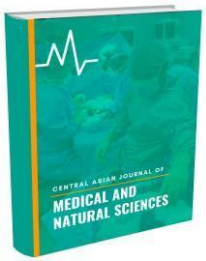

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Article

Interplay Between Estrogen Signaling and Metabolic Biomarkers in Breast Cancer Progression

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Abstract: Background: Breast cancer growth involves androgen and estrogen signaling and metabolism. Adipokines and insulin resistance modulate hormone sensitivity, invasion and growt. Aims of the study: This study aims to investigate the association between estrogen receptor pathway and metabolic factors in female patients with breast cancer, and their impact on the tumor characteristics and clinical outcomes. And to investigate the role of insulin resistance and adipokine (leptin and adiponectin) imbalance as a predictor of tumor. Methodology: A case–control study was conducted from April 2025 to February 2026 at an oncology center in Iraq, including 80 breast cancer patients and 30 matched healthy controls. Diagnosis was confirmed histopathologically, and staging followed the TNM system. ER status was assessed by immunohistochemistry (≥10% positivity). Blood samples were collected, centrifuged, and serum stored at −20°C. Glucose was measured enzymatically, while insulin, leptin, and adiponectin were analyzed using ELISA. HOMA-IR was calculated. Only newly diagnosed patients were included; those with metabolic or endocrine disorders were excluded. Result: Most patients were ≥50 years (57.5%) with grade II disease (45.0%) and 55.0% had early stage disease. 65.0% showed ER positivity. Biomarkers showed significant differences between patients and controls ($p < 0.001$) revealing insulin resistance and altered adipokines. Metabolic biomarkers were worse among ER-negative patients. ER level was negatively associated with tumor grade and stage, and biomarkers. Multivariate analysis revealed ER-negative status, HOMA-IR and leptin as indicators of disease progression, with adiponectin showing borderline significance. Conclusions: Loss of the estrogen receptor (ER) and metabolic dysfunction are key factors in the progression of breast cancer. Insulin resistance and overproduction of leptin stimulate tumor growth through the PI3K/Akt pathway, and decreased adiponectin levels diminish anti-proliferative activity increasing tumor inviveness.

Keywords: Estrogen receptor, Breast cancer, Insulin resistance, Leptin, Adiponectin

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Introduction

Breast cancer is the most common cancer and a leading cause of cancer-related deaths in women. A complex array of genetic, hormonal and metabolic pathways control its development and progression [1]. The hormone estrogen is one of the major regulators of breast development and tumourigenesis. Estrogen signalling is mediated mainly by estrogen receptors (ERs), particularly ER-α, which is a transcription factor that regulates genes that are involved in proliferation, differentiation and survival. Dysregulations in this pathway have been reported to be crucial for the growth and progression of breast cancer [2].

Estrogen receptor (ER) status is an important factor when diagnosing and treating breast cancer. Estrogen receptor (ER)-positive cancers have a better prognosis and can be

treated with hormone therapies; but ER-negative cancers are more aggressive and have a poorer prognosis [4]. However, breast cancer isn't completely hormone-driven and recent studies have revealed that metabolic alterations are crucial for the development of breast cancer. Recent studies have demonstrated that metabolism, insulin resistance and adipokines are involved in the development of breast cancer [5,6].

Breast cancer patients with metabolic dysfunction (obesity, insulin resistance) have an increased risk and poor survival. Elevated insulin levels can stimulate growth of tumours by activating certain pathways (PI3K/Akt, MAPK) that stimulate growth, and inhibit cell death [6]. And insulin can influence estrogen by decreasing sex hormone-binding globulin (SHBG), increasing the amount of free estrogen. This crosstalk reveals the interplay between metabolic and hormone pathways in developing breast cancer [7].

Adipokines, or bioactive products of fat cells, are also involved. Leptin and adiponectin are the most well-researched adipokines in cancer [8]. Leptin is known to promote cell growth, blood vessel growth and inflammation while adiponectin has anti-inflammatory and anti-proliferative properties. Elevated levels of leptin and reduced adiponectin are associated with poor prognosis and aggressive cancer in breast cancer. These opposite effects suggest that an imbalance of adipokines may play a role in tumour growth [9,10].

Estrogen and metabolic processes have been found to have a two-way interaction. Metabolism may be influenced by estrogen receptors and hormone receptors may be influenced by metabolic dysfunction [11]. For instance, inflammation and insulin resistance have been shown to down-regulate ERs, leading to a more aggressive disease. Conversely, ER activity may regulate glucose metabolism and adipokine activity, also suggesting a bidirectional relationship. This is important in the understanding of the complexity of breast cancer and treatment [12].

Although there is a growing body of evidence for immunometabolic interactions in breast cancer, the precise relationships between estrogen receptor (ER) signaling and metabolic factors during different stages of cancer development remains unknown. This could be attributed to differences in the patients, cancers and analytical approaches. Therefore, more research needs to be done to explore these associations and their significance [13,14].

In this respect, the current study seeks to assess the role of estrogen and metabolic pathways in breast cancer. The investigation of the association between ER status, insulin resistance and adipokines aim to give an overview of the combined effects of hormonal and metabolic processes on tumour development. This could assist in risk profiling and treatment of breast cancer.

Materials and Methods

A case control study was taken at the Oncology Center in Iraq from April 2025 to February 2026, including 80 cases (breast cancer patients) and 30 controls (healthy women) matched for age and body mass index (BMI). Breast cancer diagnosis was made by histopathology of biopsies and staging was according to the TNM staging system. Estrogen receptor (ER) was tested by immunohistochemistry (IHC) on paraffin sections (IHC positive if nuclear staining is observed in at least 10% of the tumor). The disease severity was also measured by tumor grade, stage and lymph node involvement. A total of 5 mL of venous blood was drawn aseptically from each participant and stored in two tubes (EDTA and non-EDTA) and centrifuged at 3000 rpm for 10 minutes to separate serum, which was stored at -20°C until used. Serum glucose concentration was assessed by enzymatic colourimetric methods, and insulin, leptin and adiponectin were measured using commercially available ELISA kits (BioTechne, USA) as per the manufacturer's instructions. The Homeostasis Model Assessment (HOMA-IR) index was used to assess insulin resistance. The inclusion criteria included patients with newly diagnosed breast cancer who had not undergone chemotherapy or radiotherapy before sample collection,

while exclusion criteria included patients with diabetes, other endocrine disorders, chronic inflammatory diseases, or under hormonal treatment. Participants' sociodemographic and clinical information, including age, BMI and medical history, were collected.

Statistical analysis:

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were represented as mean ± standard deviation (SD) and comparisons between groups were made using independent t-test and one-way ANOVA for continuous variables and Chi-square test for categorical variables. Spearman rank correlation was used to assess the correlation, while multiple logistic regression analysis was used to assess the association with tumor progression. A p-value of <0.05 was considered statistically significant

Ethical approval:

Ethical approval was obtained from the relevant institutional ethics committee, and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Results and Discussion

Result

Clinicopathological Characteristics of Breast Cancer Patients

The clinicopathological analysis demonstrated that the majority of patients were aged ≥50 years (57.5%), while 42.5% were younger than 50 years. Regarding tumor differentiation, grade II tumors were the most prevalent (45.0%), followed by grade I and grade III tumors, each accounting for 27.5%. In terms of tumor stage, 55.0% of cases were classified as early-stage disease (TNM stages I–II), whereas 45.0% presented with advanced stages (III–IV). Of the patients, 65.0% were positive for estrogen receptor (ER) and 35.0% were negative. Likewise, 60.0% of patients had no lymph node metastasis, while 40.0% did have lymph node metastasis, suggesting a fair number of patients with lymph node metastasis and that there was variability in the progression of disease in the study population. As shown in table 1 and figure1, figure 2.

Table 1. Distribution of Tumor Features and Estrogen Receptor Status in the Study Population

Variable	Category	n (%)
Age (years)	<50	34 (42.5)
	≥50	46 (57.5)
Tumor grade	Grade I	22 (27.5)
	Grade II	36 (45.0)
	Grade III	22 (27.5)
Stage (TNM)	I–II	44 (55.0)
	III–IV	36 (45.0)
ER status	Positive	52 (65.0)
	Negative	28 (35.0)
Lymph node metastasis	Absent	48 (60.0)
	Present	32 (40.0)

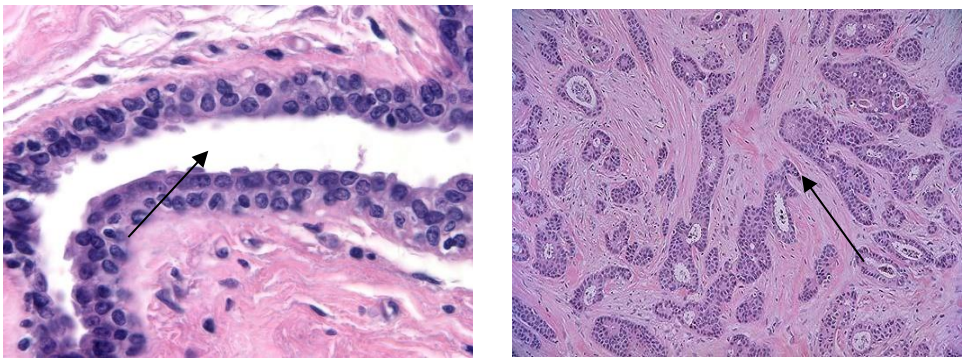

Figure 1. Invasive carcinoma with cellular atypia and stromal invasion (right) compared to normal breast tissue with well-formed ducts (left).

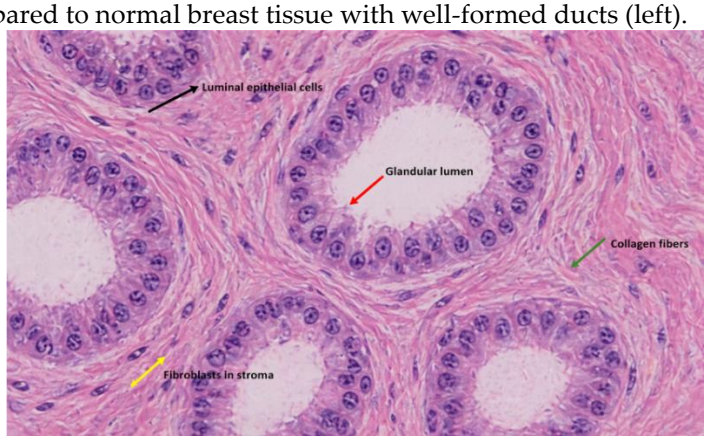

Figure 2. Breast Histology in the Normal State with Organized Glandular and Stromal Elements (H&E Stain, ×400)

Comparison of Metabolic Biomarkers Between Breast Cancer Patients and Healthy Controls

The table 2 shows a significant difference between patients and controls in all the assessed metabolic markers ($p < 0.001$ for all). The patients showed increased levels of glucose, insulin and HOMA-IR, reflecting insulin resistance and glucose metabolic dysfunction. Moreover, patients had significantly increased levels of serum leptin and significantly decreased levels of serum adiponectin compared to the control group, indicating an adipokine imbalance. These results indicate the presence of metabolic dysfunction in breast cancer patients, which may play a role in tumor development via immunometabolic mechanisms.

Table 2. Assessment of Glucose Homeostasis and Adipokine Profiles in Study Groups

Marker	Patients (Mean ± SD)	Controls	p-value
Glucose (mg/dL)	118.6 ± 21.4	95.3 ± 12.7	<0.001*
Insulin (μIU/mL)	15.2 ± 4.6	9.8 ± 3.1	<0.001*
HOMA-IR	4.4 ± 1.5	2.3 ± 0.9	<0.001*
Leptin (ng/mL)	22.1 ± 6.3	13.5 ± 4.2	<0.001*
Adiponectin (μg/mL)	6.2 ± 1.9	10.1 ± 2.5	<0.001*

Comparison of Metabolic Biomarkers According to Estrogen Receptor Status in Breast Cancer Patients

A statistically significant in the table 3, difference was observed in all evaluated metabolic biomarkers between ER-positive and ER-negative breast cancer patients. Insulin levels ($p = 0.012$) and HOMA-IR ($p = 0.008$) were significantly higher in the ER-negative group, indicating greater insulin resistance. Similarly, leptin levels were

significantly elevated in ER-negative patients (p = 0.020), whereas adiponectin levels were significantly lower compared to the ER-positive group (p = 0.005). These findings suggest that ER-negative tumors are associated with a more pronounced metabolic imbalance and adverse adipokine profile.

Table 3. Assessment of Insulin Resistance and Adipokine Profiles in ER-Positive and ER-Negative Groups

Marker	ER+ (n=52)	ER- (n=28)	p-value
Insulin	14.1 ± 3.9	17.0 ± 4.8	0.012*
HOMA-IR	4.0 ± 1.2	5.1 ± 1.6	0.008*
Leptin	20.8 ± 5.4	24.3 ± 6.9	0.020*
Adiponectin	6.8 ± 1.7	5.2 ± 1.6	0.005*

Correlation Between Estrogen Receptor Expression and Tumor Characteristics in Breast Cancer

Statistically significant inverse correlations in the table 4, were observed between estrogen receptor (ER) expression and all evaluated variables. ER expression was negatively correlated with tumor grade (p < 0.001) and tumor stage (p = 0.002), indicating lower receptor expression in more advanced and poorly differentiated tumors as shown in figure 3. Similarly, significant negative correlations were found with HOMA-IR (p = 0.004) and leptin levels (p = 0.009), suggesting that reduced ER expression is associated with increased insulin resistance and elevated adipokine imbalance. This work shows an association between reduced estrogen action and aggressive tumour development and metabolic alterations.

Table 4. Association of ER Expression with Tumor Grade, Stage, and Metabolic Biomarkers

Variable	ER expression (r)	p-value
Tumor grade	-0.42	<0.001*
Tumor stage	-0.38	0.002*
HOMA-IR	-0.35	0.004*
Leptin	-0.31	0.009*

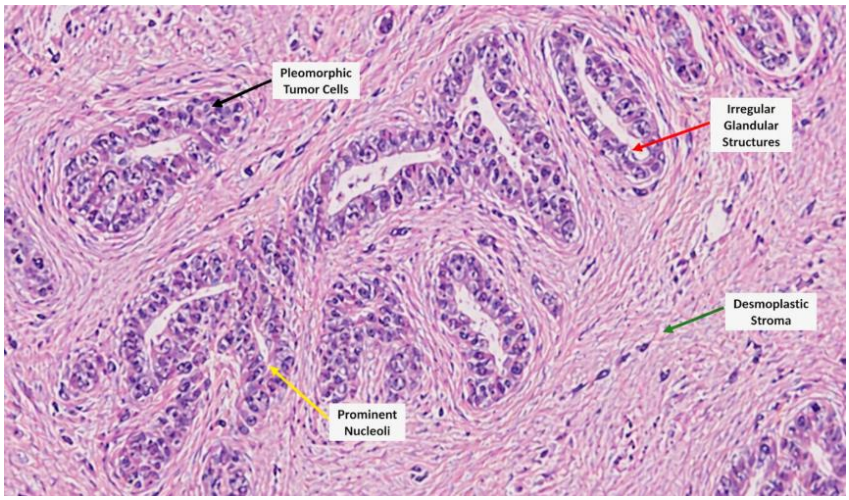

Figure 3. Histopathological Features of Invasive Breast Carcinoma Showing Irregular Glandular Architecture, Cellular Atypia, and Desmoplastic Stromal Reaction (Hematoxylin and Eosin Stain, ×400)

Multivariate Logistic Regression Analysis of Factors Associated with Advanced Breast Cancer

Multivariate logistic regression analysis revealed ER negativity (p = 0.021), as presented in the figure 4, high HOMA-IR (p = 0.014), and high leptin (p = 0.028) all predicted advanced stage breast cancer. On the other hand, low adiponectin levels were marginally significant (0.056). These results suggest that both estrogen dysfunction and metabolic alterations play a role in cancer progression as shown in the table 5.

Table 5. Independent Predictors Based on Estrogen Receptor Status and Metabolic Biomarkers

Variable	OR	95% CI	p-value
ER negative	2.95	1.18–7.32	0.021*
High HOMA-IR	3.44	1.29–9.18	0.014*
High leptin	2.87	1.12–7.33	0.028*
Low adiponectin	2.51	0.98–6.40	0.056

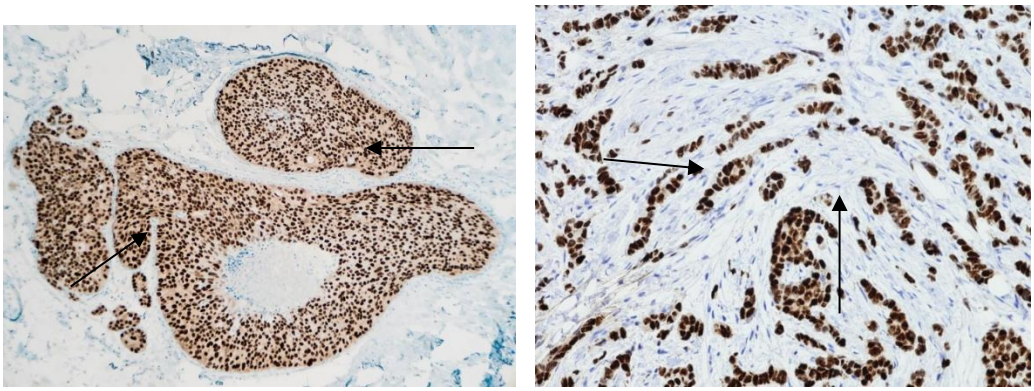

Figure 4. Immunohistochemical staining of estrogen receptor demonstrating strong nuclear positivity in ER+ tumors and weak/absent staining in ER− tumors.

Discussion

The current study highlights a strong interaction between the estrogen receptor (ER) status and metabolic aberrations in the development of breast cancer, as evidenced by the strong correlations between the changes in adipokines, insulin resistance and the aggressive nature of the disease. The high proportion of ER-positive (65%) tumors in the present study is consistent with the epidemiological data worldwide that breast cancers are mostly hormone receptor-positive, especially in postmenopausal women [15]. However, the high frequency (35%) of ER-negative tumors in the present study suggests a heterogenous nature of tumors and is consistent with reports that ER-negative tumors are more aggressive [16].

The significant rise in glucose, insulin and HOMA-IR observed in the case group than in the control group may indicate metabolic dysfunction and insulin resistance. This is in line with previous studies that found a strong association between hyperinsulinemia and risk of developing breast cancer, and insulin promoting tumour growth through the PI3K/Akt and MAPK pathways [17,18]. Elevated insulin levels could possibly increase the bioavailable estrogen levels by reducing sex hormone-binding globulin levels and thus indirectly promote tumor growth [19]. Similarly, increase in leptin and decrease in adiponectin levels observed in this study are in agreement with earlier reports of a role of adipokines in the tumor microenvironment and cancer development [20].

Leptin, which was found to be significantly elevated in patients, has been shown to promote cell proliferation, inflammation and angiogenesis (new blood vessel formation) through the JAK/STAT and NF-κB pathways [21]. Adiponectin, which is lower in patients, has anti-inflammatory and anti-proliferative effects, and its reduction in cancer patients

may remove a tumor growth inhibitor [22]. These findings are in line with reports that higher leptin-adiponectin ratios are associated with a higher risk and worse survival of breast cancer [23]. But other studies have shown weaker associations between adiponectin and cancer growth, particularly early cancers, which may be due to differences in the study population, the size of the population, or the statistical approaches chosen [24].

A key finding of this study is the poorer metabolic status among ER-negative patients than ER-positive patients. The increase in insulin resistance, leptin and the decrease in adiponectin suggests that ER-negative tumors are more closely linked to metabolic diseases. This finding is in line with previous studies that ER-negative breast cancers are frequently associated with metabolic disorders of obesity and are more aggressive [25,26]. The inverse association between ER expression and tumor grade and stage also suggests estrogen regulation of breast cancer. There was a negative correlation between ER and tumor grade and stage that suggests estrogen regulation and tumor aggressiveness [27,28].

In our correlation analyses, we showed ER expression was negatively correlated with metabolic factors and tumour features, and this suggests that the loss of estrogen signalling is related to metabolic dysfunction and tumour aggressiveness. This is consistent with other reports that estrogen signaling may prevent some diseases through regulating cell proliferation and metabolic processes [29]. However, some studies have also reported non-significant correlation between ER and metabolic factors in some populations. This might be attributed to genetic and tumour subtypes and lifestyle, including diet and physical activity [30].

In the multivariate regression analysis, ER-negative status, high HOMA-IR and high leptin were independently associated with advanced breast cancer, with a borderline significance for adiponectin. Our findings are in line with previous reports that have shown insulin resistance and adipokine dysregulations were major factors in tumor growth [32]. The borderline effect of adiponectin could be attributed to its multifaceted nature, as its impact may depend on the tumor microenvironment and receptor availability [32]. Also, differences in assay techniques and sample preparation may influence the results.

At the molecular level, the associations can be understood as interactions between metabolic and hormonal pathways. Insulin resistance results in hyperinsulinemia, which activates pathways involved in tumor growth and survival, and leptin augments inflammatory responses and blood vessel formation. Meanwhile, lowered adiponectin decreases the anti-inflammatory and anti-proliferative actions, thus providing a permissive environment for tumor growth [33]. Additionally, ER loss further drives this process by eliminating feedback regulation of cell proliferation and differentiation.

Conclusion

Overall, the results of this study provide evidence that the development of breast cancer is affected by the interaction between estrogen and metabolic factors. The findings are generally in line with previous studies, but discrepancies between studies indicate the complexity of the disease and the impact of biological and technical differences. The combination of hormonal and metabolic markers could help predict risk and give an indication of treatments.

REFERENCES

[1] J. Kim et al., "Global patterns and trends in breast cancer incidence and mortality across 185 countries," Nature Medicine, vol. 31, no. 4, pp. 1154–1162, 2025.

[2] Y. Zhang et al., "Global burden of female breast cancer: New estimates in 2022, temporal trend and future projections up to 2050 based on the latest release from GLOBOCAN," Journal of the National Cancer Center, vol. 5, no. 3, pp. 287–296, 2025.

[3] N. Kim and K. E. Lukong, "Treating ER-positive breast cancer: A review of the current FDA-approved SERMs and SERDs and their mechanisms of action," Oncology Reviews, vol. 19, p. 1564642, 2025.
[4] N. Kim and K. E. Lukong, "Treating ER-positive breast cancer: A review of the current FDA-approved SERMs and SERDs and their mechanisms of action," Oncology Reviews, vol. 19, p. 1564642, 2025.
[5] S. Mazloomi, "Comparing clinical characteristics and outcomes of single versus double positive and negative hormone receptor breast tumors: Results from a 27-year follow-up study," 2025.
[6] C. Reytor-González et al., "Obesity and breast cancer: Exploring the nexus of chronic inflammation, metabolic dysregulation, and nutritional strategies," Food and Agricultural Immunology, vol. 36, no. 1, p. 2521270, 2025.
[7] A. Caturano et al., "Insulin resistance and cancer: Molecular links and clinical perspectives," Molecular and Cellular Biochemistry, vol. 480, no. 7, pp. 3995–4014, 2025.
[8] J. Ngugi Mwaura, "Natural product modulators of adipokine signaling: A new frontier in obesity-associated cancer therapy."
[9] G. H. Sakban et al., "Exploring biomarkers, adipokines, and cytokines in patients with colon cancer: A comparative study with healthy controls," Regulatory Mechanisms in Biosystems, vol. 16, no. 3, p. e25150, 2025.
[10] X. Ma, S. Yang, and D. Li, "New insights into adipokines and the tumor microenvironment in breast cancer," Cancer Control, vol. 32, 2025.
[11] J. Dong et al., "The impact of estrogen deficiency on liver metabolism: Implications for hormone replacement therapy," Endocrine Reviews, vol. 46, no. 6, pp. 790–809, 2025.
[12] J. Dong et al., "The impact of estrogen deficiency on liver metabolism: Implications for hormone replacement therapy," Endocrine Reviews, vol. 46, no. 6, pp. 790–809, 2025.
[13] A. Dehghani, "The immunoregulatory roles of ERα in breast cancer: Mechanisms, crosstalk, and therapeutic insights," Journal of Cancer Prevention, vol. 31, no. 1, p. 1, 2026.
[14] Y. Zhang et al., "Metformin and oncogenic pathways: Crosstalk between energy sensing and tumor progression," Molecular and Cellular Probes, 2026.
[15] S. Mazloomi, "Comparing clinical characteristics and outcomes of single versus double positive and negative hormone receptor breast tumors: Results from a 27-year follow-up study," 2025.
[16] N. McShane et al., "Hormone receptor positive breast cancer in young women: A review," Journal of Surgical Oncology, vol. 131, no. 4, pp. 580–586, 2025.
[17] Y. Karadeniz et al., "Comparison of triglyceride-glucose index and HOMA-IR in assessing insulin resistance in acromegaly: A case-control study," Endokrynologia Polska, vol. 76, no. 4, pp. 442–449, 2025.
[18] M. Mustari et al., "Triglyceride/high-density lipoprotein cholesterol ratio and triglyceride–glucose index: Potential cost-effective markers of insulin resistance in polycystic ovary syndrome," Bangladesh Journal of Endocrinology and Metabolism, vol. 4, no. 3, pp. 164–170, 2025.
[19] F. Namukasa Mugerwa, "The impact of hyperinsulinemia and hyperglycemia on cancer risk and progression in obese diabetics."
[20] A. Caturano et al., "Insulin resistance and cancer: Molecular links and clinical perspectives," Molecular and Cellular Biochemistry, vol. 480, no. 7, pp. 3995–4014, 2025.
[21] A. S. Neamah et al., "The potential role of targeting the leptin receptor as a treatment for breast cancer in the context of hyperleptinemia: A literature review," Naunyn-Schmiedeberg's Archives of Pharmacology, vol. 398, no. 4, pp. 3451–3466, 2025.
[22] S. Modak et al., "A systematic review on leptin's role in defining cancer: Special emphasis on immunomodulation, inflammation, and therapeutic interventions," Genes & Immunity, vol. 26, no. 3, pp. 266–286, 2025.
[23] M. Gaber et al., "Obesity increases DNA damage in the breast epithelium," Breast Cancer Research, vol. 27, no. 1, p. 11, 2025.
[24] M. Gaber et al., "Obesity increases DNA damage in the breast epithelium," Breast Cancer Research, vol. 27, no. 1, p. 11, 2025.
[25] Y. Liu et al., "Multidimensional risk impact of obesity on breast cancer incidence, treatment, and prognosis: Bariatric surgery," International Journal of Obesity, 2026.
[26] Y. Liu et al., "Multidimensional risk impact of obesity on breast cancer incidence, treatment, and prognosis: Bariatric surgery," International Journal of Obesity, 2026.
[27] S. Loi et al., "Neoadjuvant nivolumab and chemotherapy in early estrogen receptor-positive breast cancer: A randomized phase 3 trial," Nature Medicine, vol. 31, no. 2, pp. 433–441, 2025.

[28] F. Viehweger et al., “Estrogen receptor expression in human tumors: A tissue microarray study evaluating more than 18,000 tumors from 149 different entities,” Human Pathology, vol. 157, p. 105757, 2025.
[29] W. Ren et al., “Comprehensive analysis of metabolism-related gene biomarkers reveals their impact on the diagnosis and prognosis of triple-negative breast cancer,” BMC Cancer, vol. 25, no. 1, p. 668, 2025.
[30] E. W. Pierro et al., “TREM2 expressing macrophages are not associated with prognostic markers or metabolic syndrome in early stage ER positive breast cancer,” Scientific Reports, vol. 15, no. 1, p. 38888, 2025.
[31] T. O. Lawal, B. A. Adeniyi, and G. B. Mahady, “Vitamins A and D and their combinations for breast and colorectal cancers: Analysis of the clinical, epidemiological, preclinical and transcriptomic data,” Pharmaceuticals, vol. 18, no. 11, p. 1684, 2025.
[32] P. P. Strømland et al., “Effects of metformin on transcriptomic and metabolomic profiles in breast cancer survivors enrolled in the randomized placebo-controlled MetBreCS trial,” Scientific Reports, vol. 15, no. 1, p. 16897, 2025.
[33] E. J. Houston and N. M. Templeman, “Reappraising the relationship between hyperinsulinemia and insulin resistance in PCOS,” Journal of Endocrinology, vol. 265, no. 2, 2025.