Influence of obesity on breast cancer development in relation to menopausal status (Review)

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Abstract. Breast cancer (BC) ranks as the second most prevalent malignant tumor among women globally, posing a significant threat to female health. Obesity is recognized as an independent risk factor for both the development and progression of BC. Nevertheless, due to the complex mechanism through which obesity affects BC, coupled with the considerable variations in hormone levels, metabolic states, and treatment responses between premenopausal and postmenopausal women, epidemiological studies examining the relationship between obesity and BC incidence often produce inconsistent results. Consequently, it is imperative to stratify analyses by menopausal status to elucidate the specific impact of obesity on BC and to inform targeted prevention strategies.

Contents

1. Introduction

Projections by the American Cancer Society indicate that the number of new breast cancer (BC) diagnoses in the United States is expected to exceed 310,000 by 2025, constituting 32% of all new cancer cases (1). Similarly, the 2024 National Cancer Survey Report of China disclosed that in 2022, there were 2.29 million new cancer cases among women, with BC comprising 15.6% of the total, ranking as the second most prevalent malignancy following lung cancer (2). Concurrently, BC mortality remains significantly high, with ~500,000 deaths annually worldwide, posing a substantial threat to women's health (3). In China, both the incidence and mortality rates of BC have shown a consistent increase, rendering it a critical public health concern among women.

The 2024 World Obesity Atlas indicates that in 2020, ~42% of adults globally were categorized as overweight or obese, with projections indicating an increase to 50% by 2030 (4). Overweight and obesity, particularly the latter, have been strongly correlated with a heightened risk of BC and poorer clinical outcomes across various subtypes of the disease (5). Consequently, elucidating the mechanisms by which obesity contributes to BC progression is essential for developing effective prevention and treatment strategies. This research area has been a major focus in BC studies for numerous years (6-8). Clinical research has demonstrated that premenopausal and postmenopausal women exhibit substantial differences in hormone levels, metabolic status, and therapeutic responses, which are reflected in the distinct biology and treatment needs of BC (9,10). The influence of obesity on patients with BC varies considerably with menopausal status. Thus, stratifying studies by menopausal status to investigate obesity's effects on BC, while systematically evaluating discrepancies in obesity diagnostic criteria, will enhance understanding of BC pathogenesis and support the development of optimized clinical treatment strategies.

The present study offers a comprehensive review of recent advancements in understanding the relationship between obesity, menopausal status and BC, drawing on both domestic and international research. Through an analysis of extensive epidemiological and clinical evidence, the correlation and underlying mechanisms by which obesity affects BC initiation, progression and therapeutic outcomes across various menopausal stages, were explored. The current findings provide valuable insights for BC prevention and clinical management.

2. Obesity and BC risk in premenopausal and postmenopausal women

Menopause is a natural physiological process characterized by the permanent cessation of menstruation, typically occurring in women between the ages of 45 and 55, marking the

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end of reproductive capability. Epidemiological studies have consistently demonstrated that postmenopausal women exhibit a significantly higher incidence of BC compared with their premenopausal counterparts, primarily due to factors such as aging and diminished ovarian function. Additionally, risk factors such as obesity exert differential influence on BC development in premenopausal and postmenopausal women.

Postmenopausal. Current evidence consistently indicates a positive correlation between elevated body mass index (BMI) in postmenopausal women and an increased risk of BC, with higher levels of obesity being significantly associated with a greater likelihood of disease development (11). Multiple studies have corroborated this trend, revealing notable disparities that underscore the necessity of underlying modifying factors. In a study focusing on Asian women, Suzuki *et al* (12) found a markedly increased risk of BC (HR=1.90, 95% CI: 1.20-3.01) for every 5-unit rise in BMI among postmenopausal participants. Similarly, Bhaskaran *et al* (13) identified a dose-response relationship in a comprehensive follow-up study involving 5.24 million UK women, where each incremental rise in BMI was linked to an ~5% higher risk of BC. A meta-analysis of prospective studies (14) further illustrated regional differences: The Asia-Pacific region showed the most significant risk increase (31%) with increasing BMI. In comparison, North America and Europe exhibited relatively smaller increments (15 and 8%, respectively). However, Wang *et al* (15) did not find a significant association between general obesity and BC risk in a study of Chinese postmenopausal women, an inconsistency that may be attributed to several interrelated factors.

Ethnic genetic differences are likely to play a crucial role in the relationship between obesity and BC. Asian populations, including Chinese women, often display distinct patterns of adipose tissue distribution (for example, greater visceral fat accumulation at lower BMI thresholds) and unique hormonal profiles compared with Western populations. These differences may influence the metabolic and endocrine pathways that link obesity to BC (16). Additionally, the pattern of hormone replacement therapy (HRT) varies significantly across regions. The lower prevalence of HRT in Asian cohorts, including the study population by Wang *et al* (15), may mitigate the obesity-related risk enhancement, as HRT use is known to interact with adipose estrogen production, a key mediator in the development of postmenopausal BC (17). Third, dietary and lifestyle factors may contribute to these disparities: Traditional Asian diets, which are rich in soy isoflavones (phytoestrogens with potential protective effects) or variations in physical activity levels, could counteract the pro-carcinogenic impacts of obesity in certain populations (18). Finally, the definitions of BMI threshold for obesity may not be universally applicable: The World Health Organization's standard BMI cutoffs ($\geq$25 kg/m^2 for overweight, $\geq$30 kg/m^2 for obesity) may underestimate adiposity-related health risks in Asian populations, where metabolic abnormalities and cancer risk often manifest at lower BMI values, potentially obscuring associations in studies using conventional thresholds, such as Wang *et al* (15) analysis of 'general obesity' (19). Collectively, these factors underscore the complexity of the relationship between obesity and BC in postmenopausal women, emphasizing the need to consider regional and population-specific characteristics to reconcile inconsistent findings.

Premenopausal. The association between premenopausal obesity and BC risk remains a subject of debate, with significant regional differences observed. For instance, Tehard *et al* (20) conducted a longitudinal study involving premenopausal women in France and identified no significant correlation between obesity and BC risk. Conversely, a U.S.-based research of 100,000 premenopausal women (21) indicated that individuals with a BMI >27.5 kg/m^2 exhibited only 75% of the BC risk compared with those with a BMI <20.9 kg/m^2, suggesting an inverse correlation. This finding is supported by a Spanish case-control study (22). However, RicvanDana *et al* (23) found that among Asian populations, both overweight and obesity in premenopausal women were linked to an increased incidence of BC.

3. Mechanisms linking obesity to BC development

Given the varied association between obesity and BC risk across different populations, researchers are increasingly examining the mechanistic underpinnings of this relationship to elucidate its differential effects based on menopausal status.

Cholesterol. Cholesterol in humans is primarily found in two forms: Low-density lipoprotein cholesterol (LDL-C), which accumulates on vascular walls and heightens cardiovascular risk, and high-density lipoprotein cholesterol (HDL-C), which aids cholesterol clearance. Evidence indicates that hypercholesterolemia may increase the risk of BC, potentially through LDL-C-mediated enhancement of tumor cell proliferation and inhibition of apoptosis. Oxidized LDL-C derivatives may activate pro-inflammatory pathways such as NF-κB, thereby expediting tumor progression (24,25). Baek *et al* (26) identified 27-hydroxycholesterol (27HC), a cholesterol metabolite, as the principal mediator of cholesterol's oncogenic effects in BC. Their research demonstrated that 27HC advances tumor progression through dual mechanisms: i) Serving as an estrogen receptor (ER) modulator to stimulate ERα$^+$ tumor growth, and ii) acting as a liver X receptor ligand in bone marrow-derived immune cells to induce immunosuppression. Notably, elevated 27HC levels in obese patients may facilitate the initiation and progression of early-stage breast tumors, thereby increasing BC risk (27).

Insulin. Insulin, a peptide hormone secreted by pancreatic β-cells, plays a crucial role in glucose homeostasis by facilitating cellular glucose uptake and inhibiting hepatic glucose production. In the context of obesity-associated insulin resistance, impaired insulin signaling results in compensatory hyperinsulinemia. Elevated insulin levels, whether as a cause or a consequence of tumor metabolic reprogramming, can activate the insulin receptor (IR) and the downstream PI3K/Akt/mTOR pathway. Mechanistic studies have demonstrated that this signaling axis significantly promotes the proliferation of mammary epithelial cells while inhibiting apoptosis (28-32). Nonetheless, epidemiological studies have yet to determine whether hyperinsulinemia is a precursor to or consequence of BC. Large-scale prospective cohort

studies have identified only modest, non-linear correlations between fasting insulin or C-peptide and the risk of postmenopausal BC (33,34), and Mendelian randomization analyses employing genetic proxies for fasting insulin have produced null findings (35).

By contrast, tumor-derived cytokines (for example, IL-6 and TNF-α) and adipocyte-derived factors can induce systemic insulin resistance, thereby elevating insulin and IGF-1 concentrations following the establishment of malignancy (36,37). Consequently, the insulin-PI3K/Akt/mTOR axis may function bidirectionally: It can be activated by obesity-related insulin resistance. Still, it can also be augmented by the tumor itself once metabolic reprogramming has commenced.

Dalamaga (38) analyzed 760 non-diabetic patients with BC, revealing that 26.4% exhibited insulin resistance. Their study identified a significant correlation between insulin resistance and factors such as obesity, tumor proliferation and Luminal B subtype BC in postmenopausal women. Corroborating these findings, Chen *et al* (39) observed significantly elevated serum levels of IGF-1 and IGF-1R in patients with BC compared with healthy controls. Although recent studies have established associations between dysregulated insulin signaling, including hyperinsulinemia and insulin resistance, and BC pathogenesis (40-42), the precise molecular mechanisms by which elevated insulin levels increase BC risk require further investigation.

Leptin and adiponectin. Leptin, predominantly secreted by white adipocytes, is integral to maintaining metabolic homeostasis through the regulation of appetite mediated by the nervous system under physiological conditions. Circulating leptin levels exhibit a positive correlation with adipose tissue mass. In the context of obesity, persistently elevated leptin concentrations often lead to leptin resistance, thereby impairing its capacity for metabolic regulation (43).

Upon binding to the leptin receptor, leptin activates several oncogenic pathways, including JAK/STAT3, PI3K/Akt and MAPK signaling cascades, which collectively facilitate BC cell proliferation, invasion and angiogenesis (44,45). Emerging evidence indicates that activation of the leptin pathway may advance the progression of triple-negative BC (TNBC) through two principal mechanisms: i) Augmenting cancer stem cell accumulation and ii) Promoting epithelial-mesenchymal transition. Although the precise role of leptin in TNBC pathogenesis remains a subject of debate, current data clearly demonstrate that obesity-associated hyperleptinemia initiates complex interactions among multiple signaling pathways. This interaction ultimately fosters a pro-tumorigenic microenvironment conducive to BC cell proliferation (46).

Adiponectin, an adipokine primarily secreted by subcutaneous adipose tissue, functions as an insulin sensitizer with established anti-inflammatory and anti-atherosclerotic properties. Mechanistically, adiponectin exerts antitumor effects in BC through the activation of the AMPK pathway and inhibition of mTOR signaling, resulting in G1/S phase cell cycle arrest and promotion of apoptosis (47). Adiponectin has been shown to counteract leptin-mediated oncogenesis by inhibiting downstream STAT3 phosphorylation of the leptin receptor and attenuating the production of pro-inflammatory cytokines such as IL-6 and TNF-α (48). Notably, obese individuals exhibit significantly reduced adiponectin secretion, which may facilitate BC progression through the loss of these protective mechanisms (44).

Estrogen and ER. Estrogens, which are steroid hormones including estradiol (E2) and estrone (E1), play a pivotal role as regulators of human physiology by influencing both sexual development and energy metabolism. These hormones are synthesized in various tissues, such as the ovaries, adrenal glands and adipose tissue. The ER, a member of the nuclear receptor superfamily, exists in two primary isoforms: ERα (NR3A1) and ERβ (NR3A2). Notably, ERα is predominantly expressed in mammary epithelial cells, where it facilitates the proliferative and differentiative effects of estrogen.

Upon binding to ERs, estrogens influence breast tissue proliferation and repair through two distinct mechanisms: i) The classical genomic pathway, which involves binding to estrogen response elements and subsequent transcription of target gene (for example, Cyclin D1); and ii) the non-genomic pathway, which mediates rapid activation of kinase cascades, including PI3K/Akt and MAPK signaling. These coordinated pathways regulate cell cycle progression in breast tissue (49). In obese individuals, excess adipose tissue promotes aberrant elevation of estrogen, whose mitogenic effects drive abnormal cellular proliferation. This proliferative stress increases mutational burden and ultimately contributes to breast carcinogenesis (50).

Estrogen plays a significant role in breast carcinogenesis through two distinct yet potentially synergistic pathways: The ER-dependent proliferative signaling and ER-independent genotoxic effects of its metabolites. In the ER-dependent pathway, ligand-bound ERα not only promotes cell proliferation but also directly interferes with the DNA damage response (DDR). For example, estrogen signaling has been shown to downregulate key DDR proteins. It may inhibit the activation of critical kinases such as ATM/ATR, resulting in impaired capacity, genomic instability and malignant transformation (51). In the ER-independent (genotoxic) pathway, the metabolism of estradiol produces reactive catechol estrogens (for example, 4-hydroxyestradiol and 4OHE2), which are oxidized to quinones. These quinones induce DNA damage through two primary mechanisms: i) Direct DNA adduct formation: They covalently bind to DNA bases (mainly guanine), forming depurinating adducts (for example, 4OHE2-N7-Guanine) that can lead to mutagenic apurinic sites (52); ii) oxidative stress: Redox cycling during quinone formation generates reactive oxygen species, resulting in oxidative DNA lesions such as 8-oxo-deoxyguanosine (52). Notably, genome-wide mapping indicates that these metabolites preferentially damage accessible chromatin regions independent of ER-binding sites, representing a direct, receptor-independent genotoxic insult.

Inflammatory factor. In the context of obesity, the enlarged and dysfunctional adipose tissue, particularly within visceral depots, serves as a significant source of pro-inflammatory cytokines, including TNF-α, IL-6 and IL-1β. These cytokines are pivotal in establishing a tumor-promoting microenvironment (53). Beyond their traditional inflammatory functions, these cytokines engage in extensive interactions with estrogen

biosynthesis and signaling, forming synergistic, feed-forward loops that facilitate breast carcinogenesis.

A critical component of this network is the IL-6/estrogen positive feedback loop. IL-6, which exhibits a positive correlation with BMI, not only sustains cancer stemness through JAK/STAT3 signaling but also directly enhances the expression and activity of aromatase in breast adipose tissue, thereby increasing local estrogen synthesis (54). This estrogen-enriched milieu subsequently facilitates the polarization of tumor-associated macrophages towards an IL-6-secreting phenotype, thus establishing a self-perpetuating cycle that supports chronic inflammation and tumor progression. Epidemiological studies corroborate that elevated serum IL-6 serves as an independent predictor of adverse outcomes in patients with BC (55). In a similar vein, TNF-α plays a role in this interconnected network by promoting cancer cell proliferation, invasion and angiogenesis via the NF-κB pathway activation. Moreover, TNF-α can synergize with IL-6 to significantly enhance aromatase activity, thereby amplifying local estrogen production (54). This results in a pathogenic nexus where inflammatory signals and hormone synthesis are co-amplified.

The pro-tumorigenic function of IL-1β further illustrates this integration. It facilitates the progression of hormone receptor-positive BC by inducing COX-2/PGE2 production and suppressing antitumor immunity, while also contributing to the activation of aromatase, thereby directly linking inflammation to the local estrogenic environment. Simultaneously, obesity-associated suppression of anti-inflammatory cytokines such as IL-10 exacerbates immunosuppression, allowing these pro-inflammatory and pro-estrogenic pathways to continue unimpeded.

A comprehensive analysis of the evidence suggests that in postmenopausal obesity, breast carcinogenesis is driven not by isolated cytokines but by a complex inflammatory-hormonal network. This network, exemplified by feed-forward mechanisms such as the IL-6/aromatase/estrogen axis, alters the breast microenvironment into a state of chronic inflammation and estrogen abundance, thereby facilitating tumor initiation, growth and metastasis (56).

Gut microbiota. The gut microbiota, a complex ecosystem within the gastrointestinal tract, plays a crucial role in host metabolism and immune function. In the context of obesity, gut dysbiosis is commonly observed and may contribute to metabolic dysfunction and systemic inflammation. Observational studies have consistently identified associations between altered gut microbial composition and BC, including reduced microbial diversity in affected patients (57). Nevertheless, the causal nature of this relationship remains uncertain. Recent, large-scale Mendelian randomization analyses, a method designed to infer causality, have produced inconsistent findings regarding direct causal links between specific gut microbes and BC risk, suggesting that observed associations may be influenced by confounding factors or reverse causality (58,59). Current evidence indicates that the gut microbiota may affect BC risk indirectly through metabolic and immune pathways, rather than directly initiating tumorigenesis.

Two principal mechanistic hypotheses are proposed: The first is regulation of estrogen metabolism: The gut microbial 'estrobolome' has the capacity to influence the enterohepatic circulation of estrogens. Dysbiosis may modify the prevalence of bacteria that encode β-glucuronidase, an enzyme responsible for deconjugation of estrogen, thereby potentially impacting systemic estrogen levels pertinent to hormone receptor-positive BC (59). The second mechanism consists of modulation of systemic inflammation and immunity: Gut dysbiosis can impair intestinal barrier function, resulting in increased systemic exposure to microbial products and chronic, low-grade inflammation, which is a recognized risk factor for cancer (60). Additionally, the composition of the gut can shape host immune responses. Specific microbial signatures have been associated with immune cell profiles (for example, $CD38^+$ B cells) and may influence the tumor immune microenvironment. Emerging metabolomic studies in patients with TNBC reveal distinct correlations between gut microbes and both systemic and fecal metabolites, underscoring a potential microbiome-metabolite-immune axis in disease progression (61,62).

In summary, although a direct causal relationship between gut microbiome and initiation of BC has not yet been definitely established, it is postulated to act as a modulating factor. Its potential impact is likely mediated through intricate interactions involving host estrogen metabolism, immune regulation and metabolites derived from microbial activity.

4. Divergent mechanisms underlying obesity's influence on BC by menopausal status

Premenopausal vs. postmenopausal. Obesity exerts different effects on BC risk during the menopausal transition, with distinct mechanisms influenced by changes in hormonal sources, adipose tissue distribution and inflammatory profiles. In premenopausal women, obesity may lead to ovulatory dysfunction and chronic anovulation, resulting in progesterone deficiency. This condition may paradoxically reduce estrogen-driven mammary epithelial proliferation, thereby partially mitigating risk (63). In this demographic, the primary risk factors are obesity-related metabolic disturbances (for example, hyperinsulinemia) and systemic inflammation.

The oncogenic effects of obesity become increasingly evident and direct following menopause. The cessation of ovarian function results in a shift of the primary site of estrogen synthesis to adipose tissue, where aromatase facilitates the conversion of androgens to estrone (50). Obesity, particularly the accumulation of visceral fat, exacerbates this process in two distinct ways: By augmenting the substrate mass available for aromatization and fostering a pro-inflammatory microenvironment (for example, elevated TNF-α and IL-6) that further enhances local aromatase activity in the breast, thereby creating a potent, estrogen-rich environment conducive to hormone receptor-positive tumor growth (53). Additionally, obesity is characterized by a state of chronic, low-grade inflammation, predominantly driven by dysfunctional visceral adipose tissue, which independently promotes tumorigenic signaling (53).

In summary, while metabolic dysregulation remains a constant factor, the transition from ovarian to adipose hormone production, coupled with increased visceral fat and persistent inflammation, elucidates the stronger and more consistent association between obesity and BC post-menopause.

Supplementary pathways linking obesity to BC. BMI remains the predominant metric for evaluating obesity in BC research due to its simplicity and cost-effectiveness. However, BMI's reliance solely on height and weight measurements limits its capacity to characterize body fat distribution accurately. This limitation is significant, as distribution and volume of adipose tissue critically influence hormonal secretion patterns, including insulin, leptin, adiponectin and estrogen, which modulate BC pathogenesis. These physiological differences may elucidate the menopausal status-dependent variations in obesity associated BC risk. Compared with BMI, body fat percentage and waist-to-hip ratio provide a more accurate quantification of both the amount and distribution of adipose tissue. These measures more precisely capture obesity-related endocrine dysfunction, particularly alterations in insulin, leptin/adiponectin balance and estrogen metabolism, thereby offering superior insight into obesity's role in BC pathogenesis. Emerging evidence suggests visceral adipose tissue may be the primary mediator of this association (64). The variability in findings from epidemiological studies across diverse populations suggests that BMI may be an overly simplistic measure of obesity, potentially limiting its efficacy in accurately assessing the risk of obesity-related BC (65-67). Currently, research utilizing alternative metrics of adiposity is limited. Future studies and clinical interventions should incorporate comprehensive assessments of both body composition analysis and hormonal profiling as assessment indicators, to develop more precise diagnostic and therapeutic strategies. Multidimensional evaluation could provide valuable epidemiological data to inform BC prevention strategies.

5. Conclusion

The present review synthesizes current epidemiological evidence regarding the differential impacts of obesity on BC risk across menopausal statuses. The molecular mechanisms linking obesity to breast carcinogenesis were systematically examined through hormonal, metabolic, inflammatory and gut microbiota-mediated pathways. The present analysis reveals population-specific epidemiological variations and distinct pathophysiological mechanisms, including: i) Obesity induced hyperestrogenemia, ii) insulin resistance, iii) chronic low-grade inflammation, and iv) leptin/adiponectin dysregulation, each exhibiting menopausal status-dependent effects. For clinical practice, these findings underscore the necessity of menopausal status-specific risk assessment and intervention. In premenopausal women, particularly those with abdominal obesity, strategies may prioritize mitigating hyperinsulinemia and inflammation through combined physical activity and dietary modifications (for example, reducing high-glycemic load foods). For postmenopausal women, addressing hyperestrogenemia through weight reduction, potentially supplemented with metformin for those with insulin resistance, is of critical importance. Future prevention strategies should transition from generic weight-loss recommendations to comprehensive, pathway-specific approaches. This includes: i) Precision Lifestyle Medicine: Tailoring dietary patterns (for example, Mediterranean or time-restricted eating to improve insulin sensitivity) and exercise regimens (combining aerobic and resistance training) based on individual metabolic and inflammatory profiles. A pooled analysis of 31 studies demonstrated that adherence to the Mediterranean diet was significantly associated with a 13% reduction in BC risk. Specifically, a significant 12% risk reduction was observed among postmenopausal women, whereas no significant effect was found in premenopausal women. From a geographical perspective, the protective effect was most evident among Asian populations (68). ii) Pharmacological repurposing: Accumulating research supports the antitumor potential of metformin for reducing BC risk in phenotypes of high adiposity and metabolic syndrome (69,70). iii) Beyond BMI: Incorporating metrics of adipose tissue distribution (for example, waist-to-hip ratio and visceral fat imaging) and quality (for example, circulating leptin/adiponectin ratio) into risk prediction models to identify beneficiaries of targeted interventions more accurately (71-74). Translational research is key to bridging this gap. Current clinical trials examining lifestyle interventions aimed at addressing components of metabolic syndrome in BC survivors (for example, NCT number examples) serve as a model for prevention studies. Future research should prioritize the validation of non-invasive biomarkers (for example, specific adipokine panels and gut microbiota signatures) to stratify risk and assess the efficacy of interventions, ultimately facilitating precision prevention in obesity-associated BC.

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Authors' contributions

ZY wrote the original draft, conducted investigation, formal analysis and data curation, and developed methodology. ZS wrote, reviewed and edited the manuscript, provided resources, acquired funding, conceptualized and supervised the study. Both authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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