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The Risk of Breast Cancer in Obese Individuals, the Role of Leptin: A Review

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Abstract:
Obesity, a growing global issue, has been closely associated with an increased risk of various cancers, especially breast cancer. Elevated leptin levels, a hormone produced by fat cells, are commonly seen in obese individuals and play a pivotal role in regulating energy balance and metabolism. However, high leptin concentrations contribute to tumor growth, metastasis, and resistance to chemotherapy in breast cancer. This review delves into the intricate relationship between leptin and breast cancer, shedding light on how leptin fosters cancer progression in obese individuals by influencing inflammation, immune responses, and critical cell survival pathways. Obese breast cancer patients tend to experience poorer prognoses, greater chemotherapy resistance, and higher recurrence rates, which make the management of obesity a vital factor in breast cancer prevention and treatment. Given leptin's involvement in cancer development and progression, further research into its role could lead to innovative therapeutic strategies aimed at targeting leptin signalling, thereby improving outcomes for obese breast cancer patients. In the long term, addressing obesity as part of cancer management could significantly reduce the global burden of breast cancer, benefiting both patient health and healthcare systems worldwide.

Keywords: Breast cancer, Tumor progression, Leptin signalling, Prognosis

Introduction:

The metabolic syndrome, which is defined by a number of conditions like high blood pressure, raised blood sugar, abnormal lipid levels, and abdominal obesity, has been linked to a number of negative health consequences, including the advancement of cancer. There is new evidence that it contributes to a worse prognosis for breast cancer. According to a 2025 meta-analysis by Harborg et al., showed individuals with metabolic syndrome had an 83% higher chance of dying from breast cancer and a 22% higher risk of disease recurrence, based on 18 studies with over 36,000 patients. The necessity of integrating metabolic health evaluation and intervention into standard breast cancer treatment and monitoring is highlighted by these findings. (Harborg *et al.,* 2025) The burden of non-communicable diseases (NCDs) is greatly increased by the global increase in obesity, which has emerged as a serious public health concern. Obesity is a major contributing factor to the development of these illnesses, which cause around 74% of deaths globally. More than 70% of NCDs are associated with obesity, according to their 2025 review, highlighting the urgent need for focused preventative initiatives.

As per survey it has been stated by 2035, obesity may overtake all other avoidable risk factors for NCDs if current trends continue. Effective public health measures must be put into place in order to stop obesity's increasing influence on international health systems. (Staffan *et al.*, 2025) Adipose tissue is the

primary source of the hormone leptin, which is essential for controlling hunger and energy balance. In addition to its metabolic roles, leptin plays a role in immunological modulation and hormone regulation, among other physiological processes. Elevated leptin levels in obesity are linked to a chronic inflammatory state, which is known to be a characteristic of cancer. By attaching itself to its receptor (LEPR), leptin activates a number of carcinogenic pathways, including PI3K/AKT, MAPK, and JAK/STAT. Leptin also affects the immune response by increasing T-cell fatigue and encouraging pro-inflammatory polarization. Although the underlying mechanisms are still unclear and are impacted by variables such as menopausal status and immunological response, obesity-related hyperleptinemia has been associated with an increased risk of developing breast cancer. To address the relationship between obesity and breast cancer, focused therapy approaches must take into account the function of leptin. (Roberto *et al.*, 2022)

1. Prevalence among Individuals:

As the second most common cause of cancer-related deaths among women in the United States, breast cancer continues to pose a serious public health concern. As per 2024 breast cancer statistics report emphasizes notable racial and ethnic differences in outcomes as well as a persistent increase in incidence, especially among women under 50. Although survival rates have increased due to improvements in early detection and treatment, the growing disease load need new preventative techniques and focused therapies. With implications for clinical practice and public health, this study looks at the most recent trends in breast cancer incidence, death, and disparities. (Angela *et al.*, 2024) Previously the most common cancer in the 1990s, cervical cancer has been surpassed by breast cancer as the most common cancer among Indian women. Between 1990 and 2016, there was a 39.1% increase in the age-standardized incidence rate, with significant increases in each state.

Inadequate healthcare infrastructure, delayed diagnosis, and restricted access to cutting-edge treatment facilities are some of the causes of this increase. Even though multimodal treatment and early detection strategies have showed potential, issues including unequal access to healthcare and the COVID-19 pandemic's effects on service delivery still exist. (Ravi *et al.*, 2022) By 2040, it is anticipated that the number of Indian people who are overweight and obese will have increased significantly, with overweight more than doubling and obesity almost quadrupling for both sexes. These patterns highlight the pressing need for age- and region-specific preventative efforts to slow the rise in weight-related health disorders, pointing to an expanding public health challenge. (Shammi *et al.*, 2022)

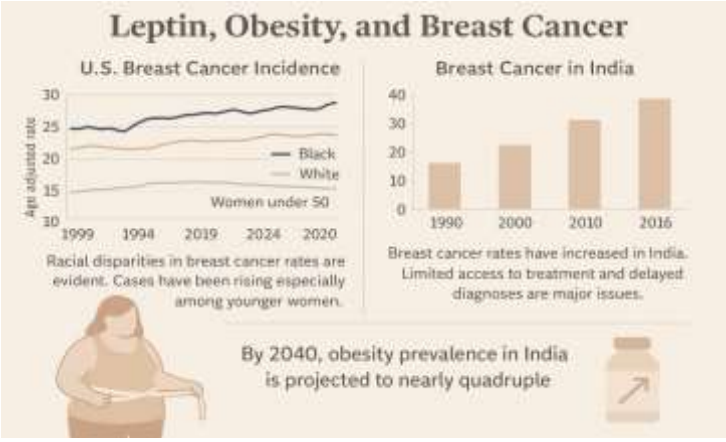

Fig 1 Representing Prevalence worldwide

2. Obesity and Breast Cancer Risk:

As a major public health concern, obesity is now universally acknowledged to be a significant risk factor for the development of a number of malignancies, including those of the breast, colon, endometrial, liver, and oesophagus. The fundamental processes that lead to the development and spread of cancer include increased oxidative stress, chronic inflammation, and changes in hormone levels like insulin and leptin. Developing successful preventative and management methods requires an understanding of the connection between obesity and cancer. (Nikolaos *et al.*, 2023) The onset and spread of breast cancer are greatly accelerated by obesity, particularly in postmenopausal women. Hormonal imbalances, insulin resistance, chronic low-grade inflammation, and changes in adipokine levels, including leptin and adiponectin, are important physiologic factors. These elements lessen the efficiency of treatment and encourage tumor growth. (Atilla *et al.*, 2024)

2.1 Contributing Factors to Obesity:

The distribution of fat is tightly related to the health hazards associated with obesity; visceral adipose tissue, not subcutaneous fat, is highly linked to obesity-related comorbidities such cardiovascular disease, type-2 diabetes, non-alcoholic fatty liver disease, and some types of cancer. According to recent studies, the development of disease is influenced by adipokine imbalances, immune system modifications, disruption of the balance between white and brown fat, and genetic and epigenetic changes. (Xiang *et al.*, 2023)

2.1.1 Visceral Adipose Tissue: The body's distribution of fat is very important. Obesity-related comorbidities including type-2 diabetes, heart disease, and some types of cancer are closely linked to visceral fat, or fat that is stored around internal organs.

2.1.2 Genetic and Epigenetic Factors: The emergence of obesity and its problems are influenced by both genetic and epigenetic changes. These elements may have an effect on energy metabolism, appetite control, and fat accumulation.

2.1.3 Adipokine deregulation: Obesity can cause deregulation of adipokines, which are signalling chemicals discharged by fat cells. Metabolic problems and inflammation are exacerbated by this imbalance.

2.1.4 Immune System Alterations: Low-grade chronic inflammation linked to obesity involves the activation of immune cells in adipose tissue. This inflammation is a major factor in the pathophysiology of disorders linked to obesity.

2.1.5 Disproportion between White and Brown Adipose Tissue: White and brown fat are out of balance in obesity. Because obese people have less active brown adipose tissue, which aids in calorie burning, excess fat builds up.

2.1.6 Gut Microbial Dysbiosis: Obesity and metabolic disorders have been connected to disturbances in the gut microbiome. Food digestion and fat storage may be impacted by changes in gut flora.

3. Leptin, a Hormone:

The hormone leptin, which is generated by fat cells and the small intestine, controls energy balance by reducing appetite and encouraging the breakdown of fat. Through its effects on brain receptors, especially the hypothalamus, it regulates metabolism and hunger. Reduced satiety and increased food intake might result from leptin resistance in obesity. Leptin regulates appetite, but it also affects the

immune system, lactation, bone density, and reproduction. Additionally, it influences insulin sensitivity and glucose metabolism. (Hany *et al.*, 2021)

3.1: Structure of Leptin: The protein hormone leptin is made up of a single 167 amino acid polypeptide chain in humans, which is compact and globular in shape and held together by disulfide connections. Its helix-turn-helix pattern and portions that are both hydrophobic and hydrophilic allow it to work in many bodily settings. Glycosylation also occurs in leptin, influencing its stability and capacity to bind to receptors. To control hunger, energy expenditure, and metabolism, the hormone binds to particular leptin receptors, mostly in the hypothalamus. (Amrita *et al.*, 2021)

3.2: Role of Leptin:

Leptin regulates hunger, food intake, and metabolism, all of which are important aspects of the body's energy balance. Mostly secreted by fat cells, it helps to curb appetite and avoid overeating by acting on the brain's hypothalamus to communicate satiety, or a sensation of fullness. Beyond hunger management, leptin affects immunological responses, bone metabolism, glucose homeostasis, body weight regulation, and reproductive function. (Kallash *et al.*, 2025)

3.2.1: Balance of Appetite and Energy: Fat cells create leptin, which instructs the brain to reduce appetite and encourage fullness. This aids in maintaining energy balance and controlling food consumption.

3.2.1: Weight and Metabolism: Its ability to increase fat burning and decrease fat storage makes it a vital component of long-term body weight regulation. Leptin also promotes thermogenesis and energy expenditure.

3.2.3: Fertility and Reproduction: Sufficient energy reserves for reproduction are indicated by adequate leptin levels. Menstrual cycles and fertility can be affected by low leptin, particularly in malnourished people.

3.2.4: Bone and Immune Health: Leptin promotes inflammation and the activity of immune cells. Additionally, it affects bone density and development, which strengthens the skeleton.

3.2.5: Regulation of Insulin and Glucose: Leptin lowers the risk of type 2 diabetes by enhancing insulin sensitivity and assisting in the maintenance of normal blood sugar levels.

4. Leptin Levels in Obesity:

As the main source of leptin production, adipose tissue is found in greater quantities in obese people, which results in generally much higher leptin levels. Normally, when fat stores are adequate, the hormone leptin tells the brain, specifically the hypothalamus, to decrease appetite and increase energy expenditure. Leptin resistance, on the other hand, is a situation in which the body frequently becomes resistant to the effects of leptin due to obesity. The brain does not recognize the signal to stop eating, even when there is a high concentration of leptin in the blood. This results in overeating, chronic hunger, and on-going fat storage. The typical feedback loop between the brain and adipose tissue is broken by this compromised transmission, which reduces the hormone's ability to control body weight. Although the precise processes underlying leptin resistance are still being investigated, they may include chronic inflammation, changes in receptor signalling, or deficiencies in leptin trafficking across the blood-brain barrier. Because of this, elevated leptin levels in obese people do not cause the anticipated decrease in food intake or rise in energy expenditure, which helps to maintain and exacerbate their obesity. (Milan *et al.*, 2021)

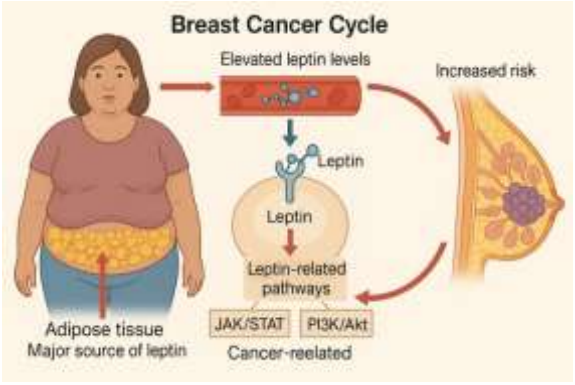

Fig 2 Representing Leptin Prognosis

4.1: Leptin Resistance: The complicated and multidimensional process of leptin resistance in obesity occurs when the body does not react to elevated leptin levels as it should, even though leptin plays a crucial role in controlling hunger, energy expenditure, and fat accumulation. When fat levels are enough, the body's energy resources are communicated to the brain by the hormone leptin, which is mostly produced by adipose tissue. This causes the body to decrease appetite and increase energy expenditure. High amounts of leptin, however, do not cause these reactions in obese people, which results in more overeating and fat storage. One of the main causes of leptin resistance is a decrease in leptin's capacity to pass the blood-brain barrier and reach the hypothalamus, where it has an effect. Furthermore, obesity may cause the brain's leptin receptors to become desensitized or down regulated, which would impair neurons' ability to react to leptin signals. Leptin function is further hampered by disruptions in important signalling networks, including those involving the JAK-STAT pathway and mTOR (mechanistic target of rapamycin).

It has been discovered that increased mTOR activity, particularly in certain neurons such as POMC (pro-opiomelanocortin) neurons, is essential for causing leptin resistance by obstructing the appetite-suppressing effects of leptin. Obesity frequently results in chronic low-grade inflammation, which makes the issue worse by encouraging the release of cytokines that disrupt leptin signalling, such as TNF-α and IL-6. The persistence and advancement of obesity, as well as the development of associated metabolic illnesses including insulin resistance and type-2 diabetes, are caused by leptin resistance, which also leads to prolonged hunger, decreased energy expenditure, and an inability to remove fat mass. In order to restore leptin sensitivity and enhance weight management, treatment therapies may target the cellular and molecular pathways underlying leptin resistance. (Bowen *et al.*, 2025)

5. Leptin in Cancer Pathogenesis:

Through its receptor, ObR, leptin activates several pathways that promote cancer, which aids in the growth of tumours'. It stimulates the signalling cascades of JAK/STAT, PI3K/AKT, and MAPK/ERK, which promote the proliferation, survival, and migration of cancer cells. By boosting VEGF synthesis, leptin also encourages the development of new blood vessels, guaranteeing the tumour gets enough oxygen and nutrients. By encouraging the epithelial–mesenchyme transition (EMT), it makes cancer cells more invasive. It also modifies the tumour microenvironment by inducing inflammation and directing supporting and immune cells to encourage tumour growth. Leptin also increases estragon activity in hormone-dependent malignancies, which accelerates tumour growth, and helps cancer cells avoid programmed cell death by increasing anti-apoptotic proteins.(Agnes *et al.*, 2023) Adipokine leptin,

which is linked to obesity, influences several malignant processes and is essential to the development of cancer. It is expressed in adipose tissue as well as in different cancer cells and tumour microenvironments, where it stimulates angiogenesis, metastasis, cell division, and chemotherapy resistance. (Tsung et al., 2021)

As obesity turns adipose tissue into an active endocrine organ, leptin levels increase, which has a variety of effects on tumour biology. By increasing inflammation, triggering the insulin/IGF-1 axis, and promoting the proliferation, survival, and migration of cancer cells, leptin not only controls metabolism, hunger, and reproduction, but also aids in the development of cancer. By promoting communication between tumour cells and adipocytes, it contributes to an environment that is conducive to tumour growth. (Amanda *et al.,* 2023) For many hormonally driven malignancies, obesity is a major risk factor that increases incidence and has a negative impact on prognosis. The estimated cancer burden will increase in tandem with obesity rates, underscoring the necessity of efficient intervention techniques. Diet, exercise, and bariatric surgery are lifestyle-based strategies that have been shown to mitigate the cancer-promoting effects of obesity.(Maria *et al.,* 2021)

6. Breast cancer pathogenesis:

Obesity contributes to breast cancer development through multiple interconnected mechanisms. It promotes insulin resistance and increases blood glucose levels, which can activate the mTOR signalling pathway involved in cell growth and proliferation. Additionally, obesity leads to higher estrogen levels due to increased aromatase activity in adipose tissue, a key factor in the progression of estrogen-receptor-positive breast cancers. Macrophages in obese individuals also release elevated levels of reactive oxygen species (ROS), which can induce oxidative stress and damage cellular components, further supporting tumour growth. These changes create a biological environment that favours breast cancer initiation and progression, making obesity a significant modifiable risk factor. (Ira *et al.,* 2023) Obesity is associated with an increased risk of cancer-related death and has a role in the onset and spread of cancer. Obesity causes cancer through a variety of intricate processes, including metabolic deregulation, chronic inflammation, and hormone abnormalities.

To achieve significant weight loss, bariatric surgery and pharmaceutical treatments may be recommended in some circumstances, especially for obese cancer survivors.(Sukanya *et al.,* 2023) Breast cancer is a complicated and diverse disease that is impacted by intra-tumoral microbiome, tumour stemness, and circadian rhythm abnormalities. Improvements in detection and treatment planning have been made possible by advances in diagnostic technology, particularly those that use artificial intelligence. The creation of treatments based on unique risk profiles and molecular subtypes has resulted from the increased emphasis on precision medicine, highlighting the significance of individualized strategies for improved patient outcomes and long-term care. (Xin *et al.*, 2025)

7. Leptin Receptors in Breast Cancer:

An investigation of the association between breast cancer in obese women and the leptin receptor (LEPR) Q223R gene polymorphism was carried out. PCR-RFLP was used for genotyping, and immunoassay was used to quantify serum leptin levels in 160 breast cancer patients and 160 healthy controls. Compared to the AA genotype, the odds ratio for breast cancer in obese females was 2.986 (95% CI: 1.540–5.789; $p = 0.001$), indicating a substantial relationship between the GG genotype and the disease. The GG genotype was associated with considerably higher leptin levels ($p < 0.0001$) and

was more common in patients with breast cancer who had a BMI higher than 25. (Manar *et al.*, 2022) Secreted by adipose tissue, leptin affects tumour growth and immunological activation via interacting with the leptin receptor (Ob-R) on immune cells and breast cancer. With the exception of the triple-negative subtype, breast cancer is generally not immunogenic.

Tumour-infiltrating lymphocytes (TILs), especially in some subtypes of breast cancer, are significant prognostic variables and play a crucial role in the immune response. (Laura *et al.*, 2021) The incidence and survival of breast cancer (BC) are linked to the expression of leptin (LEP) and leptin receptor (LEPR); BC tissues have higher levels of LEP and LEPR expression than benign and para-carcinoma tissues; patients with lymph node metastases have higher levels of LEP expression, and a higher Ki-67 rate indicates increased cell proliferation; however, neither LEP nor LEPR expression affects survival outcomes; elevated LEP/LEPR expression is thought to be a risk factor for the development of BC but has no effect on survival. (Yang *et al.*, 2023) In breast cancer tissues, leptin and its receptor are frequently overexpressed, and their presence is strongly associated with malignancies that express hormone receptors. Leptin may encourage the development of breast cancer, especially in hormone-sensitive subtypes, as higher levels of the hormone are linked to lower tumour grade and decreased HER2 positive. This shows leptin as a possible target for treatment of breast cancer. (Irem *et al.*, 2022)

8. Leptin and Oncogenic Pathways:

Leptin stimulates angiogenesis in breast cancer by influencing endothelial cells, tumour cells, and the tumour microenvironment through a number of important signalling pathways. (Courtney *et al.*, 2024)

- Janus Kinase 2/Signal Transducer and Activator of Transcription 3 (AK2/STAT3)Pathway
  Mechanism: JAK2 is activated when leptin interacts to its receptor (Ob-R), phosphorylatingSTAT3.
  Effect: Vascular Endothelial Growth Factor (VEGF) and other pro-angiogenic genes are expressed more when STAT3 enters the nucleus.
  Result: Promotes the development of new blood vessels to supply the tumor with blood.
- Protein Kinase B/Phosphoinositide 3-Kinase (PI3K/AKT) Pathway
  Mechanism: Phosphorylation and activation of AKT result from leptin's stimulation of PI3K.
  Effect: Increases the transcription factor HIF-1α (Hypoxia-Inducible Factor 1-alpha) and encourages cell survival.
  Result: HIF-1α promotes angiogenesis by raising VEGF expression in low oxygen environments.
- MAPK/ERK Pathway (Mitogen-Activated Protein Kinase / Extracellular Signal-Regulated Kinase)
  Mechanism: Leptin stimulation leads to activation of the MAPK cascade.
  Effect: Promotes the migration and proliferation of endothelial cells.
  Result: Encourages the growth and stability of vessels inside tumours.
- Crosstalk with Notch Signalling Mechanism and Estrogen Receptor (ER): Leptin can interact with Notch pathway components and improve ER signalling.
  Effect: VEGF expression and endothelial cell activation are further enhanced by these interactions.
  Result: Increases the pro-angiogenic effect in cancers that respond to hormones.

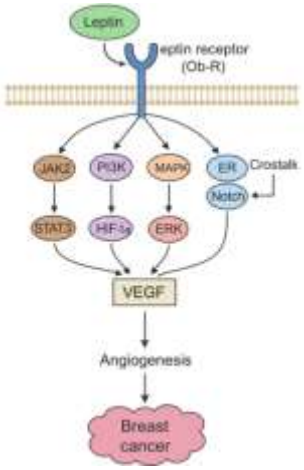

Fig 3 Representing Pathways

9. Leptin as a Clinical Biomarker:

Given its close ties to obesity, inflammation, tumor growth, and progression—particularly in hormone-sensitive malignancies like breast, endometrial, and colorectal cancers—leptin is being investigated as a potential biomarker for cancer.

- **Elevated Leptin Levels in Cancer Patients**

Individuals with obesity often exhibit increased leptin concentrations in the bloodstream.

Many cancers, such as breast and endometrial tumors, show upregulated expression of leptin and its receptor (Ob-R) within the tumor tissue.This heightened expression is commonly associated with a worse clinical outcome.

- **Leptin Facilitates Tumor Development**

Leptin activates several signaling pathways that support tumor growth:

JAK2/STAT3 pathway: Promotes cell proliferation and survival

PI3K/AKT and MAPK/ERK pathways: Enhance cell growth, prevent apoptosis, and support metastatic potential

VEGF induction: Encourages angiogenesis, enabling tumors to expand and invade new tissues

- **Clinical Importance of Leptin**

As a Diagnostic Tool: In obese patients, leptin and its receptor may serve as markers for identifying aggressive cancer types.

As a Prognostic Factor:

High leptin levels are often linked to hormone receptor-positive (ER+, PR+) breast cancers

May correlate with lower tumor grades in certain cancers

Can be associated with treatment resistance

As a Therapeutic Target: Strategies that block leptin or its receptor may help suppress tumor progression, particularly in obesity-related cancers.

10. Research Gaps and Future Directions:

Although leptin's possible function in tumor progression has been emphasized by research on its role in breast cancer, there are still a number of unanswered questions. Clarifying the precise signalling pathways of leptin, its effects on various subtypes of breast cancer, and its interactions with the tumor microenvironment—including immunological and adipocyte cells—should be the main goals of future

research. It is also necessary to investigate the connection between leptin and cancer stem cells, chemotherapy resistance, and metabolic syndrome. Furthermore, examining leptin's function in inflammation, metastasis, and its potential as a biomarker may yield important information for diagnosis and therapy. Clinical studies assessing leptin inhibitors or antagonists may open up new treatment options, especially for postmenopausal breast cancer and medication resistance. Closing these gaps may lead to more individualized and successful treatment plans for people with breast cancer.

11. Conclusion:

Leptin is a major factor in the substantial correlation between obesity and the development of breast cancer. By promoting tumor development, survival, and metastasis, elevated leptin levels in obese people aid in the advancement of cancer. Because leptin is overexpressed in breast cancer tissues, particularly in hormone-sensitive subtypes, it may be used as a biomarker for targeted therapy and early detection. With obesity rates on the rise worldwide, it is increasingly important to incorporate obesity management into breast cancer prevention and treatment strategies. Leptin, a key factor in the connection between obesity and breast cancer, significantly influences tumor development and progression. On-going research into leptin's role in cancer could lead to innovative treatment options, potentially enhancing outcomes for obese breast cancer patients. Tackling obesity could therefore play a major role in both preventing breast cancer and alleviating its global impact.

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