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# The Impact of Estrogen Levels on the Development of Breast Cancer in Postmenopausal Women with Diagnosed Obesity or Overweight

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**Abstract**

Breast cancer is one of the most commonly diagnosed malignancies in women. Its development is largely influenced by hormonal factors. Estrogens, as key female sex hormones, play a crucial role in the proliferation of mammary gland cells, which may contribute to the initiation and progression of tumorigenesis. In postmenopausal women, estrogens are primarily derived from the conversion of androgens in adipose tissue, leading to hormonal changes that impact breast cancer risk.

This study aims to examine the influence of estrogen levels on breast cancer development in postmenopausal women with overweight and obesity, as well as to elucidate the underlying biological mechanisms of this association. The molecular actions of estrogens and their effects on estrogen receptor (ER) expression in the context of breast cancer will be discussed. Additionally, the role of obesity as a risk factor for breast cancer in postmenopausal women will be presented.

This article seeks to enhance the understanding of the role of obesity in oncogenesis among women whose physiological estrogen levels should correspond to their age-appropriate hormonal balance.

**Keywords**: breast cancer, estrogens, postmenopausal, estrogen receptors, hormone therapy, aromatase inhibitors, oncogenesis, tumor cell proliferation, estrogen receptor modulators, therapeutic strategies, obesity.

## 1. Introduction:

### 1.1 Background

The mammary gland is a paired organ located in the chest, between the skin, subcutaneous tissue, and the pectoralis major muscle. Its main structural components include glandular tissue, the nipple, and the areola. The glandular tissue consists of lobules separated by connective tissue septa and adipose tissue. Milk ducts emerge from the lobules and open at the apex of the nipple. The functional unit of the breast is the lobule, embedded within the intralobular stroma.

Histologically, the mammary gland comprises luminal (epithelial) cells responsible for milk secretion and surrounding myoepithelial cells that facilitate ductal contraction and assist in milk ejection during lactation. The growth regulation of the breast, epithelial proliferation, and milk production are primarily controlled by sex hormones, including estrogens. Estrogens play a pivotal role in mammary gland development, particularly during puberty, the menstrual cycle, pregnancy, and lactation.

Estrogens are steroid sex hormones synthesized mainly in the ovaries (estradiol - E2) and, to a lesser extent, in the adrenal glands and adipose tissue (estrone - E1). During pregnancy, the placenta becomes a significant source of estrogens, producing estriol (E3). The synthesis of estrogens begins with cholesterol, which is converted into pregnenolone and subsequently into androgens (testosterone and androstenedione). These androgens are then aromatized into estrogens via the enzyme aromatase.

Adipose tissue produces estrogens, primarily in the form of estrone (E1). This process occurs through the aromatization of androgens (androstenedione and testosterone) via aromatase, an enzyme active in adipocytes (fat cells). This mechanism is particularly significant during menopause when ovarian function ceases, and adipose tissue becomes the primary source of estrogens.

**Fluctuations in Estrogen Levels in Various Physiological and Pathological States:**

- **Pregnancy** - Elevated estrogen levels, particularly estriol, contribute to intensive glandular epithelial proliferation and breast preparation for lactation.
- **Menopause** - Decreased estrogen levels lead to involution of glandular tissue, which is progressively replaced by adipose tissue.
- **Hormonal Disorders** - Excess estrogens may be observed in conditions such as polycystic ovary syndrome (PCOS) or hormonally active ovarian tumors, which can promote breast pathologies, including estrogen-dependent cancers.
- **Pharmacotherapy** - Hormone replacement therapy (HRT) used during menopause can influence estrogen levels and may be associated with an increased risk of breast cancer with prolonged use.
- **Obesity** - Excess adipose tissue can lead to increased estrogen production, potentially influencing the development of estrogen-dependent pathologies, including breast cancer.

Both benign and malignant changes can affect any component of breast tissue. Increased estrogen levels may contribute to the development of fibrocystic mastopathy, fibroadenomas, and malignant tumors, underscoring the importance of hormonal balance for breast health and an appropriate adipose tissue level in postmenopausal women.

### 1.2 Objective and Scope:

This dissertation aims to provide a comprehensive analysis of the impact of obesity on the risk of developing estrogen-dependent cancers in women. Specifically, the study focuses on the mechanisms through which excessive adipose tissue mass affects hormonal homeostasis, leading to an increased risk of breast cancer. The issue of breast cancer concerns not only women with elevated ovarian estrogen levels but also patients with excessive adipose tissue accumulation, which serves as an additional source of estrogens synthesized via androgen aromatization.

Excessive estrogen production by adipose tissue represents a significant risk factor comparable to the overproduction of estrogens in pathological conditions such as ovarian cancer, polycystic ovary syndrome (PCOS), and other hormonal disorders. The scope of this study includes analyzing strategies for minimizing risk factors through therapeutic and preventive interventions, including lifestyle modifications and pharmacotherapy. Proper metabolic and hormonal regulation plays a crucial role in breast cancer prevention, highlighting the importance of a healthy lifestyle at every stage of a woman's life. Proper dietary habits and weight control can help maintain hormonal balance and, consequently, reduce the risk of estrogen-dependent cancers.

### 1.3 Dissertation Structure:

To comprehensively address all aspects, this dissertation will first present the pathogenesis and etiology of breast cancer, with particular emphasis on the role of estrogens in tumor development and prognosis (S2). The next section will discuss the aspect of obesity and overweight and their influence on increased breast cancer risk, including biochemical mechanisms occurring in adipose tissue (S3). The subsequent part of the analysis will focus on presenting statistical data, risk groups, and population comparisons between women with normal body weight and those with obesity (S4).

In the following section, laboratory diagnostics and tumor marker testing characteristic of breast cancer will be presented, considering results in overweight women (S5). The conclusion will summarize the most important findings from the analysis and provide recommendations for further research and potential therapeutic interventions (S6).

## 2. The Role of Estrogens in Breast Cancer Development

Breast cancer is one of the most frequently diagnosed malignancies in women. Based on molecular and histological evidence, breast cancer can be classified into three major groups: hormone receptor-positive breast cancer (expressing estrogen receptors [ER+] or progesterone receptors [PR+]), HER2-positive breast cancer (characterized by overexpression of human epidermal growth factor receptor 2), and triple-negative breast cancer (TNBC), which lacks expression of ER, PR, and HER2 and is associated with the worst prognosis.[1] The molecular structure of breast cancer exhibits significant heterogeneity, depending on the presence of various receptor combinations.[2]

Estrogens play a crucial role in regulating mammary epithelial cell proliferation, and their excessive activity, particularly in postmenopausal obesity, may contribute to tumor transformation. Their action occurs primarily through binding to estrogen receptors (ER), which regulate gene expression controlling cell growth, differentiation, and survival.[3] Two main isoforms of estrogen receptors exist: ERα, which promotes tumor cell proliferation, and ERβ, which often acts anti-proliferatively.[4] Upon estrogen (estradiol, E2) binding to ERα, the receptor undergoes a conformational change, dimerizes, and binds to estrogen response elements (ERE) in gene promoters, activating transcription.[5]

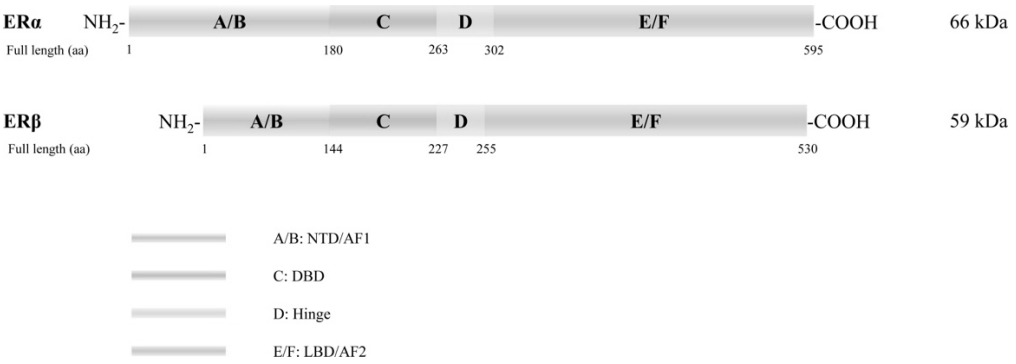


Figure 1. Structure of estrogen receptors (ERs).

Furthermore, estrogens influence cells by activating non-genomic signaling pathways, such as PI3K/AKT, which promotes proliferation and inhibits apoptosis, and MAPK/ERK, which stimulates cell division and tumor migration. Estrogens also enhance the activation of the proto-oncogene c-Myc, intensifying mitogenic signaling.[6] ER activation leads to the induction of proliferation-related genes, including CCND1 (encoding cyclin D1), MYC (enhancing cellular metabolism), and BCL2 (exerting anti-apoptotic effects).[7]

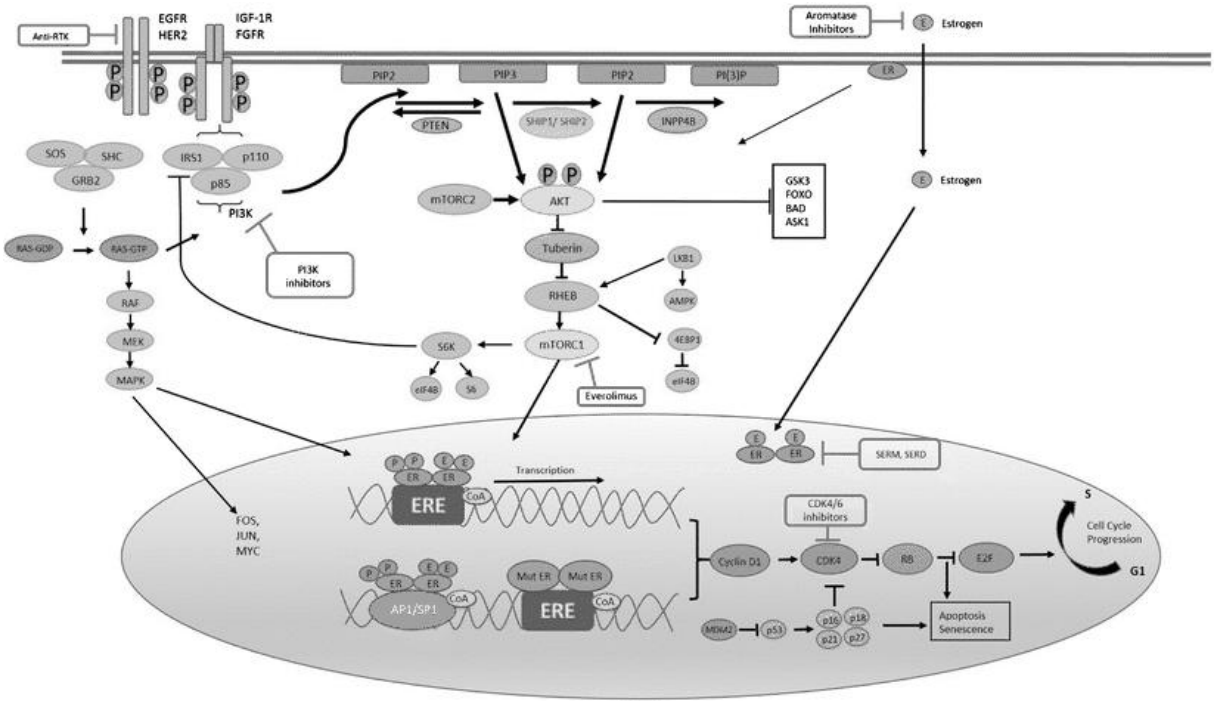


Figure 2. Schematic diagram of estrogen receptor signaling in breast cancer.

Under the influence of estrogens, breast epithelial cells progress more rapidly through the cell cycle, increasing the rate of cell divisions and the risk of mutations. A key regulator of the G1-to-S phase transition is cyclin D1, which activates the CDK4/6 complex. This complex phosphorylates the retinoblastoma protein (pRb), thereby allowing the E2F transcription factor to stimulate the expression of genes essential for DNA replication. [8] Additionally, estrogens suppress the expression of cell cycle inhibitors such as p21 and p27, further accelerating cellular proliferation. [9] High estrogen levels also enhance the activity of topoisomerase II, facilitating DNA replication but simultaneously increasing the likelihood of replication errors and mutations. Another critical mechanism involves the downregulation of the **BRCA1** gene, resulting in impaired DNA repair and increased genomic instability, thereby elevating the risk of malignant transformation. [10]

Estrogens not only stimulate proliferation but also contribute to genomic instability, promoting the accumulation of mutations that favor tumorigenesis. The metabolism of estrogens within cells leads to the production of reactive oxygen species (ROS), including **4-hydroxyestradiol (4-OH-E2),** which induces DNA damage, such as double-strand breaks, and DNA base adduct formation. [11] Excessive ROS production in cancer cells results in oxidative stress and the accumulation of mutations, thereby facilitating cancer progression. Furthermore, estrogens can impact genomic stability through epigenetic modifications, such as **hyperactivation of histone acetyltransferase (HAT),** leading to chromatin relaxation and

increased expression of proliferative genes. Additionally, BRCA1 promoter methylation results in its silencing, thereby impairing the cell's ability to repair DNA. [12]

The prognosis of breast cancer depends on multiple factors, including the stage of disease at diagnosis, the histological type of the tumor, the presence of hormonal receptors (ER, PR), HER2 status, the number of affected lymph nodes, and the overall health status of the patient. [13] Early detection of breast cancer, particularly in the preinvasive stage (DCIS, LCIS) or stage I, is associated with high 5-year survival rates, reaching 98-100%. As the disease progresses and its stage advances, the prognosis worsens; in stage III, the 5-year survival rate ranges from 66% to 98%, whereas in stage IV, with distant metastases, it declines to 22-25%. [14]

## 3. Molecular Mechanisms Linking Obesity, Overweight, and Estrogen Levels to the Pathogenesis and Progression of Breast Cancer

In the context of breast tumors, excess adipose tissue leads to increased estrogen production, chronic low-grade inflammation, insulin resistance, and metabolic disturbances that promote tumorigenic transformation. [15] Adipose tissue, functioning as an active endocrine organ, produces the enzyme aromatase, which converts androgens (androstenedione and testosterone) into estrogens (estrone and estradiol). [16] After menopause, when the ovaries cease estrogen production, adipose tissue becomes the primary source of these hormones, resulting in chronic hyperestrogenemia. [17] Elevated estrogen levels stimulate the proliferation of breast epithelial cells through the activation of estrogen receptors (ERα), thereby increasing the risk of mutations and tumorigenic transformation. Additionally, obese women exhibit lower levels of sex hormone-binding globulin (SHBG), which increases the bioavailability of free estrogens, enhancing their impact on breast glandular tissue. [18]

Obesity is also frequently associated with insulin resistance and hyperinsulinemia, both of which significantly influence breast cancer development. Elevated insulin levels act as mitogenic factors by activating insulin receptors (IR) and insulin-like growth factor-1 receptors (IGF-1R), which subsequently trigger the PI3K/AKT and MAPK/ERK signaling pathways, promoting cancer cell proliferation and inhibiting apoptosis. [19] Excess insulin also reduces SHBG levels, further increasing the concentration of bioavailable estrogens in the bloodstream. [20] Additionally, high insulin levels regulate cyclin D1 expression, a key regulator of the G1-to-S phase transition, thereby accelerating the cell cycle and increasing the risk of replication errors, facilitating the accumulation of oncogenic mutations. [21]

Another key mechanism linking obesity to breast cancer is chronic low-grade inflammation, a hallmark of excessive adipose tissue. Adipocytes and infiltrating macrophages in adipose tissue secrete numerous proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β). These cytokines activate the NF-κB pathway, which upregulates the expression of genes associated with proliferation and survival of cancer cells. Elevated TNF-α levels may also suppress the expression of DNA repair genes, such as BRCA1, leading to genomic instability and tumor progression. [22] In the context of obesity, leptin, an adipokine produced by adipose tissue, plays a crucial role by exerting mitogenic effects, increasing breast epithelial cell proliferation, and stimulating angiogenesis via upregulation of vascular endothelial growth factor (VEGF). Leptin also activates the PI3K/AKT and JAK/STAT pathways, further promoting cancer cell survival. In contrast, adiponectin, another key adipokine, exhibits tumor-suppressive properties by inhibiting the proliferation and migration of breast cancer cells. [23] However, in obesity, adiponectin levels are significantly reduced, thereby eliminating its protective effect and facilitating cancer development. [24]

Obesity also contributes to genetic instability by increasing the production of reactive oxygen species (ROS), which damage DNA and induce mutations that favor carcinogenesis. Elevated estrogen levels in obese postmenopausal women further enhance ROS production through the metabolism of estrogens into genotoxic derivatives, such as 4-hydroxyestradiol (4-OH-E2), which induce DNA double-strand breaks. [25] Moreover, obesity is associated with epigenetic modifications affecting gene expression related to tumorigenesis, including BRCA1 promoter hypermethylation, leading to its silencing and impaired DNA repair capacity. Reduced BRCA1 activity compromises the homologous recombination repair mechanism, increasing the accumulation of mutations that drive oncogenesis. [26]

Obese women are more frequently diagnosed with breast cancer at a more advanced clinical stage, which is attributed both to diagnostic challenges (as excessive adipose tissue can obscure malignant lesions in imaging studies) and to the more rapid progression of the disease. In patients with a high BMI, there is a higher prevalence of tumor subtypes associated with a poorer prognosis, including triple-negative breast cancer (TNBC) and HER2-positive breast cancer. [27] Elevated levels of leptin and insulin in obese women contribute to the activation of the PI3K/AKT and JAK/STAT pathways, which enhance the survival and invasiveness of cancer cells. Additionally, chronic inflammation and increased levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), exacerbate angiogenesis and metastasis, leading to an increased risk of tumor dissemination to lymph nodes and distant organs. [28]

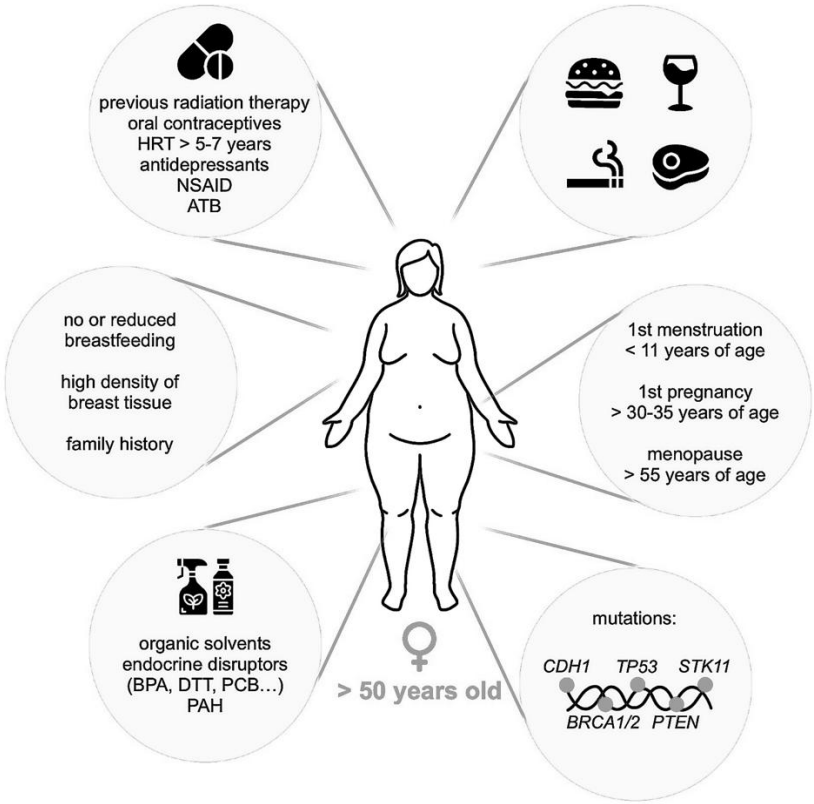


Figure 3. Risk factors of breast cancer

Obesity also affects the efficacy of anticancer treatment. In the case of hormone therapy used in patients with hormone receptor-positive breast cancer (ER+/PR+), high estrogen levels in obese women may weaken the effects of drugs such as tamoxifen and aromatase inhibitors (letrozole, anastrozole). Studies indicate that in obese women, treatment with aromatase inhibitors may be less effective because excessive estrogen production in adipose tissue surpasses the capacity of these drugs to inhibit aromatase.[29] Moreover, insulin resistance and hyperinsulinemia may reduce cancer cell sensitivity to chemotherapy by activating pro-proliferative and anti-apoptotic pathways.

Obese patients tend to have a poorer tolerance to chemotherapy and radiotherapy, which may be due to a higher incidence of complications such as cardiotoxicity, thromboembolism, and increased susceptibility to infections.[30] Additionally, alterations in drug pharmacokinetics in individuals with a high BMI may lead to subtherapeutic drug concentrations or an increased risk of adverse effects. The impact of obesity on the metabolism of cytotoxic drugs may result in poorer treatment responses and a shorter progression-free survival time.[31]

In terms of survival, numerous studies show that women with breast cancer and obesity have a higher risk of disease recurrence and lower overall survival compared to patients with a normal body weight.[32] Obesity is a particularly unfavorable prognostic factor in ER+/PR+ tumors, where high estrogen levels may stimulate cancer cells to continue growing despite hormone therapy.[33] In triple-negative breast cancer (TNBC), which lacks hormone receptor

and HER2 expression, chronic inflammation and insulin resistance may contribute to a more aggressive tumor phenotype and an increased tendency for metastasis.[34]

## 4. Incidence of Postmenopausal Breast Cancer in Women with Obesity or Overweight Compared to Women with Normal BMI

Numerous epidemiological studies indicate that obesity is a significant risk factor for the development of breast cancer in postmenopausal women. According to research conducted by the Women's Health Initiative (WHI), women with a BMI exceeding 30 kg/m² have a 30% to 50% higher risk of developing breast cancer compared to women with a normal body weight. Data analysis from the Nurses' Health Study showed that each unit increase in BMI above 25 kg/m² is associated with a 2% increase in breast cancer risk, and in the group of women with a BMI >35 kg/m², this risk rises by up to 60% compared to women with a BMI <25 kg/m².[35]

The mechanism of this phenomenon is primarily related to excessive estrogen production in adipose tissue. After menopause, the ovaries cease synthesizing estrogens, and their primary source becomes the conversion of androgens to estrogens by the enzyme aromatase, present in adipocytes. In obese women, this process is intensified, leading to chronic hyperestrogenemia, which promotes the proliferation of breast cancer cells. Furthermore, studies indicate that in postmenopausal women, estrone and estradiol levels are 30%–70% higher in the obese group compared to women with normal body weight, which may lead to increased expression of estrogen (ER) and progesterone (PR) receptors, thereby elevating the risk of hormone-dependent cancers.

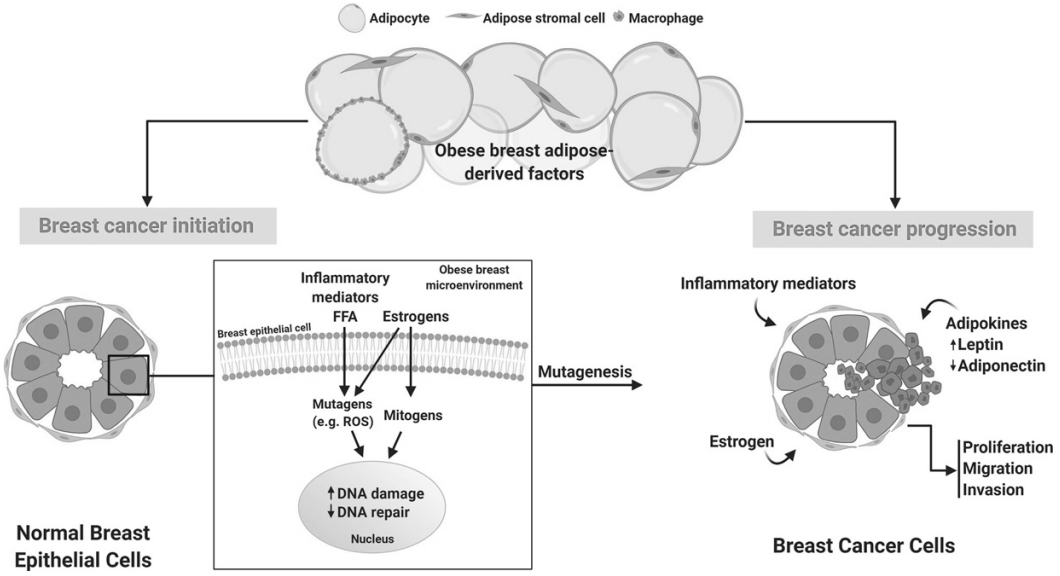


Figure 4. Obese breast adipose-derived factors contribute to the initiation and progression of breast cancer.

Regarding breast cancer subtypes, obesity exerts a particularly strong effect on ER+/PR+ tumors, which rely on estrogenic activity for growth and progression. Analyses conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC) Study demonstrated that obese women had a 40% higher risk of developing ER+ breast cancer compared to women with BMI below 25 kg/m². For triple-negative breast cancer (TNBC), which lacks ER, PR, and HER2 expression, the association between obesity and cancer risk is less conclusive. However, some studies suggest that visceral obesity, which is linked to insulin resistance and chronic inflammation, may be associated with an increased risk of TNBC.

In terms of cancer subtypes, obesity has a particularly strong impact on ER+/PR+ tumors, which are dependent on estrogen activity. Analyses conducted as part of the European Prospective Investigation into Cancer and Nutrition (EPIC) study revealed that obese women had a 40% higher risk of developing ER+ tumors compared to women with a BMI below 25 kg/m². In the case of triple-negative breast cancer (TNBC), which lacks ER, PR, and HER2 expression, the effect of obesity on disease risk is less clear, although some studies suggest an increased risk associated with visceral obesity, which is linked to insulin resistance and chronic inflammation.

Population-based comparisons confirm that women with normal body weight have a significantly lower risk of breast cancer than obese women, particularly in the presence of coexisting metabolic disorders such as insulin resistance, type 2 diabetes, or metabolic syndrome. According to data from the Women's Health Initiative study, women with a BMI over 35 kg/m² and concurrent insulin resistance had nearly twice the risk of breast cancer compared to women with normal body weight and normal glucose metabolism.[36] Moreover, a meta-analysis of 82 studies conducted by the Collaborative Group on Hormonal Factors in Breast Cancer found that each additional BMI unit above 25 kg/m² increases the risk of breast cancer by approximately 3%, with this increase being particularly evident in postmenopausal women.[37]

These findings indicate that obesity is a significant risk factor for postmenopausal breast cancer, especially in ER+/PR+ tumors, emphasizing the need for preventive measures such as weight management, physical activity, and metabolic parameter monitoring in overweight and obese women.

## 5. Analysis of Laboratory Results for Selected Indicators in the Context of Breast Cancer in Overweight Women and Women with Normal Body Weight

Accurate diagnostics play a crucial role in assessing breast cancer risk and selecting appropriate treatment strategies, particularly in postmenopausal women, where hormonal and metabolic changes significantly influence disease development. Biomarkers, including estrogen levels, metabolic markers, and cancer-specific indicators, provide valuable insights into cancer progression mechanisms and potential therapeutic approaches.

### 5.1 Estrogens

Estrogen levels in postmenopausal women are primarily assessed through blood tests measuring estradiol (E2), estrone (E1), and sex hormone-binding globulin (SHBG). These parameters help determine estrogenic activity, especially in obese and non-obese women, who may exhibit significant hormonal differences.

| Biomarker | Mean Levels in Obese Women | Mean Levels in Nonobese Women |
|---|---|---|
| **Estradiol (E2) (pg/mL)** | 20.6 (95% CI: 17.2-24.7) | 12.2 (95% CI: 10.1-14.8) |
| **Estrone (E1) (pg/mL)** | 85.1 ± 28.2 | 94.3 ± 39.2 |
| **SHBG (nmol/L)** | 44,40 (95% CI: 32,36-60,92) | 88,83 (95% CI: 65,39-120,68) |

Research consistently demonstrates that obese postmenopausal women exhibit higher serum estradiol (E2) concentrations compared to their nonobese counterparts. A study reported that the mean estradiol level in obese women was 20.6 pg/mL (95% CI: 17.2-24.7), whereas in nonobese women, the mean level was 12.2 pg/mL (95% CI: 10.1-14.8). The elevated estradiol levels in obese women may contribute to an increased risk of estrogen-dependent pathologies, including breast and endometrial carcinomas [38].

Similarly, estrone (E1) concentrations tend to be higher in obese women, as adipose tissue serves as a primary site for the aromatization of androgens into estrogens. In overweight and obese women, the mean estrone level was reported to be 85.1 ± 28.2 pg/mL, while in women of normal weight, the mean level was 94.3 ± 39.2 pg/mL [39]. This shift in estrogen metabolism in obese postmenopausal women is particularly important, as estrone becomes the predominant estrogen in this population.

SHBG levels also exhibit inverse correlation with body weight in postmenopausal women. Studies indicate that overweight and obese women have significantly lower SHBG concentrations compared to nonobese individuals. The mean SHBG level in obese women was 44,40 nmol/L (95% CI: 32,36-60,92), in overweight women: 76,90 nmol/L (95% CI: 55,21-107,10) while in women with normal weight, it was significantly higher, reaching 88,83 nmol/L (95% CI: 65,39-120,68) [40]. The reduction in SHBG is attributed to the suppressive effects of insulin, which is frequently elevated in obese individuals due to insulin resistance.

Lower SHBG levels lead to an increased fraction of bioavailable estrogens, which can enhance estrogenic stimulation of breast tissue. This heightened estrogenic activity is associated with a greater risk of hormone-dependent malignancies, such as breast and endometrial cancers [41]. Given the significant hormonal alterations observed in obese postmenopausal women, further investigation into the metabolic and oncogenic consequences of these changes is warranted.

## 5.2 Insulin, Glucose, and Lipid Profile

Metabolic markers, such as insulin, glucose, and lipid profile (lipidogram), provide additional information about breast cancer risk, particularly among obese women, who frequently exhibit metabolic disorders.

| Biomarker | Postmenopausal Women with Obesity | Postmenopausal Women without Obesity |
|---|---|---|
| **BMI ($kg/m^2$)** | 38,6 ± 5,4 | 24,5 ± 2,1 |
| **Fasting Glucose (mmol/L)** | 5,2 ± 1,1 | 3,9-5,5 [43] |
| **Fasting Insulin (µIU/mL)** | 15,8 ± 7,6 | 2,54-13,30 [44] |
| **Total Cholesterol (mmol/L)** | 5,3 ± 1,1 | < 5,2 [45] |
| **LDL Cholesterol (mmol/L)** | 3,2 ± 0,9 | < 2,6 [45] |
| **Triglicerides (mmol/L)** | 2,08 ± 2,3 | < 1,7 [45] |
| **HDL Cholesterol (mmol/L)** | 1,3 ± 0,3 | >1,3 [45] |

The study included 62 women (88.6% of the study population) who presented to the Obesity Treatment Clinic at the Metabolic Diseases Department between 2001 and 2004. Anthropometric assessment was conducted, including body weight, waist and hip circumference, and blood pressure measurements, along with biochemical analysis, which included lipid profile, fasting glucose, and fasting insulin levels.

Among the study participants, the mean body mass index (BMI) was 38.6 ± 5.4 $kg/m^2$, with a mean age of 57.0 ± 13.7 years. The mean fasting glucose concentration was 5.2 ± 1.1 mmol/L, while the mean fasting insulin level was 15.8 ± 7.6 µIU/mL, indicating significant disturbances in carbohydrate metabolism. Analysis of the lipid profile revealed a mean total cholesterol level of 5.3 ± 1.1 mmol/L, LDL cholesterol of 3.2 ± 0.9 mmol/L, triglycerides of 2.08 ± 2.3 mmol/L, and HDL cholesterol of 1.3 ± 0.3 mmol/L, suggesting dyslipidemia characteristic of metabolic syndrome in obese postmenopausal women.[42] Obesity in postmenopausal women is associated with significant metabolic dysregulation, which may contribute to an increased risk of breast cancer. Compared to nonobese women [43, 44, 45], those with obesity exhibit higher insulin levels and greater insulin resistance, which promote

cell proliferation and survival through the activation of mitogenic pathways such as PI3K/AKT and MAPK/ERK. Chronic hyperglycemia further exacerbates cancer risk by inducing oxidative stress, inflammation, and increased insulin-like growth factor-1 (IGF-1), all of which support tumor growth and progression.

Additionally, dyslipidemia is more prevalent in obese postmenopausal women, characterized by higher LDL cholesterol and triglycerides and lower HDL cholesterol. This unfavorable lipid profile contributes to chronic inflammation and oxidative stress, creating a pro-carcinogenic microenvironment. Moreover, obesity leads to increased aromatization of androgens to estrogens in adipose tissue, resulting in elevated estrone (E1) and estradiol (E2) levels, which are strongly linked to estrogen receptor-positive (ER+) breast cancer. Together, these metabolic disturbances: hyperinsulinemia, chronic inflammation, dyslipidemia, and estrogen excess, form a tumor-promoting environment, increasing the likelihood of breast cancer development in obese postmenopausal women.

### 5.3 Tumor and Hormonal Biomarkers - Estrogen Receptors (ER):

Obesity in postmenopausal women has been strongly associated with an increased prevalence of estrogen receptor-positive (ER+) breast cancer, primarily due to elevated estrogen levels resulting from the aromatization of androgens in adipose tissue. In obese women, estrone levels are approximately 35% higher, and estradiol levels can be up to 130% higher compared to non-obese counterparts. Moreover, the bioavailable fractions of estradiol and testosterone are 2 to 3 times greater in overweight and obese women, further enhancing estrogen-driven tumor proliferation. Epidemiological studies indicate that postmenopausal obese women who have never undergone hormone replacement therapy (HRT) have a 1.7 to 2.3 times higher risk of developing ER+ ductal carcinoma compared to non-obese women [46]. This correlation is particularly significant, as estrogen-dependent signaling plays a pivotal role in tumor initiation and progression. Aging is another contributing factor to the increased prevalence of ER+ breast cancer. With advancing age, ovarian estrogen production declines, making adipose tissue the primary source of circulating estrogens. In obese elderly women, increased adiposity enhances estrogen biosynthesis, promoting the growth of ER+ breast tumors. Additionally, obesity-related metabolic changes contribute to a pro-tumorigenic microenvironment. Elevated leptin and interleukin-6 (IL-6) levels, which are markedly increased in obese individuals, correlate with larger tumor size and increased lymph node metastases, particularly in ER+ breast cancer patients. These inflammatory mediators are known to activate signaling pathways that support tumor growth and progression.

### 5.4 Leptin and Adiponectin:

Leptin, which is elevated in obesity, stimulates tumor growth, increases angiogenesis, and promotes cancer cell proliferation through activation of JAK/STAT and PI3K/AKT pathways. Adiponectin, which has anti-tumor properties, is significantly lower in obese individuals, reducing its protective effects against cancer.

Research indicates that this population exhibits elevated leptin levels and decreased adiponectin concentrations. While these hormonal alterations have been primarily linked to endometrial cancer, similar mechanisms may contribute to the pathogenesis of breast cancer.

Leptin, a hormone produced by adipocytes, correlates with adipose tissue mass, with its levels increasing proportionally to the degree of obesity. Elevated leptin concentrations have been shown to promote tumor cell proliferation and angiogenesis, facilitating carcinogenic processes and potentially increasing breast cancer risk. Furthermore, leptin interacts with signaling pathways involved in tumor progression, including estrogen receptor activation, which may further exacerbate oncogenic processes [47, 48].

Conversely, adiponectin, a hormone with anti-inflammatory properties that enhances insulin sensitivity, demonstrates an inverse relationship with body mass, its levels are significantly reduced in obese individuals. Adiponectin deficiency contributes to chronic low-grade inflammation and insulin resistance, both of which are implicated in tumorigenesis. Additionally, adiponectin exerts antiproliferative and proapoptotic effects, and its reduced levels may impair cellular growth regulation, thereby increasing susceptibility to malignancies, including breast cancer. A high leptin-to-adiponectin ratio has been identified as a strong predictor of increased breast cancer risk in postmenopausal women, particularly those with obesity. Studies suggest that this imbalance creates a pro-inflammatory environment conducive to tumor progression.

### 5.5 Conclusion from the Statistical Data Analysis:

Postmenopausal women with obesity exhibit a distinct biochemical profile, including elevated estrogen levels, reduced SHBG, hyperinsulinemia, and dyslipidemia, all of which contribute to an increased risk of breast cancer. The higher prevalence of ER+ tumors among obese women highlights the importance of estrogen-driven carcinogenesis in this group. Additionally, altered adipokine levels, particularly increased leptin and reduced adiponectin, create a tumor-promoting metabolic environment. Given these findings, monitoring hormonal, metabolic, and adipokine-related biomarkers in postmenopausal women (especially those with obesity) may provide valuable insights into breast cancer risk stratification and guide preventive interventions.

## 6. Conclusions from the conducted analyses:

The analysis of the relationship between estrogen levels, obesity, and breast cancer risk in postmenopausal women provides strong evidence that excess adipose tissue significantly contributes to the development and progression of estrogen-dependent breast cancer. Several mechanisms have been identified through which obesity influences breast cancer risk, including increased estrogen production, insulin resistance, chronic inflammation, and altered adipokine levels. Given the rising global prevalence of obesity, integrating effective screening, prevention, and therapeutic strategies into clinical practice is essential to mitigate this risk.

Postmenopausal women with obesity experience hormonal and metabolic imbalances, including elevated estradiol (E2) and estrone (E1) levels due to increased aromatization of androgens in adipose tissue. Lower levels of SHBG (sex hormone-binding globulin) in these individuals further increase the bioavailability of free estrogens, thereby intensifying estrogenic stimulation of breast epithelial cells. Additionally, hyperinsulinemia and insulin resistance

contribute to breast cancer progression by activating mitogenic pathways such as PI3K/AKT and MAPK/ERK, which promote uncontrolled cell proliferation and inhibit apoptosis. Women with obesity are at a higher risk of developing ER+/PR+ tumors, with prevalence rates of 75-85% compared to 60-70% in non-obese women. Moreover, chronic low-grade inflammation and altered adipokine levels - characterized by increased leptin and decreased adiponectin - further contribute to a tumor-promoting environment.

To reduce breast cancer risk in postmenopausal women with obesity, targeted screening, lifestyle modifications, and pharmacological interventions should be prioritized. Regular laboratory and imaging diagnostics are necessary to identify high-risk individuals and monitor metabolic and hormonal imbalances. Essential hormonal assessments include estradiol (E2), estrone (E1), SHBG, and estrogen (ER) and progesterone (PR) receptor status, particularly in patients with suspected hormone-dependent malignancies. Metabolic and inflammatory markers, such as fasting insulin, glucose levels, lipid profile (total cholesterol, LDL, HDL, triglycerides), leptin, adiponectin, and inflammatory cytokines (TNF-α, IL-6, C-reactive protein [CRP]), should also be monitored. Imaging techniques such as annual mammography and breast ultrasound remain crucial for breast cancer screening, with MRI recommended for high-risk patients. Additionally, DEXA scanning should be considered to assess bone density, particularly in obese postmenopausal women undergoing hormonal therapies.

Given the complexity of obesity-driven breast carcinogenesis, multidisciplinary medical care is essential. Endocrinologists should assess hormonal dysfunction, insulin resistance, and metabolic imbalances, particularly in women with coexisting diabetes or polycystic ovary syndrome (PCOS). Oncologists should be consulted for risk stratification and tumor surveillance in patients with abnormal imaging findings or elevated estrogen levels. Women receiving hormone replacement therapy (HRT) should be closely monitored by gynecologists, who can evaluate the risks and benefits of continued treatment in the context of breast cancer risk. Nutritionists and dietitians should provide personalized dietary interventions focused on weight reduction, insulin sensitivity improvement, and anti-inflammatory nutrition strategies. Furthermore, a specialized obesity management program involving bariatric specialists should be considered for patients with severe obesity (BMI >35 $kg/m^2$) and metabolic syndrome, as weight loss interventions, including pharmacological therapy or bariatric surgery, have been shown to significantly reduce estrogen levels and breast cancer risk. Exercise specialists and physical therapists should design individualized physical activity programs, as regular exercise not only reduces body fat but also modulates inflammation and insulin resistance, key factors in obesity-related breast cancer pathogenesis.

Future research should focus on improving our understanding of obesity-driven breast carcinogenesis and developing effective therapeutic interventions. Investigating precision medicine approaches, such as identifying genetic and epigenetic markers that predispose obese women to aggressive tumor phenotypes, may improve early detection and treatment strategies. Clinical trials evaluating the impact of weight loss, metformin therapy (for insulin resistance), and aromatase inhibitors (for obesity-induced estrogen excess) in postmenopausal women are warranted. Additionally, exploring novel anti-inflammatory agents or adipokine-targeted therapies to modulate leptin and adiponectin levels may offer new avenues for breast cancer prevention. Longitudinal studies assessing the long-term impact of lifestyle interventions,

including diet and exercise, on breast cancer incidence and recurrence rates, should also be conducted.

The strong association between obesity, estrogen levels, and breast cancer risk in postmenopausal women underscores the urgent need for integrated prevention and intervention strategies. Given the increasing prevalence of obesity worldwide, monitoring hormonal, metabolic, and adipokine-related biomarkers should be a routine part of clinical care for postmenopausal women, especially those with excess body weight. Preventive strategies such as weight management, metabolic control, and lifestyle interventions should be prioritized. Future research should focus on personalized risk assessment models and obesity-targeted therapies to enhance breast cancer prevention and improve patient outcomes.

## 7. List of Figures

Figure 1. Chen Peng , Li Bo , Ou-Yang Ling, Role of estrogen receptors in health and disease, Frontiers in Endocrinology, 2022, DOI=10.3389/fendo.2022.839005, ISSN=1664-2392

Figure 2. Oza, Aabha & Ma, Cynthia. (2017). New Insights in Estrogen Receptor (ER) Biology and Implications for Treatment. Current Breast Cancer Reports. 9. 10.1007/s12609-017-0231-1.

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