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Evaluation of the Association Between Tumor Markers, Hormonal Receptors, Inflammatory Biomarkers, and Breast Cancer

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ABSTRACT

Background: Male breast cancer, though rare, requires reliable diagnostic and prognostic markers. This study evaluated tumor markers, hormonal receptors, and inflammatory biomarkers in male breast cancer.

Methods: A case-control study included 150 men with breast cancer and 50 matched controls (aged 38–52 years). Diagnosis was confirmed by clinical evaluation, mammography, and histopathology. Serum was collected and stored at −80 °C. Tumor markers—cancer antigen 15-3 (CA15-3), carcinoembryonic antigen (CEA), and α-fetoprotein (AFP)—and inflammatory biomarkers—interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and C-reactive protein (CRP)—were measured using enzyme-linked immunosorbent assay. Hormonal receptors, estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR), were measured by Cobas e411 immunoassay.

Results: Age and education were similar between the groups. Patients had higher smoking rates (45% vs 20%) and body mass index (28.6 [3.2] vs 26.1 [2.8]). Tumor markers, hormonal receptors, and inflammatory biomarkers were significantly elevated in patients. Strong correlations were found between CA15-3 and IL-6 ($r = 0.68$), ER and CRP ($r = 0.55$), and PR and TNF-α ($r = 0.61$).

Conclusions: Elevated tumor markers, hormonal receptors, and inflammatory biomarkers indicate a link between inflammation, hormonal regulation, and tumor progression, highlighting their diagnostic and prognostic value in male breast cancer.

INTRODUCTION

Cancer is a complex disease involving genetic and epigenetic alterations that disrupt the balance between cell proliferation and death, leading to significant global mortality.[1] For cancer to develop, molecular and tissue-level changes occur. By studying biomolecules such as nucleic acids, proteins, lipids, and metabolites, researchers can identify biomarkers useful for diagnosis and prognosis.[2] Early detection is essential to reducing morbidity and mortality, making the identification of reliable biomarkers critical.[3]

Breast cancer is the most prevalent tumor among women and a leading cause of cancer-related deaths globally. Male breast cancer (MBC), though rare (<1% of cases), is increasing and resembles postmenopausal female breast cancer in behavior. It primarily affects older men, and its risk factors include age, hormonal imbalances, radiation exposure, and family history.[4] The *BRCA2* gene

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mutation is considered the most significant hereditary risk factor.[5] Papillary carcinomas, both in situ and invasive, are more frequent in men, with generally favorable outcomes.[6]

Despite advancements in breast cancer research, MBC remains underexplored and presents distinct clinical and biological challenges compared with female breast cancer. Although accounting for less than 1% of all breast cancer cases, MBC often exhibits delayed diagnosis, higher stage at presentation, and limited treatment options due to the lack of male-specific clinical trials.[6,7] Recent studies highlight differences in hormonal receptor expression, genetic predisposition (particularly *BRCA2* mutations), and tumor biology in men, necessitating tailored diagnostic and therapeutic approaches.[8] Furthermore, social and psychological factors often contribute to diagnostic delays in men, exacerbating poor outcomes.[4] Given these unique aspects, investigating biomarkers specific to MBC is crucial for improving early detection, prognostication, and personalized therapy in this population.[7,8]

Biomarkers play a vital role in identifying, classifying, and monitoring diseases, guiding personalized treatments, and predicting outcomes.[7] Imaging remains essential for breast cancer management, but serum biomarkers can offer earlier insights into disease progression or therapeutic response than imaging alone.[8] However, imaging techniques vary in effectiveness due to differences in technology and practice quality.[9]

Tissue biomarkers like estrogen receptor (ER), progesterone receptor (PR), and HER2 are widely used to guide breast cancer treatment strategies.[10] Blood-based biomarkers are inexpensive and accessible, enhancing their clinical value, although relying on a single marker is limiting.[11] Common tumor-associated autoantibodies include α-fetoprotein (AFP), cancer antigen 125 (CA125), cancer antigen 19-9 (CA19-9), and cancer antigen 15-3 (CA15-3).[12] AFP, typically produced during pregnancy, is also elevated in several tumors, including liver and testicular cancers, and is used primarily for hepatocellular carcinoma detection.[13]

Tumor necrosis factor α (TNF-α) influences cancer cell survival and death and modulates inflammation. While low in healthy serum, it is elevated in patients with breast cancer. One study found 97% of breast cancer samples were positive for TNF-α, although no correlation with survival was noted. Anti–TNF-α therapies, such as infliximab, showed tumor-suppressive effects in animal models.[14,15]

Interleukin 6 (IL-6) also correlates with breast cancer severity. In patients with hormone-refractory breast cancer, elevated IL-6 levels predicted poorer survival.[16] Hormonal receptors—ER, PR, and androgen receptor (AR)—are key in tumor biology and therapeutic response. ER is a strong prognostic marker, especially in men, indicating potential responsiveness to endocrine therapy like tamoxifen. PR coexpression with ER suggests better outcomes, while AR, although less studied in men, also contributes to tumor behavior through androgen interactions.[17,18]

Understanding these hormonal pathways is crucial for diagnosis and targeted therapy, as hormone receptor–positive tumors often respond better to treatment.[19] This study aims to evaluate the diagnostic and prognostic value of tumor markers, hormonal receptors, and inflammatory biomarkers in male breast cancer, with the goal of improving treatment and disease management.

METHODS

A case-control study was conducted on 150 male patients diagnosed with breast cancer and a control group of 50 healthy men. Subjects were aged 38 to 52 years, and the diagnosis was made by specialized physicians based on established clinical criteria. Inclusion criteria were patients diagnosed with breast cancer who agreed to participate; exclusion criteria were patients with severe comorbid conditions, recent infections, or those undergoing immunosuppressive therapy. Ethical approval was obtained from all participants, who signed informed consent forms before enrollment. The study was approved by the Human Ethics Committee of the Thi-Qar Health Directorate, Al-Habbobi Teaching Hospital, Thi-Qar, Iraq (Approval No. 465, January 2024).

The control group consisted of 50 healthy men who were matched to cases by age, body mass index (BMI) category, and smoking status to minimize confounding. Lifestyle factors, including alcohol use and physical activity, were assessed through structured interviews to ensure comparability. All controls were selected from the same geographic region and had no history of cancer, chronic illness, or recent infections. To address potential residual confounding, statistical adjustments were made for age, BMI, and smoking status in the analysis. The previously noted discrepancy in average ages was corrected to maintain consistency across all sections. Frequency matching was used for age (5-year intervals), BMI category, and smoking status to enhance comparability between groups. Due to lower smoking prevalence among the controls, a perfect balance was not achieved; thus, analyses were adjusted for these variables.

Blood samples were collected via venipuncture into sterile tubes, and serum was separated by

centrifugation at 3000 rpm for 10 minutes and stored at −80 °C until analysis. Biomarkers, including IL-6, TNF-α, CRP, CA15-3, carcinoembryonic antigen (CEA), and AFP, were measured using enzyme-linked immunosorbent assay kits from BioTech. Hormone levels (ER, PR, and AR) were analyzed using the Cobas e411 analyzer (Roche). This study was conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline for observational research. All biomarkers, including tumor markers (CA15-3, CEA, AFP), hormonal receptors (ER, PR, AR), and inflammatory biomarkers (IL-6, TNF-α, CRP), were measured after the confirmation of breast cancer diagnosis and prior to the initiation of any therapeutic intervention. Blood samples were collected immediately after diagnosis to ensure baseline values without treatment influence.

Statistical analysis

Statistical analyses were performed using both parametric and non-parametric methods, as appropriate. The normality of continuous variables was evaluated using the Shapiro-Wilk test. For variables following a normal distribution, comparisons between independent groups were conducted using the independent 2-tailed *t* test. For nonnormally distributed variables, the Mann-Whitney *U* test was applied for independent samples. Categorical variables were assessed using the χ^2 test. A *P* value of less than .05 was considered indicative of statistical significance. Associations among key biomarkers were evaluated using Pearson correlation coefficient (*r*), with *P* values indicating statistical significance. Multinomial logistic regression analysis was performed to identify independent predictors of tumor regression grade. The dependent variable was tumor regression grade, and clinicopathologic features were included as predictors. Odds ratios (ORs) with 95% CIs were calculated to quantify the associations, with *P* values <0.05 considered statistically significant.

RESULTS

Sociodemographic and lifestyle characteristics of study participants

Table 1 shows the sociodemographic characteristics of the participants. No significant differences were recorded in age or educational level between the patients and the control group ($P = 0.60$ and $P = 0.20$, respectively), indicating that the 2 groups were similar in these variables. However, the results showed statistically significant differences in some lifestyle-related factors, as the smoking rate was higher among patients compared with healthy controls (45.3% vs 20.0%; $P = 0.01$). It was also found that the BMI was higher among patients, with higher rates of overweight and obesity ($P = 0.02$).

Table 1. Sociodemographic Characteristics of Study Participants

Variable	Patients (n = 150)	Controls (n = 50)	*P* value
Age, y			
<40	35 (23.3%)	14 (28.0%)	0.60
40–49	80 (53.3%)	25 (50.0%)	
≥50	35 (23.3%)	11 (22.0%)	
Education level			
High school	90 (60.0%)	35 (70.0%)	0.20
Higher education	60 (40.0%)	15 (30.0%)	
Smoking status			
Smokers	68 (45.3%)	10 (20.0%)	0.01
Nonsmokers	82 (54.7%)	40 (80.0%)	
Body mass index			
Normal (<25)	25 (16.7%)	18 (36.0%)	0.02
Overweight (25–29.9)	70 (46.7%)	22 (44.0%)	
Obese (≥30)	55 (36.7%)	10 (20.0%)	

Tumor marker levels in study participants

As shown in Table 2, serum levels of tumor markers were significantly elevated in patients compared with the control group. The mean (SD) level of CA15-3 in the cases was 45.2 (15.6) U/mL, which was significantly higher than the control group's level of 18.5 (6.4) U/mL ($P < 0.001$). The amount of CEA in the blood was also significantly higher in the patients (8.3 [2.5] ng/mL) compared with the control group (2.1 [0.9] ng/mL) ($P < 0.001$). Their AFP level in patients was 7.8 (3.4) ng/mL, which was significantly higher than the controls' level of 3.2 (1.2) ng/mL ($P < 0.001$). These statistically significant differences show how these markers can be useful across subjects in differentiating patients from healthy controls.

Table 2. Comparison of Tumor Marker Levels Between Patients and Controls

Marker	Patients, mean (SD)	Controls, mean (SD)	*P* value
CA15-3, U/mL	45.2 (15.6)	18.5 (6.4)	<0.001
CEA, ng/mL	8.3 (2.5)	2.1 (0.9)	<0.001
AFP, ng/mL	7.8 (3.4)	3.2 (1.2)	<0.001

AFP, α-fetoprotein; CA15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen.

Hormonal receptor levels in study participants

Table 3 shows significant differences in hormone receptor levels between patients and controls. ER expression was 65.4% (10.2%) in patients vs 12.3% (4.5%) in controls ($P < 0.001$). PR expression was significantly higher in patients (54.8% [9.6%]) than in controls (10.1% [3.8%]; $P < 0.001$). AR levels were also higher in patients (48.6% [8.7%]) than in

controls (15.2% [5.2%]) ($P < 0.001$). These findings suggest a strong association between elevated hormone receptor expression and the development of the disease.

Table 3. Comparative Assessment Between Patients and Controls

Hormonal receptor	Patients, mean (SD)	Controls, mean (SD)	*P* value
Estrogen receptor, %	65.4 (10.2)	12.3 (4.5)	<0.001
Progesterone receptor, %	54.8 (9.6)	10.1 (3.8)	<0.001
Androgen receptor, %	48.6 (8.7)	15.2 (5.2)	<0.001

Inflammatory biomarker levels in study participants

As shown in Table 4, all assessed inflammatory markers were significantly elevated in patients compared with controls ($P < 0.001$). This included IL-6, TNF-α, and CRP, indicating a pronounced systemic inflammatory response in male breast cancer. These findings emphasize the potential role of inflammation in disease pathogenesis and highlight these biomarkers as valuable indicators for risk assessment and monitoring.

Table 4. Comparative Analysis between Patients and Controls

Biomarker	Patients, mean (SD)	Controls, mean (SD)	*P* value
IL-6, pg/mL	18.2 (5.7)	4.6 (1.2)	<0.001
TNF-α, pg/mL	32.5 (9.4)	12.3 (3.8)	<0.001
CRP, mg/L	15.8 (4.2)	3.1 (1.0)	<0.001

CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.

Correlation between tumor markers, hormonal receptors, and inflammatory biomarkers

As shown in Table 5, significant correlations ($P < 0.05$) were observed between inflammatory markers, hormonal receptors (ER and PR), and tumor markers (CA15-3 and CEA). A strong positive correlation was identified between CA15-3 and IL-6 ($r = 0.68$; $P < 0.001$). A moderate positive correlation was found between ER levels and CRP ($r = 0.55$; $P < 0.001$), suggesting that inflammation may influence hormonal expression. Similarly, a strong positive relationship was observed between PR levels and TNF-α ($r = 0.61$; $P < 0.001$). These findings illustrate the complex interconnections between inflammatory processes, hormonal regulation, and tumor progression.

Table 5. Statistical Associations Among Key Biomarkers

Variable 1	Variable 2	Correlation coefficient (r)	*P* value
CA15-3	IL-6	0.68	<0.001
Estrogen receptor	CRP	0.55	<0.001
Progesterone receptor	TNF-α	0.61	<0.001

CA15-3, cancer antigen 15-3; CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.

Adjusted odds ratios of biomarkers for male breast cancer

The results presented in Table 6 demonstrate that all investigated biomarkers were significantly associated with male breast cancer, even after adjustment for potential confounders, including age, BMI, and smoking. Adjusted logistic regression analyses revealed that tumor markers, namely CA15-3 (adjusted OR [AOR], 4.85; 95% CI, 2.60–9.05), CEA (AOR, 5.10; 95% CI, 2.40–10.8), and AFP (AOR, 3.95; 95% CI, 1.95–8.00), were significantly associated with an increased risk of male breast cancer. Likewise, hormonal receptors, including ER (AOR, 6.25; 95% CI, 3.10–12.6), PR (AOR, 5.40; 95% CI, 2.80–10.2), and AR (AOR, 4.10; 95% CI, 2.00–8.35) showed strong positive associations with the disease. Among inflammatory biomarkers, IL-6 (AOR, 7.20; 95% CI, 3.50–14.9), TNF-α (AOR, 4.85; 95% CI, 2.30–10.2), and CRP (AOR, 6.10; 95% CI, 2.95–12.6) were identified as the most strongly associated markers, highlighting their potential role in the pathogenesis of male breast cancer.

Table 6. Adjusted Odds Ratios (OR) for Biomarkers Associated with Male Breast Cancer After Controlling for Age, Body Mass Index, and Smoking

Biomarkers	Crude OR (95% CI)	Adjusted OR (95% CI)
Tumor markers		
CA15-3, U/mL	4.50 (2.40-8.50)	4.85 (2.60-9.05)
CEA, ng/mL	4.90 (2.30-10.0)	5.10 (2.40-10.8)
AFP, ng/mL	3.80 (1.85-7.80)	3.95 (1.95-8.00)
Hormonal receptors		
ER, %	6.00 (2.95-12.2)	6.25 (3.10-12.6)
PR, %	5.15 (2.65-9.90)	5.40 (2.80-10.2)
AR, %	3.95 (1.90-8.10)	4.10 (2.00-8.35)
Inflammatory biomarkers		
IL-6, pg/mL	7.00 (3.40-14.5)	7.20 (3.50-14.9)
TNF-α, pg/mL	4.65 (2.20-9.85)	4.85 (2.30-10.2)
CRP, mg/L	5.95 (2.85-12.3)	6.10 (2.95-12.6)

AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor. *P* for all values <0.001

DISCUSSION

The present study provides a comprehensive analysis of demographic, biochemical, immunological, and hormonal factors in relation to male breast cancer incidence and progression. Although age ($P = 0.60$) and education level ($P = 0.20$) did not differ significantly between patients and controls, indicating a potentially limited role in disease susceptibility, smoking ($P = 0.01$) and BMI ($P = 0.02$) were significantly higher among patients. These results corroborate previous findings that identify smoking as a contributor to oxidative stress and chronic inflammation, key drivers of carcinogenesis.[20] Elevated BMI is similarly implicated in enhancing systemic inflammation and metabolic dysfunction, which may facilitate tumor development, as noted by Konishi *et al.*[21]

Contrasting reports, such as those by Brown *et al.* (2019) and Alsayer *et al.*[22], have observed no significant links between these risk factors and male breast cancer, reflecting the multifactorial nature and heterogeneity of this disease. These discrepancies suggest that the impact of smoking and obesity may vary across populations, influenced by genetic predispositions and environmental exposures. Our findings emphasize the importance of considering lifestyle factors in male breast cancer risk assessment and highlight the need for further research to elucidate their mechanistic roles.[23]

Tumor marker analysis revealed significantly elevated levels of CA15-3, CEA, and AFP in patients compared with controls ($P < 0.001$). This agrees with Ryu *et al.*[24], who highlighted CA15-3 as a reliable tumor progression marker, and Zou *et al.*[25], who emphasized the role of CEA in cancer-related inflammation. The rise in AFP supports the findings reported by Zhu *et al.*[26], who recognized AFP's diagnostic value in several malignancies, although Khan and Tirona[27] raised concerns regarding marker specificity, as elevations may also occur in benign or inflammatory conditions. These findings support the utility of tumor markers in diagnosis and prognosis but also stress the importance of enhancing their specificity through integrated clinical evaluation.

Regarding hormonal receptors, patients exhibited significantly higher expression of ER, PR, and AR ($P < 0.001$), with increases of 92%, 61%, and 86%, respectively. These findings align with those reported by Reinisch *et al.*[28], who reported overexpression of ER and PR in hormone-sensitive cancers, and Wang *et al.*[29], who emphasized the role of AR in hormonally influenced malignancies. However, Yardley *et al.*[30] noted heterogeneity in receptor expression, reflecting variability in tumor subtypes and disease biology.

Elevated hormone receptor levels in male breast cancer have important clinical implications. Hormone receptor positivity suggests that tumor growth is driven by hormonal signaling, making patients suitable candidates for endocrine therapies such as tamoxifen or aromatase inhibitors, which have demonstrated efficacy in improving patient outcomes.[31] Given the unique endocrine environment in men, understanding receptor status is critical to tailoring treatment strategies. Moreover, receptor heterogeneity and dysregulated hormonal signaling, including receptor cross-talk, may influence treatment response and resistance, highlighting the necessity of comprehensive hormonal profiling. Integrating hormone receptor evaluation into clinical decision-making enhances personalized therapy, potentially improving prognosis and disease management in male breast cancer.[32]

Inflammatory biomarkers IL-6, TNF-α, and CRP were also significantly elevated in patients ($P < 0.001$), suggesting a strong link between inflammation and disease presence. These findings are in line with those reported by Tsoi *et al.*[33], who identified IL-6 as a central inflammatory mediator in disease progression, and Gu *et al.*,[34] who underlined TNF-α's role in immune modulation. Romero-Elías *et al.*[35] also supported CRP as a sensitive inflammation marker. While Parimelazhagan *et al.*[36] reported variability in biomarker levels across individuals, our results confirm the central role of chronic inflammation, oxidative stress, and immune activation in disease pathology.[37]

Correlations among biomarkers further enhance understanding of the disease mechanisms. A strong positive correlation was observed between the tumor marker CA15-3 and IL-6 ($r = 0.68$; $P < 0.001$), consistent with findings by Tarighati *et al.*[38], indicating an inflammatory component in tumor progression. ER levels showed a moderate positive correlation with CRP ($r = 0.55$; $P < 0.001$), in line with the results reported by Cairat *et al.*[39], suggesting a link between hormonal activity and systemic inflammation. Furthermore, PR expression was strongly correlated with TNF-α ($r = 0.61$; $P < 0.001$), supporting Hussain *et al.*[40] regarding the immunomodulatory role of hormone receptors in tumor biology. These significant correlations highlight the interconnected roles of inflammation, hormone receptor expression, and tumor markers in male breast cancer pathophysiology, emphasizing the clinical relevance of integrated biomarker evaluation for improved diagnosis and prognosis.

While this study provides valuable insights into the diagnostic and prognostic role of tumor markers, hormonal receptors, and inflammatory biomarkers in male breast cancer, certain limitations should be noted. The limited sample size and narrow demographic and geographic focus may limit the

generalizability of the result. Additionally, the case-control design does not establish causality and may introduce selection bias. Despite these limitations, the strong biomarker associations observed highlight the potential clinical relevance of these indicators and support further large-scale, longitudinal investigations.

CONCLUSION

In conclusion, the interconnection between tumor markers, hormone receptors, and inflammatory biomarkers suggests an integrated disease mechanism, where inflammation, hormonal dysregulation, and tumor activity interact. The findings support the combined assessment of these variables for better diagnosis, prognosis, and therapeutic targeting. However, interindividual variability and conflicting findings in the literature highlight the need for larger, longitudinal studies to further explore these complex interactions.

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CONFLICTS OF INTEREST

The authors in this study have no financial or nonfinancial interests to disclose.

ETHICAL CONSIDERATIONS

The study was approved by the Human Ethics Committee of the Thi-Qar Health Directorate, Al-Habbobi Teaching Hospital, Thi-Qar, Iraq (Approval No. 465, January 2024). All participants were fully informed about the purpose and procedures of the study and provided written informed consent. Participants were also assured that their personal information would be kept strictly confidential.

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DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. All data supporting the findings of this study are included in the article and its supplementary materials. No publicly available repositories were used for this study.

AI DISCLOSURE

Artificial intelligence tools were used only for language editing. The authors take full responsibility for the content of the manuscript.

AUTHOR CONTRIBUTIONS

MHG: Conceptualization; Methodology; Formal analysis; Writing–original draft; ZAM: Data curation; Investigation; Writing–review & editing; SKA: Visualization; Validation; Resources; OAM: Supervision; Project administration; Funding acquisition; Writing–review & editing.

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