in existing lifestyle or metformin trials, leaving the magnitude of obesity-modifiable recurrence risk uncertain (91); and iv) pharmacokinetic studies evaluating chemotherapy or endocrine-agent dosing in mammary fat volumes >35% of breast mass have not been performed, potentially contributing to under-dosing in obese women (45). Addressing these deficiencies through dedicated early-phase studies will be critical to disrupt the obesity-inflammation-carcinogenesis axis in clinical settings.

9. Conclusion

Obesity fuels breast carcinogenesis via chronic inflammation, metabolic dysfunction and adipokine dysregulation, worsening BC prognosis and treatment response. Metformin, ω-3 and biomarker-driven approaches show promise in mitigating these risks. Future efforts must prioritize large-scale studies, personalized medicine and novel targets (such as the gut microbiota) to disrupt the obesity-BC axis and reduce the global disease burden.

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Authors' contributions

FL and ZG conceived the study and designed its methodology. FL curated the data and prepared the initial manuscript, while both authors jointly investigated and visualized the findings and supervised the project. The manuscript was reviewed and edited collaboratively by FL and ZG, who also serves as the guarantor of the work. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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