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# THE IMPACT OF INFLAMMATORY AND ADIPOKINE BIOMARKERS ON BREAST CANCER PROGRESSION AND PATIENT OUTCOMES

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*This case-control study investigated the association between inflammatory and metabolic biomarkers and breast cancer progression in 150 patients and 50 healthy controls aged 40–60 years. The results showed that IL-6, TNF-α, MCP-1, and leptin levels were significantly higher in breast cancer patients, while IL-10 showed no significant difference. IL-6, TNF-α, and MCP-1 were moderately correlated with disease severity, whereas IL-10 showed a weak association. IL-6 and MCP-1 levels also demonstrated a strong statistical association with survival outcomes, while TNF-α, IL-10, and leptin showed no significant impact. No notable changes were observed in biomarker levels over time. These findings reinforce the role of inflammation and lipid metabolism in breast cancer progression. The positive correlation of IL-6, TNF-α, and MCP-1 with disease severity suggests their involvement in tumor microenvironment alterations and systemic inflammation. Moreover, IL-6 and MCP-1 levels were strongly linked to survival outcomes, highlighting their potential as prognostic biomarkers. These results align with prior studies linking adipokines to breast cancer risk, particularly in obesity-driven inflammation. In conclusion the study underscores the prognostic value of IL-6 and MCP-1 and suggests their potential utility in disease assessment and targeted therapy, offering insights into the interplay between chronic inflammation and breast cancer progression.*

***Keyword:*** *Breast Neoplasms, Inflammation, Adipokines, Biomarkers, Cytokines*

## INTRODUCTION

Adipose tissue (AT) is no longer merely regarded as an organ responsible for fat storage and thermoregulation. The discovery of leptin in 1994 further reinforced the endocrine function of adipose tissue. Over time, additional hormones were identified, establishing adipose tissue as a dynamic endocrine organ. This discovery fundamentally shifted scientific perceptions, demonstrating its role in numerous physiological processes, including inflammation and the progression of cancer, particularly breast cancer[1]. Breast cancer (BC) is a common malignancy, with adenocarcinomas being the most prevalent type. It is the second leading cause of cancer-related deaths among women in the U.S., affecting about one in eight women. Its rising incidence is linked to lower birth rates, obesity, and a Western diet high in processed foods and fats, coupled with insufficient physical activity[2]. Obesity can be considered a distinct epidemic. Furthermore, it is strongly associated with an increased risk of breast cancer metastasis and poorer outcomes for patients[3]. Individuals who are overweight or obese are at a higher risk of developing serious health conditions such as dyslipidemia, high blood pressure, cardiovascular disease (CVD), type 2

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diabetes mellitus (DM), stroke, chronic kidney disease, and cancer. Moreover, their prognosis is generally poorer[3,4]. The International Agency for Research on Cancer (IARC) has found strong evidence linking excess weight to the development of several cancers, including esophageal, gastric, liver, kidney, colon, and rectal cancers. Although a low body mass index offers some protection against cancers like thyroid and ovarian, a strong negative correlation exists between waist circumference and the risk of postmenopausal breast cancer[5,6]. A recent study has highlighted the role of adipokines, bioactive molecules released by adipose tissue, in cancer progression[7,8]. Adipokines such as adiponectin, leptin, resistin, visfatin, osteopontin, apelin, and lipocalin have been found to be elevated in individuals with breast cancer[9,10]. Obesity, recognized for its impact on tissue microenvironments, plays a significant role in the pathophysiological mechanisms contributing to cancer. Alterations in the microenvironment, occurring externally to cells, initiate the aforementioned pathways[11,12]. Oxidative stress is known to play a critical role in influencing hormonal changes in obese individuals. Increased levels of pro-inflammatory cytokines, driven by alterations in adipokine levels, promote the synthesis of additional adipokines, thereby creating a molecular feedback loop [13,14]. Recent research suggests that cancer cells with impaired regulation of reactive oxygen species can modify mitoepigenetics. This alteration may lead to changes in the mitochondrial genome of breast adipose cells, which play a crucial role in the growth and metastasis of cancer[15]. Elevated triglyceride concentrations in adipocytes are linked to changes in the cellular environment, including increased levels of reactive oxygen species (ROS). This triggers two key cellular responses, inflammation and endoplasmic reticulum stress[16,17]. Comprehending the various functions of adipokines within the context of breast cancer tumors will enhance established therapy modalities by revealing novel biomarkers of disease progression and potential therapeutic targets[18]. The study aims to investigate the IL-6, TNF-α, MCP-1, and leptin act synergistically to promote breast cancer progression by influencing disease severity and clinical outcomes. This study also examines the correlation between these biomarkers and patient survival, highlighting their potential as prognostic indicators and providing deeper insights into the pathophysiology of breast cancer.

**Methodology**

A case-control study of 150 women with breast cancer (cases) and 50 apparently healthy women (controls) aged 40 to 60 years who were attended at the Cancer Centre of Al-Haboubi Teaching Hospital from 1/2/2024 to 2/2/2025. If the study contained human or animal experiments:Ethical consent was obtained from all the participants, and Ethical approval was obtained from Al-Haboubi Teaching Hospital with approval NO : NO 4877 in 1/2/2024. Study population and inclusion criteria Women aged 40 to 60 years who had been recently diagnosed with breast cancer and had not previously received treatment were included in the study. Women with chronic illnesses or who were taking medications that might affect study outcomes were excluded. Blood sample (5 mL) were obtained carefully from each participant and transferred into a gel tube, and allowed to clot at room temperature for 15 minutes. Serum was separated by centrifugation (3,500 rpm) and stored at -20°C for further use. IL-6, TNF-α, IL-10, MCP-1, and Leptin levels were measured using ELISA kits (BioTechne, USA), according to the manufacturer's instructions. The reagents used and their catalog numbers were IL-6 (QK206), TNF-α (DTA00), IL-10 (D1000B), MCP-1 (DCP00), and Leptin (DLP00). Clinical data such as disease stage, type of treatment (surgery, chemotherapy, radiotherapy), and follow-up outcomes were also included in the study. Participants were followed for 1 years for treatment response and clinical outcomes. Tumor grade, stage and classification were used to assess disease severity in patients with breast cancer. Tumor grade was assessed according to the degree of differentiation of the cancer cells and classified as being low (Grade 1), moderate (Grade 2) or high (Grade 3). Tumor staging via the TNM system, which assesses tumor size, lymph node involvement, and metastases, was used and ranges from I (early-stage)– IV (metastatic cancer). Tumor classification was categorized by breast cancer subtypes — invasive ductal

carcinoma (IDC), invasive lobular carcinoma (ILC), and other subtypes. These specifications gave information about the aggressiveness of the illness and specified prognosis as well as treatment methods. Survival data were analyzed using statistical methods, including Kaplan-Meier survival analysis and log-rank tests. There were 150 patients survived in the study and follow up was carried out for 12 months from the commencement of the study. All cases of survival during follow-up were noted. Data were assessed using appropriate statistical analyses, including the Chi-square test and regression analysis, to illustrate the association between different biomarker levels and survival rates.

**Statistical analysis**

A statistical analysis was performed in this study to analyze the association between the different biomarkers and the breast cancer patients. In the control group, there were 50 controls; in the patients group, 150 breast cancer patients were enrolled. Moreover, statistical analyses were performed with normally distributed variables by using dependent t-test (two-tailed) and independent t-test (two-tailed), while Mann-Whitney U test and Wilcoxon test were used for non-normally distributed variables. With unequal group sizes, such methods are also used to ensure the robustness of the results with $P < 0.05$ representing statistical significance.

**Ethical approval**

All patients who were included in the study were informed about the study and gave their verbal consent before sample collection. The study was approved by the Committee on Publication Ethics at the Thi-Qar Health Directorate and Al-Habboubi Teaching Hospital.

## RESULTS AND DISCUSSION

**Sociodemographic Characteristics of Breast Cancer Patients Compared to Healthy Controls**

Regarding socio-demographic characteristics, the mean age of breast cancer patients was 52.3 ± 10.5 years, significantly higher than that of healthy individuals (45.6 ± 12.3 years, p=0.02). All patients were female, as were the healthy controls. Education level: 20% of patients had a high school diploma vs. 30% of controls (p=0.15), while 35% of patients had a bachelor's degree vs. 25% of controls (p=0.10). Postgraduate degree holders were 45% in both groups. Marital status: 10% of patients were unmarried vs. 15% of controls (p=0.40), 70% were married vs. 55% of controls (p=0.12), and 20% were divorced/widowed vs. 30% of controls (p=0.25), **Table 1** and **Fig. 1**.

**Table 1:** Age, Gender, Education Level, and Marital Status Distribution**.**

| Characteristic | Breast Cancer Patients (N=150) | Healthy Controls (N=50) | p-value |
|---|---|---|---|
| Age (Mean ± SD) | 52.3 ± 10.5 | 45.6 ± 12.3 | 0.02 |
| Gender (Female %) | 100% | 100% | - |
| BMI | 31.58± 8.98 | 24.43± 4.13 | <0.001 |
| Education Level (%) | | | |
| - High School | 20% | 30% | 0.15 |
| - Bachelor's Degree | 35% | 25% | 0.10 |
| - Postgraduate | 45% | 45% | 1.00 |
| Marital Status (%) | | | |
| - Single | 10% | 15% | 0.40 |
| - Married | 70% | 55% | 0.12 |
| - Divorced/Widowed | 20% | 30% | 0.25 |

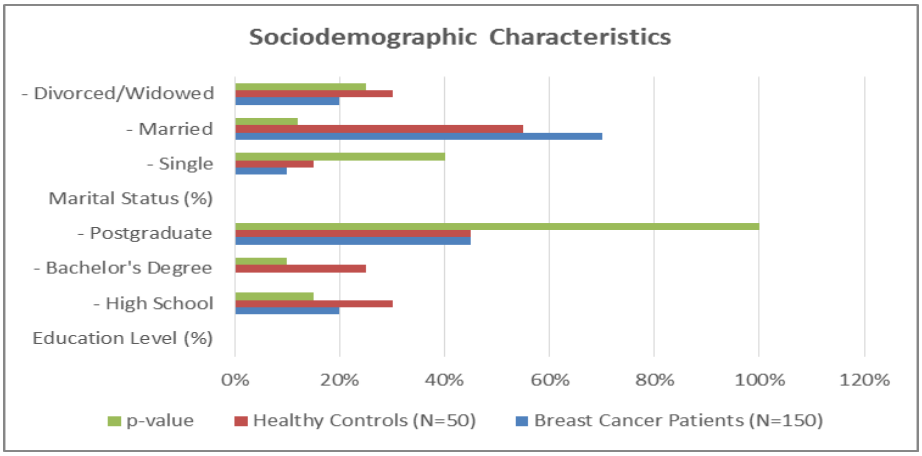


**Fig. 1:** Sociodemographic Characteristics of the study population.

**Levels of Cytokines, Chemokines, and Adipokines in Breast Cancer Patients versus Healthy Controls**

Regarding cytokines, chemokines, and adipokines, the mean IL-6 level in breast cancer patients was 48.2 ± 15.3 pg/mL, significantly higher than in healthy subjects (28.7 ± 10.2 pg/mL, p=0.01). The TNF-α level was also higher in patients (75.4 ± 22.1 pg/mL) compared to healthy subjects (55.9 ± 18.7 pg/mL, p=0.03). For IL-10, the level was 16.3 ± 6.8 pg/mL in patients versus 12.1 ± 5.4 pg/mL in healthy subjects, but the difference was not statistically significant (p=0.07). The MCP-1 level was significantly higher in patients (550.8 ± 130.5 pg/mL) compared to healthy subjects (420.3 ± 110.7 pg/mL, p=0.02). Finally, the leptin level in patients was 18.6 ± 7.2 ng/mL, compared to 12.4 ± 5.8 ng/mL in healthy subjects (p=0.04), **Table 2** and **Fig. 2**.

**Table 2:** Comparative Analysis of Biomarker Levels.

| Biomarker | Breast Cancer Patients (N=150) | Healthy Controls (N=50) | p-value |
|---|---|---|---|
| IL-6 (pg/mL) | 48.2 ± 15.3 | 28.7 ± 10.2 | 0.01 |
| TNF-α (pg/mL) | 75.4 ± 22.1 | 55.9 ± 18.7 | 0.03 |
| IL-10 (pg/mL) | 16.3 ± 6.8 | 12.1 ± 5.4 | 0.07 |
| MCP-1 (pg/mL) | 550.8 ± 130.5 | 420.3 ± 110.7 | 0.02 |
| Leptin (ng/mL) | 18.6 ± 7.2 | 12.4 ± 5.8 | 0.04 |

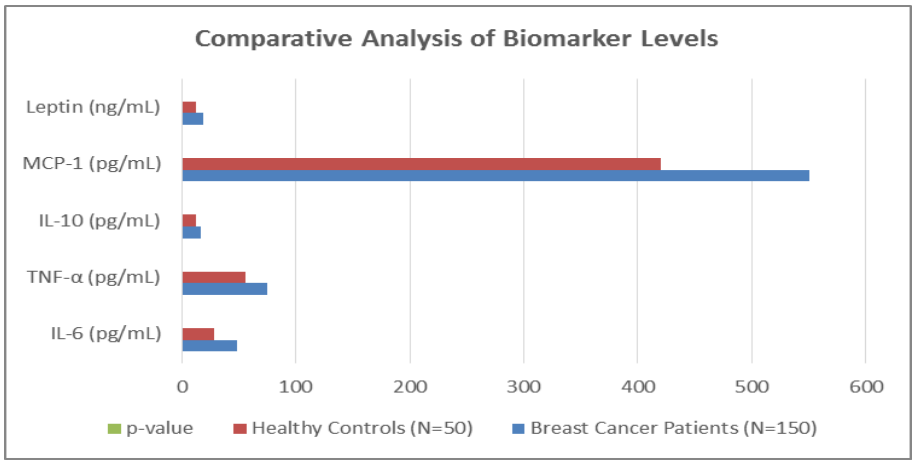


**Fig. 2:** Levels of Cytokines, Chemokines, and Adipokines in Breast Cancer Patients.

**Correlation Between Biomarkers and Disease Severity in Breast Cancer Patients**

The research revealed a moderate correlation coefficient of 0.50 and a p-value of 0.01, demonstrating a significant positive association between IL-6 levels and disease severity in breast cancer patients. TNF-α exhibited a positive correlation with disease severity, indicated by a correlation coefficient of 0.45 and a p-value of 0.03. With a correlation coefficient of -0.30 and a p-value of 0.07, IL-10 showed a negative association with disease severity, indicating a lack of statistical significance. MCP-1 exhibited a positive correlation with disease severity, evidenced by a correlation coefficient of 0.40 and a p-value of 0.02. Leptin also showed a positive correlation with disease severity, with a correlation coefficient of 0.35 and a p-value of 0.04 (**Table 3** and **Fig. 3**).

**Impact of Biomarkers on Survival Rates in Breast Cancer Patients**

The results demonstrated the impact of biomarker levels on breast cancer patient survival rates. For IL-6, the survival rate for high levels was 65%, compared to 50% for low levels, with a p-value of 0.03, indicating strong statistical significance. For TNF-α, the survival rate for high levels was 60%, compared to 55% for low levels, but a p-value of 0.25 indicated no strong statistical significance. For IL-10, the survival rate for patients with high levels was 70%, compared to 60% for low levels, with a p-value of 0.15, indicating no strong statistical significance. For MCP-1, the survival rate for patients with high levels was 68%, compared to 55% for low levels, with a p-value of 0.05, indicating acceptable statistical significance. Finally, the survival rate of patients with high leptin levels was 62%, compared to 55% for low levels, with a p-value of 0.20, indicating no strong statistical significance (**Table 4** and **Fig. 4**).

**Table 3:** Associations of Cytokines, Chemokines, and Adipokines with Disease Severity

| Biomarker | Correlation Coefficient (r) | p-value |
|---|---|---|
| IL-6 | 0.50 | 0.01 |
| TNF-α | 0.45 | 0.03 |
| IL-10 | -0.30 | 0.07 |
| MCP-1 | 0.40 | 0.02 |
| Leptin | 0.35 | 0.04 |

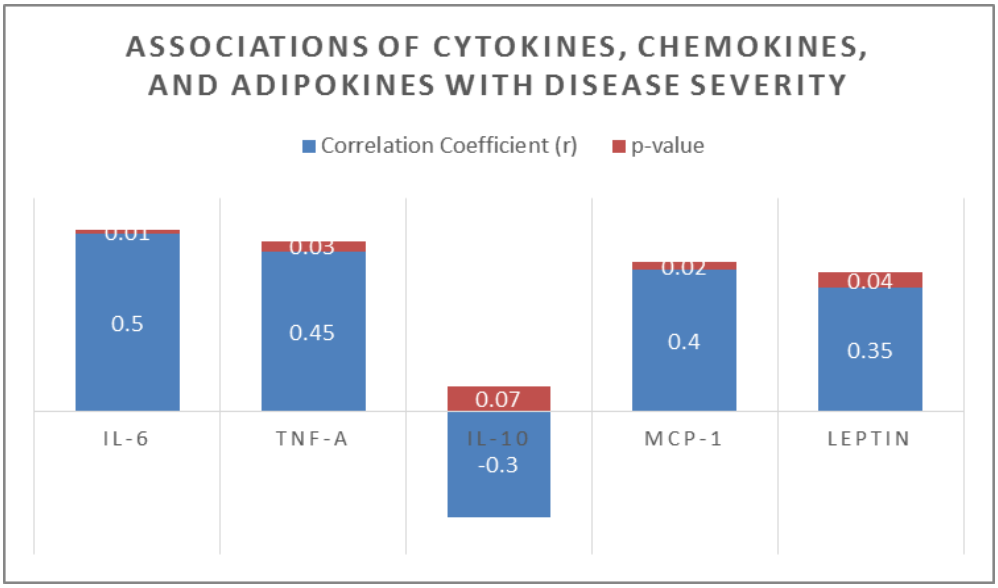


**Fig. 3:** The Cytokines, Chemokines, and Adipokines with Disease Severity.

**Table 4:** Survival Rate Comparisons by Biomarker Levels.

| Biomarker | High Level Survival Rate (%) | Low Level Survival Rate (%) | p-value |
|---|---|---|---|
| IL-6 | 65% | 50% | 0.03 |
| TNF-α | 60% | 55% | 0.25 |
| IL-10 | 70% | 60% | 0.15 |
| MCP-1 | 68% | 55% | 0.05 |
| Leptin | 62% | 55% | 0.20 |

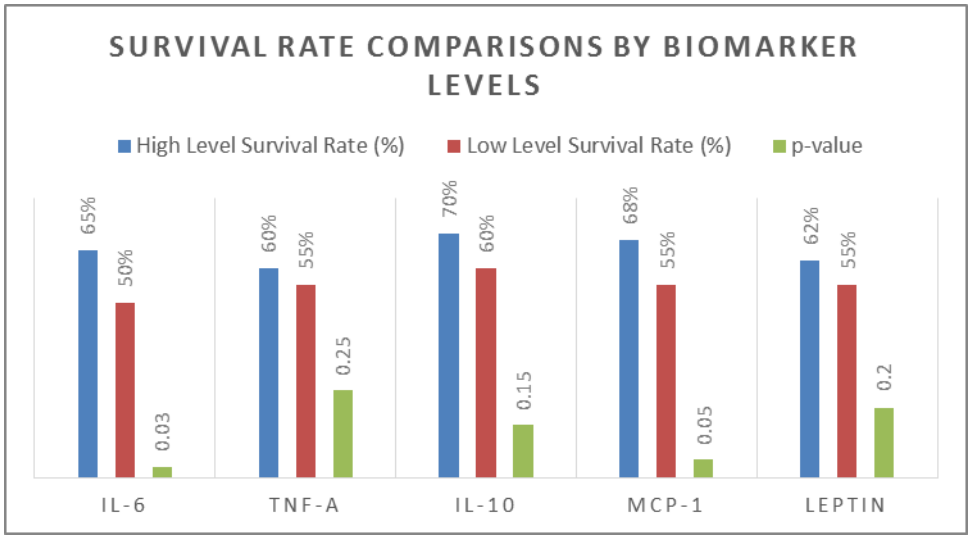


**Fig. 4:** The Survival Rates in Breast Cancer Patients.

**Changes in Biomarker Levels Over Time in Breast Cancer Patients**

Researchers examined changes in biomarker levels over time in breast cancer patients and found that IL-6 levels increased from 47.5 ± 14.8 pg/mL to 49.0 ± 16.0 pg/mL, but the p-value of 0.30 indicated no strong statistical association. TNF-α levels rose from 74.0 ± 21.9 pg/mL to 76.0 ± 22.3 pg/mL, but the p-value of 0.40 also indicated no strong statistical significance. IL-10 levels increased from 16.0 ± 6.7 pg/mL to 16.5 ± 6.9 pg/mL, but the p-value of 0.50 confirmed no statistically significant change. MCP-1 levels rose from 548.0 ± 130.0 pg/mL to 552.0 ± 132.0 pg/mL, with a p-value of 0.60, indicating no statistical significance. Finally, leptin levels increased from 18.5 ± 7.1 ng/mL to 18.7 ± 7.3 ng/mL, but the p-value of 0.70 confirmed that the changes were not statistically significant (**Table 5** and **Fig. 5**).

**Table 5:** Initial and Follow-up Biomarker Levels and Their Statistical Significance.

| Biomarker | Initial Level (Mean ± SD) | Follow-up Level (Mean ± SD) | p-value |
|---|---|---|---|
| IL-6 | 47.5 ± 14.8 | 49.0 ± 16.0 | 0.30 |
| TNF-α | 74.0 ± 21.9 | 76.0 ± 22.3 | 0.40 |
| IL-10 | 16.0 ± 6.7 | 16.5 ± 6.9 | 0.50 |
| MCP-1 | 548.0 ± 130.0 | 552.0 ± 132.0 | 0.60 |
| Leptin | 18.5 ± 7.1 | 18.7 ± 7.3 | 0.70 |

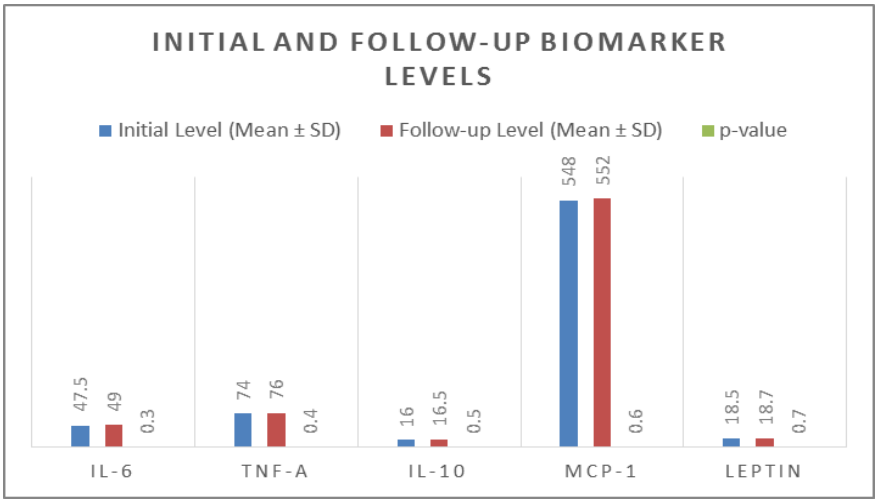


**Fig. 5:** The Changes in Biomarker Levels Over Time**.**

**Association of Biomarker Levels with Tumor Characteristics in Breast Cancer**

The results showed that biomarker levels varied significantly depending on tumor characteristics in cancer patients. Regarding tumor grade, levels of IL-6, TNF-α, MCP-1, and leptin were significantly higher in tumor grade III (high) compared to grades I (low) and II (intermediate), with tumor grade III having the highest mean values for the studied biomarkers. Regarding tumor stage, levels of IL-6, TNF-α, MCP-1, and leptin were also higher in stage III (advanced) compared to stage I (early) and stage II (intermediate). Regarding tumor classification, biomarker levels were higher in invasive ductal adenocarcinomas than in invasive papillary adenocarcinomas, with minor differences in other tumor outcomes. P values were less than 0.05 in most cases, indicating a statistically significant relationship between tumor characteristics and biomarker levels.

**Table 6:** Tumor Grade, Stage, and Classification Impact on IL-6, TNF-α, IL-10, MCP-1, and Leptin Levels.

| Tumor Characteristic | IL-6 (pg/mL) | TNF-α (pg/mL) | IL-10 (pg/mL) | MCP-1 (pg/mL) | Leptin (ng/mL) | p-value |
|---|---|---|---|---|---|---|
| **Tumor Grade** | | | | | | |
| Grade 1 (Low) | 38.5 ± 12.1 | 65.3 ± 19.5 | 15.2 ± 5.3 | 485.3 ± 110.4 | 16.2 ± 5.8 | 0.02 |
| Grade 2 (Moderate) | 45.2 ± 13.7 | 70.1 ± 20.2 | 16.8 ± 6.1 | 522.3 ± 125.5 | 17.8 ± 6.1 | 0.03 |
| Grade 3 (High) | 56.8 ± 17.9 | 82.3 ± 24.8 | 17.4 ± 6.9 | 585.7 ± 135.3 | 20.1 ± 7.5 | 0.01 |
| **Tumor Stage** | | | | | | |
| Stage I (Early) | 43.3 ± 14.4 | 68.2 ± 21.1 | 15.6 ± 5.5 | 510.4 ± 120.9 | 18.1 ± 6.2 | 0.04 |
| Stage II (Intermediate) | 49.1 ± 16.3 | 74.0 ± 23.4 | 16.3 ± 5.9 | 540.9 ± 128.7 | 18.5 ± 6.5 | 0.02 |
| Stage III (Advanced) | 58.3 ± 19.2 | 85.6 ± 26.2 | 18.1 ± 7.3 | 600.2 ± 140.0 | 21.3 ± 8.0 | 0.01 |
| **Tumor Classification** | | | | | | |
| Invasive Ductal Carcinoma | 52.4 ± 16.8 | 76.4 ± 22.0 | 16.6 ± 6.3 | 563.0 ± 130.0 | 19.2 ± 7.1 | 0.03 |
| Invasive Lobular Carcinoma | 47.1 ± 14.2 | 70.5 ± 19.8 | 15.9 ± 5.8 | 530.7 ± 118.4 | 18.4 ± 6.3 | 0.05 |
| Other Types | 55.2 ± 17.5 | 80.3 ± 24.3 | 17.2 ± 6.7 | 575.4 ± 134.5 | 20.7 ± 7.9 | 0.02 |

**Discussion**

The levels of IL-6, TNF-α, MCP-1, and leptin were significantly higher in patients, while IL-10 showed no statistically significant difference. A moderate correlation was observed between IL-6, TNF-α, and MCP-1 with disease severity, whereas IL-10 exhibited a weak association, and no significant longitudinal changes were noted, aligning with previous findings[19,20]. Adipose tissue is increasingly recognized as a key contributor to breast cancer etiology, supported by evidence linking obesity to an elevated risk of postmenopausal breast cancer. Additionally, adipose tissue provides a critical microenvironment for tumor survival, independent of BMI. The chronic low-grade inflammation observed in obesity is characterized by the secretion of adipocyte-derived factors that can directly alter metabolic pathways and promote mutations or indirectly influence tumor progression by recruiting inflammatory cells[21]. Despite immune infiltration, these cells fail to suppress tumor growth and instead facilitate immune evasion by upregulating specific receptors in cancer cells, preventing effective immune surveillance[22]. While tumor microenvironment alterations are often perceived as localized events, systemic inflammatory effects mediated by adipose tissue can originate from distant sites, reinforcing the obesity-cancer link through low-grade inflammation and adipokine activity, particularly IL-6 and TNF-α[23]. Breast adipocytes secrete inflammatory mediators, while visceral and subcutaneous fat release factors regulating oxidative stress, with emerging evidence suggesting intercommunication between adipose tissue depots via exosomal signaling[24]. Extracellular vesicles, notably thrombospondin-5 (TSP-5), contribute to the epithelial-mesenchymal transition in breast adipocytes, facilitating tumor proliferation and dissemination[25]. Obesity-driven alterations in breast tissue involve cancer-associated fibroblasts, which, upon activation by adipokines, modify the extracellular matrix to support malignant adipocyte expansion, as demonstrated in co-culture studies with subcutaneous adipose cells[26]. Notably, metabolically active visceral fat correlates with poorer recurrence-free survival, with clinical trials confirming the adverse impact of visceral obesity on breast cancer prognosis[27]. Leptin, beyond its endocrine role, exerts pro-tumorigenic effects via the LEPR receptor, primarily expressed in breast cancer cells, activating PI3K/AKT and JAK/STAT pathways to promote proliferation and inhibit apoptosis through Bcl-2 and Bax regulation, while also enhancing angiogenesis via VEGF secretion [28]. Although meta-analyses, including that by Niu et al., support a positive correlation between leptin and breast cancer risk[29], conflicting findings exist. Leptin levels are significantly higher in ER+ than ER− tumors, with studies linking its expression to estrogen signaling, where inhibition of the estrogen receptor decelerates the cell cycle and induces autophagy[30]. Leptin can also transactivate estrogen receptors through MAP-kinase signaling[31], and its levels are notably elevated in patients with lymph node metastasis and in postmenopausal women compared to premenopausal counterparts[32]. Recent studies suggest that obesity negatively impacts breast cancer outcomes independent of menopausal status, tumor size, or hormonal factors, with inflammatory cytokines like IL-6 playing a central role. IL-6 facilitates interactions between preadipocytes and ductal carcinoma cells, promoting early tumor progression[33,34]. IL-6 is a key driver of tumor growth, with its deregulated signaling supporting adhesion, migration, and proliferation [35]. Elevated IL-6 in breast tumors enhances Jagged-1 expression, fostering cell proliferation and aggressive phenotypes while simultaneously decreasing apoptosis and stimulating angiogenesis. Notably, IL-6Rα overexpression has been linked to breast cancer cell survival[36]. High IL-6 levels in metastatic breast cancer may contribute to chemotherapy resistance, particularly against paclitaxel. Research into adipocyte-cancer interactions highlights IL-6's role in upregulating PLOD2 and activating JAK/STAT3 and PI3K/AKT pathways, driving cancer progression. In triple-negative breast cancer (TNBC), IL-6 and IL-8 inhibition significantly reduced tumor growth in vitro and in vivo[37]. Chronic inflammation is a hallmark of cancer, and while some reports suggest TNF-α induces apoptosis in certain breast cancer subtypes, most studies indicate that TNF-α primarily regulates tumor cell growth, survival, and progression, with variations

possibly linked to TNFR expression levels, Bcl-2 family interactions, caspase activity, or ceramide signaling[38,39]. Obese breast cancer patients exhibit elevated MCP-1 and GROα levels, particularly in TNBC, where MCP-1 promotes metastasis. Our findings highlight that breast cancer cells, especially TNBC subtypes, produce substantial MCP-1, which enhances cellular invasiveness via the p44/42 MAPK pathway without affecting proliferation, suggesting MCP-1 as a potential TNBC biomarker[40].

**Conclusion**

The results indicate that IL-6, TNF-α, MCP-1, and leptin levels were significantly higher in breast cancer patients than in healthy controls, reinforcing the role of inflammation and lipid metabolism in disease progression. IL-6, TNF-α, and MCP-1 were positively correlated with disease severity, suggesting their involvement in tumor microenvironment alterations and systemic inflammatory responses. These findings align with previous studies linking adipokines to breast cancer risk, particularly in obese individuals, where chronic inflammation and oxidative stress contribute to disease progression. Additionally, our study highlights the prognostic potential of IL-6 and MCP-1, as their levels showed a strong association with survival outcomes. These biomarkers could serve as valuable tools for assessing disease severity and guiding targeted therapeutic approaches.

## REFERENCES


1. Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold and J.M. Friedman, "Positional cloning of the mouse obese gene and its human homologue", ***Nature,*** 372 (6505), 425–432 (1994).
2. R.L. Siegel, K.D. Miller, H.E. Fuchs and A. Jemal, "Cancer statistics, 2022", ***CA Cancer J Clin,*** 72(1), 7–33 (2022).
3. M. Ng, T. Fleming, M. Robinson, B. Thomson, N. Graetz, C. Margono, E.C. Mullany, S. Biryukov, C. Abbafati, S.F. Abera, *et al.*, "Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013", ***Lancet,*** 384 (9945), 766–781 (2014).
4. C. Kang, D. LeRoith and E.J. Gallagher, "Diabetes, obesity, and breast cancer", ***Endocrinology,*** 159(11), 3801–3812 (2018).
5. Y. Lu, K. Hajifathalian, M. Ezzati, M. Woodward, E.B. Rimm, G. Danaei, R. Selmer, B.H. Strand, A. Dobson, A. Hozawa, *et al.*, "Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: A pooled analysis of 97 prospective cohorts with 1.8 million participants", ***Lancet,*** 383 (9921), 970–983 (2014).
6. B. Lauby-Secretan, C. Scoccianti, D. Loomis, Y. Grosse, F. Bianchini and K. Straif, "Body fatness and cancer—Viewpoint of the IARC Working Group", ***N Engl J Med,*** 375(8), 794–798 (2016).
7. A.G. Renehan, M. Tyson, M. Egger, R.F. Heller and M. Zwahlen, "Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies", ***Lancet,*** 371 (9612), 569–578 (2008).
8. P.J. Goodwin and V. Stambolic, "Impact of the obesity epidemic on cancer", ***Annu Rev Med,*** 66, 281–296 (2015).
9. X. Lyu, Q. Zhang, H.M. Fares, Y. Wang, Y. Han and L. Sun, "Contribution of adipocytes in the tumor microenvironment to breast cancer metabolism", ***Cancer Lett,*** 534, 215616 (2022).
10. D. Lateef, N. Nasser and O. Mohsein, "The relationships between Aplein, Vaspin and thyroid hormone levels in obese diabetic and non-diabetic women", ***J Exp Clin Med,*** 41(2), 239–245 (2024).
11. K. Chen, P. Lu, N.M. Beeraka, O.A. Sukocheva, S.R.V. Madhunapantula, J. Liu, M.Y. Sinelnikov, V.N. Nikolenko, K.V. Bulygin, L.M. Mikhaleva, *et al.*, "Mitochondrial mutations and mitoepigenetics: Focus on regulation of oxidative stress-induced responses in breast cancers", ***Semin Cancer Biol,*** 83, 556–569 (2022).
12. Y. Liu, C. Chen, X. Wang, Y. Sun, J. Zhang, J. Chen and Y. Shi, "An epigenetic

role of mitochondria in cancer", ***Cells,*** 11(16), 2518 (2022).
13. L. Marseglia, S. Manti, G. D'Angelo, A. Nicotera, E. Parisi, G. Di Rosa, E. Gitto and T. Arrigo, "Oxidative stress in obesity: A critical component in human diseases", ***Int J Mol Sci,*** 16(1), 378-400 (2015).
14. K. Chen, J. Zhang, N.M. Beeraka, C. Tang, Y.V. Babayeva, M.Y. Sinelnikov, X. Zhang, J. Zhang, J. Liu, I.V. Reshetov, *et al.*, "Advances in the prevention and treatment of obesity-driven effects in breast cancers", ***Front Oncol,*** 12, 2663 (2022).
15. X. Zhou, J. Zhang, W. Lv, C. Zhao, Y. Xia, Y. Wu and Q. Zhang, "The pleiotropic roles of adipocyte secretome in remodeling breast cancer", ***J Exp Clin Cancer Res,*** 41(1), 1–18 (2022).
16. E. Bandini, T. Rossi, G. Gallerani and F. Fabbri, "Adipocytes and microRNAs crosstalk: A key tile in the mosaic of breast cancer microenvironment", ***Cancers,*** 11(10), 1451 (2019).
17. A.A. Zimta, A.B. Tigu, M. Muntean, D. Cenariu, O. Slaby and I. Berindan-Neagoe, "Molecular links between central obesity and breast cancer", ***Int J Mol Sci,*** 20(21), 5364 (2019).
18. T.L. Whiteside, "The tumor microenvironment and its role in promoting tumor growth", ***Oncogene,*** 27(45), 5904–5912 (2008).
19. A. Schäffler, J. Schölmerich and C. Buechler, "Mechanisms of disease: Adipokines and breast cancer—Endocrine and paracrine mechanisms that connect adiposity and breast cancer", ***Nat Clin Pract Endocrinol Metab***, 3(4), 345–354 (2007).
20. L. Crudele, E. Piccinin and A. Moschetta, "Visceral adiposity and cancer: Role in pathogenesis and prognosis", ***Nutrients,*** 13(6), 2101 (2021).
21. A.A. Hamad, H.M. Mustafa, and O.A. Mohsein, "Correction: Detection of the levels of immune cytokines (IL4, IL5, TNF-α) in school-age and preschoolers with an Ascaris lumbricoides infection," ***J. Parasit. Dis.,***48, 788(2024). doi: 10.1007/s12639-024-01718-7.).
22. T A.D. Hussein et al., "Emerging biomarkers in cancer detection and prognosis: A comprehensive review," ***Int. J. Immunol.,***.7(1), 01–12(2025)
23. Z.K. Abbas, Z.Q.M. Hilo, W.S.A. Hussein, and O.A. Mohsein, "Immunological biomarkers and their role in the diagnosis and prognosis of leishmaniasis: A case–control study," ***Trop. Parasitol.,*** 15(1), 33–41(2025).
24. N. Jafari, M. Kolla, T. Meshulam, J.S. Shafran, Y. Qiu, A.N. Casey, I.R. Pompa, C.S. Ennis, C.S. Mazzeo, N. Rabhi, *et al.*, "Adipocyte-derived exosomes may promote breast cancer progression in type 2 diabetes", ***Sci Signal,*** 14 (710), 2467–2470 (2021).
25. L.E. Hillers-Ziemer, G. Kuziel, A.E. Williams, B.N. Moore and L.M. Arendt, "Breast cancer microenvironment and obesity: Challenges for therapy", ***Cancer Metastasis Rev,*** 41(3), 627–647 (2022).
26. Q.M. Sahi, K.M. Al-Khazal, I.S. Jalil, and O.A. Mohsein, "Assessing the prevalence of bacterial vaginosis among infertile women in Thi-Qar Province, Iraq," ***Int. J. Eval. Med.,*****10(**4), 287–296(2024).
27. H.J. Kim, D. Kim, S.J. Bae, S.G. Ahn, J. Jeong, W.C. Park, Y.H. Ryu, T.J. Jeon, Y. Lee, Y.J. Cha, *et al.*, "18F-FDG uptake of visceral adipose tissue on preoperative PET/CT as a predictive marker for breast cancer recurrence", ***Sci Rep,*** 12(1), 21109 (2022)..
28. J. Niu, L. Jiang, W. Guo, L. Shao, Y. Liu and L. Wang, "The association between leptin level and breast cancer: A meta-analysis", ***PLoS ONE,*** 8(6), e67349 (2013).
29. Y. Gui, Q. Pan, X. Chen, S. Xu, X. Luo and L. Chen, "The association between obesity-related adipokines and risk of breast cancer: A meta-analysis", ***Oncotarget,*** 8(43), 75389–75399 (2017).
30. C. Rodrigo, K.H. Tennekoon, E.H. Karunanayake, K. De Silva, I. Amarasinghe and A. Wijayasiri, "Circulating leptin, soluble leptin receptor, free leptin index, visfatin and selected leptin and leptin receptor gene polymorphisms in sporadic breast cancer", ***Endocr J,*** 64(4), 393–401 (2017).

31. P.K. Raut, D.Y. Choi, S.H. Kim, J.T. Hong, T.K. Kwon, J.H. Jeong and P.H. Park, "Estrogen receptor signaling mediates leptin-induced growth of breast cancer cells via autophagy induction", ***Oncotarget,*** 8(65), 109417 (2017).
32. S. Catalano, L. Mauro, S. Marsico, C. Giordano, P. Rizza, V. Rago, D. Montanaro, M. Maggiolini, M.L. Panno and S. Andó, "Leptin induces, via ERK1/ERK2 signal, functional activation of estrogen receptor alpha in MCF-7 cells", ***J Biol Chem,*** 279(19), 19908–19915 (2004).
33. B. Majed, T. Moreau, K. Senouci, R.J. Salmon, A. Fourquet and B. Asselain, "Is obesity an independent prognosis factor in women breast cancer?", ***Breast Cancer Res Treat,*** 111(2), 329–342 (2008).
34. M. Walter, S. Liang, S. Ghosh, P.J. Hornsby and R. Li, "Interleukin 6 secreted from adipose stromal cells promotes migration and invasion of breast cancer cells", ***Oncogene,*** 28(30), 2745–2755 (2009).
35. F.R. Anter, K. Malinowska, Z. Culig and I.T. Cavarretta, "Interleukin-6 trans-signalling differentially regulates proliferation, migration, adhesion, and maspin expression in human prostate cancer cells", ***Endocrine-related Cancer,*** 17(1), 241–253 (2010).
36. P. Sansone, G. Storci, S. Tavolari, T. Guarnieri, C. Giovannini, M. Taffurelli, *et al.*, "IL-6 triggers malignant features in mammospheres from human ductal breast carcinoma and normal mammary gland", ***J Clin nvest,*** 117(12), 3988–4002 (2007).
37. M. Rincon, G. Broadwater, L. Harris, A. Crocker, D. Weaver, L. Dressler, *et al.*, "Interleukin-6, multidrug resistance protein-1 expression and response to paclitaxel in women with metastatic breast cancer: Results of Cancer and Leukemia Group B Trial 159806", ***Breast Cancer Res Treat,*** 100(3), 301–308 (2006).
38. D. Hanahan and R.A. Weinberg, "Hallmarks of cancer: The next generation", ***Cell,*** 144(5), 646–674 (2011).
39. F. Balkwill, K.A. Charles and A. Mantovani, "Smoldering and polarized inflammation in the initiation and promotion of malignant disease", ***Cancer Cell,*** 7(3), 211–217 (2005).
40. K. Bhat, M. Sarkissyan, Y. Wu and J.V. Vadgama, "GROα overexpression drives cell migration and invasion in triple-negative breast cancer cells", ***Oncol Rep,*** 38(1), 21–30 (2017).

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# تأثير المؤشرات الحيوية الالتهابية والأديبوكاينات على تطور سرطان الثدي ونتائج المرضى

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هدفت دراسة الحالات والشواهد إلى تقييم العلاقة بين المؤشرات الحيوية الالتهابية والأيضية وتطور سرطان الثدي لدى ١٥٠ مريضًا و٥٠ فردًا سليمًا تتراوح أعمارهم بين ٤٠ و٦٠ عامًا. أظهرت النتائج ارتفاعًا معنويًا في مستويات IL-6 وTNF-α وMCP-1 واللبتين لدى مرضى سرطان الثدي، في حين لم يكن هناك فرق معنوي في مستويات IL-10. كما لوحظ ارتباط معتدل بين IL-6 وTNF-α وMCP-1 وشدة المرض، بينما كان ارتباط IL-10 ضعيفًا. علاوة على ذلك، أظهرت مستويات IL-6 وMCP-1 ارتباطًا إحصائيًا قويًا بمعدلات البقاء على قيد الحياة، في حين لم يكن لـ TNF-α وIL-10 واللبتين تأثير معنوي على النتائج السريرية. لم تُلاحظ تغيرات ملحوظة في مستويات المؤشرات الحيوية على مدار الوقت. تدعم هذه النتائج الدور المحوري للالتهاب واضطرابات أيض الدهون في تقدم سرطان الثدي. يشير الارتباط الإيجابي بين IL-6 وTNF-α وMCP-1 وشدة المرض إلى دورها في تعديل بيئة الورم الدقيقة وتعزيز الالتهاب الجهازي. بالإضافة إلى ذلك، ارتبطت مستويات IL-6 وMCP-1 ارتباطًا وثيقًا بنتائج البقاء على قيد الحياة، مما يعزز إمكاناتهما كمؤشرات حيوية تنبؤية. تتماشى هذه النتائج مع الدراسات السابقة التي تربط الأديبوكاينات بزيادة خطر الإصابة بسرطان الثدي، لا سيما في سياق الالتهاب المرتبط بالسمنة. في الختام، تؤكد هذه الدراسة على القيمة التنبؤية لـ IL-6 وMCP-1 وتسلط الضوء على إمكاناتهما في تقييم المرض والعلاج الموجه، مما يوفر فهمًا أعمق للعلاقة بين الالتهاب المزمن وتطور سرطان الثدي.