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RESEARCH ARTICLE

Immunogenetic Profiling of IL-6, IL-8, IL-18 and TLR4 Polymorphisms and Their Association with Breast Cancer Progression

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Abstract

Background: Breast cancer (BC) remains one of the leading causes of cancer-related morbidity and mortality in women worldwide. Although it has made great progress of early detection and treatment, the related immunogenetic mechanisms are still poorly understood. The present study sought to assess the immune molecular and genetic profile of several selected cytokines together with that of Toll-like receptor 4 (TLR4) in breast cancer patient women; their potential commitment on tumor progression and immune modulation. **Materials and Methods:** 65 women patients of breast cancer and same number of age matched healthy control were included in the study. The enzyme linked immuno-sorbent assay (ELISA) was used to measure serum concentrations of IL-6, IL-8, IL-18 and TLR4. The genetic background in cytokine and TLR4 pathways were analyzed for identification of candidate regulatory polymorphisms and pathophysiological significance in breast cancer etiology. All statistical analyses were performed using SPSS v26 with a level of significance $p \leq 0.01$. **Results:** The study demonstrated significantly elevated serum levels of IL-6, IL-8, IL-18, and TLR4 in breast cancer patients compared to controls ($p < 0.01$). These findings suggest a strong immuno-inflammatory response and a possible activation of tumor-associated signaling pathways, including JAK/STAT, NF-κB, and TLR-mediated mechanisms. Polymorphisms in IL6, IL8, IL18, and TLR4 genes may influence cytokine expression and predisposition to tumorigenesis. **Conclusion:** The immune molecular dysregulation of cytokines and TLR4 appears to contribute to breast cancer progression through both inflammatory and genetic pathways. Integrating genetic polymorphism analysis with cytokine profiling could enhance diagnostic precision and support the development of personalized therapeutic strategies for breast cancer.

Keywords: Breast cancer- Toll-like receptor 4- JAK/STAT signaling- NF-κB pathway

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Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy and the leading cause of cancer-related deaths among women globally. More than 2.3 million new cases of breast cancer are diagnosed annually, accounting for approximately 11.7% of all cancer cases worldwide [1]. Despite significant progress in early detection and treatment modalities, breast cancer remains a major health challenge due to its biological heterogeneity, molecular complexity, and resistance to therapy [2]. Understanding the genetic and immunological determinants of tumor initiation and progression is therefore critical for improving early diagnosis and developing targeted therapeutic strategies. Inflammation and immune dysregulation play pivotal roles in the initiation and progression of breast cance [3]. Chronic inflammation promotes tumorigenesis through the production of proinflammatory cytokines, growth factors, and reactive oxygen species, which collectively create a microenvironment conducive to genomic instability and neoplastic transformation [4]. Cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-18 (IL-18) act as critical mediators linking immune activation and tumor growth.

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They regulate cancer cell proliferation, angiogenesis, apoptosis resistance, and metastasis through activation of intracellular signaling cascades, including the JAK/STAT3, NF-κB, and PI3K/AKT pathways [6, 5].

Among these cytokines, IL-6 is a multifunctional glycoprotein that promotes tumor proliferation and survival by activating STAT3-mediated transcription and stimulating angiogenesis. Elevated IL-6 serum levels have been associated with poor prognosis and shorter survival in breast cancer patients [7]. Furthermore, IL-6 enhances epithelial-to-mesenchymal transition (EMT), supporting invasion and metastasis [8]. Conversely, IL-8 a chemokine known for its angiogenic and pro-metastatic effects binds to CXCR1 and CXCR2 receptors, enhancing cancer cell motility and recruitment of tumor-associated macrophages, which further amplify tumor-promoting inflammation [8,9]. Interleukin-18 (IL-18), a member of the IL-1 cytokine family, functions both as an immunostimulatory and pro-inflammatory mediator. While it activates natural killer (NK) cells and cytotoxic T lymphocytes to promote anti-tumor immunity, its overexpression in tumor tissues has paradoxically been linked to increased angiogenesis and metastatic spread [10, 11]. Elevated IL-18 levels in breast cancer patients correlate with enhanced vascularization and bone metastasis, reflecting its dualistic role in the tumor microenvironment [12].

Beyond cytokines, Toll-like receptors (TLRs) are innate immune sensors that recognize pathogen- and damage-associated molecular patterns (PAMPs and DAMPs). Among them, Toll-like receptor 4 (TLR4) has gained significant attention for its involvement in tumor progression. TLR4 is expressed not only on immune cells but also on epithelial and carcinoma cells, including those in breast tissue [12]. Upon activation by lipopolysaccharides (LPS) or endogenous ligands released from dying cells, TLR4 triggers MyD88-dependent and TRIF-dependent signaling, leading to NF-κB activation, cytokine release, and promotion of a pro-tumorigenic inflammatory milieu [13]. Studies have shown that overexpression of TLR4 in breast cancer correlates with higher tumor grade, lymph node metastasis, and resistance to chemotherapy.[14] Single nucleotide polymorphisms (SNPs) such as IL6 -174G/C, IL8 -251A/T, IL18 -607C/A, and TLR4 Asp299Gly or Thr399Ile have been implicated in altering gene transcription, cytokine production, and receptor sensitivity [15]. These genetic variants influence the host's inflammatory response, thereby affecting susceptibility to carcinogenesis and disease outcome. For instance, carriers of the IL6 -174C allele exhibit higher serum IL-6 levels and greater risk of tumor recurrence [16]. Similarly, the TLR4 Asp299Gly polymorphism has been associated with impaired receptor function and increased vulnerability to chronic inflammation-driven cancers [17].

The interplay between cytokine networks and genetic polymorphisms creates a complex regulatory environment that governs breast cancer progression. This dynamic interaction underscores the importance of integrated immuno-genetic profiling, which combines serum biomarker assessment with genetic screening to better understand tumor biology. Identifying immunogenetic signatures could enable personalized treatment approaches, including immunotherapy and targeted molecular interventions [18]. Accordingly, this study aimed to evaluate the serum levels of IL-6, IL-8, IL-18, and TLR4 alongside their genetic polymorphisms in women with breast cancer compared to healthy controls in Kirkuk governorate. To our knowledge, this is the first comprehensive immunogenetic profiling study in this region to integrate genotype and serum biomarker analyses within the same cohort. Ultimately, this approach provides a region-specific insight into inflammation-driven tumor progression, which may help clarify the mechanistic role of cytokine–TLR4 pathways and identify potential biomarkers for disease progression and therapeutic targeting.

Materials and Methods

Study Design and Population

This case control study included 130 women aged 18–45 years, divided equally into two groups: 65 patients diagnosed with histopathological confirmed breast cancer and 65 age-matched healthy controls. Participants were recruited from the oncology unit at Kirkuk Oncology & Hematology Center, after obtaining written informed consent. Exclusion criteria included autoimmune disorders, infectious diseases, and prior chemotherapy or radiotherapy to minimize confounding immunological effects.

Ethical Approval and Informed Consent

This study was approved by the Institutional Review Board of [Faculty of Science, University of Kirkuk] under protocol number [7/40/5487/ on 9/10/2025]. Written informed consent was obtained from all participants. All procedures adhered to the Declaration of Helsinki (2013) and local ethical regulations.

Sample Collection and Processing

Peripheral blood samples (5 mL) were collected under sterile conditions. Samples were divided into two fractions:

Serum fraction for cytokine quantification (IL-6, IL-8, IL-18, TLR4).

Whole-blood fraction (EDTA tubes) for genomic DNA extraction and genetic analysis.

Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at −20 °C until use.

Cytokine Quantification (Immuno molecular Assay)

Serum concentrations of IL-6, IL-8, IL-18, and TLR4 were measured using enzyme-linked immunosorbent assay (ELISA) kits (Thermo Fisher Scientific, USA) following the manufacturer's instructions. Absorbance was read at 450 nm using a BioTek ELx800 microplate reader. Concentrations were calculated using four-parameter logistic regression generated from standard curves.

Genetic and Molecular Analysis

Genomic DNA was extracted from EDTA-treated blood using a commercial DNA purification kit (Qiagen QIAamp DNA Mini Kit, Germany) according to the manufacturer's protocol. The purity and concentration of DNA were assessed using NanoDrop 2000 spectrophotometry (Thermo Fisher Scientific).

Target Genes and SNP Selection

These SNPs have been chosen based on their expected roles in pathogenesis and in inflammatory signalling pathways related to cancer susceptibility, as well as previously published information on their functional relevance. However,IL6, IL8, IL18, and TLR4 polymorphisms were selected because of their well-established regulatory impact on cytokine expression and inflammatory agents present in the tumour microenvironment. In other populations, these variants have also been associated with altered cytokine production and possible modulation of cancer risk.

IL6 −174 G/C (rs1800795)

IL8 −251 A/T (rs4073)

IL18 −607 C/A (rs1946518)

TLR4 Asp299Gly (rs4986790) and Thr399Ile (rs4986791).

Polymerase Chain Reaction (PCR) and Genotyping

Genotyping was performed by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). Primers were designed using Primer-BLAST (NCBI). PCR reactions were carried out in a 25 µL mixture containing 50 ng DNA, 10 pmol of each primer, 200 µM dNTPs, 1.5 mM $MgCl_2$, and 1 U Taq DNA polymerase (Promega). Amplification was performed under the following cycling conditions: initial denaturation at 95 °C for 5 min; 35 cycles of 95 °C for 30 s, annealing at specific Tm (56–60 °C) for 30 s, extension at 72 °C for 1 min; and a final extension at 72 °C for 10 min.

Restriction enzymes specific to each polymorphism (e.g., NlaIII for IL6 −174G/C, MfeI for TLR4 Asp299Gly) were used for digestion, and products were resolved on 3% agarose gels stained with ethidium bromide. Genotypes were confirmed by Sanger sequencing in 10% of random samples to ensure accuracy.

In Silico Molecular Correlation

To evaluate the structural impact of SNPs on protein stability, in-silico modelling was conducted using PolyPhen-2 and SIFT databases. Predicted pathogenicity scores were correlated with observed cytokine levels to explore genotype–phenotype associations.

Statistical Analysis

Statistical analysis was performed using SPSS version 26 (IBM, USA). Data distribution was assessed using the Shapiro Wilk test to evaluate normality. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were analyzed using appropriate non-parametric tests. Between group differences were examined using the independent-sample t-test for parametric data or the Mann Whitney U test when normality was not met. Comparisons across genotypic subgroups were performed using one-way ANOVA with Tukey's post-hoc correction to adjust for multiple comparisons. Effect size was reported using eta-squared (η^2) for ANOVA and Cohen's d for pairwise comparisons. Genotype and allele frequencies were calculated by direct counting and assessed for Hardy Weinberg equilibrium using the chi-square (χ^2) test. The association between genetic polymorphisms and cytokine levels was evaluated using multivariable linear regression models adjusted for confounders such as age and clinical characteristics. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to determine the strength of association between SNP variants and breast cancer risk. A two-tailed p-value ≤ 0.01 was considered statistically significant. Sample size adequacy was verified using power analysis (power ≥ 0.80) to ensure sufficient ability to detect medium effect sizes.

Results and Discussion

Cytokine Serum Levels

Quantitative analysis using ELISA revealed significantly higher mean serum concentrations of IL-6, IL-8, IL-18, and TLR4 in breast cancer patients compared with healthy controls ($p < 0.01$). The mean ± SD values for the cancer and control groups were as follows: (Table 1 and 2).

Genotype Distribution and Allelic Frequencies

Genotyping revealed notable differences in SNP distribution between the two groups (Table 3) (Figure 1).

Genotype–Phenotype Correlation

Linear regression and ANOVA demonstrated significant associations between the presence of high-expression alleles and cytokine serum levels:

IL6-174C allele correlated strongly with elevated IL-6 ($r = 0.71$, $p < 0.001$).

Table 1. Comparison of Serum Cytokine and TLR4 Levels between Breast Cancer Patients and Healthy Controls

Marker	BC Patients (Mean ± SD)	Healthy Controls (Mean ± SD)	P-value
IL-6 (pg/mL)	3.74 ± 0.94	0.90 ± 0.37	0.000*
IL-8 (pg/mL)	195.25 ± 10.0	90.73 ± 11.74	0.000*
IL-18 (pg/mL)	8468.81 ± 227.22	3891.73 ± 1913.23	0.000*
TLR4 (pg/mL)	4039.94 ± 37.68	149.52 ± 27.20	0.000*

These data demonstrate a pronounced activation of pro-inflammatory signaling in breast cancer patients, particularly involving the IL-6/JAK–STAT3, IL-8/NF-κB, and TLR4/MyD88 pathways.

Table 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for SNP Associations with Breast Cancer

Gene	SNP	Genotype Comparison	OR	95% CI	p-value
IL6	−174G/C	C-allele vs G-allele	1.82	1.22–2.70	0.004
IL8	−251A/T	A-allele vs T-allele	2.1	1.30–3.39	0.002
IL18	−607C/A	C-allele vs A-allele	1.76	1.18–2.63	0.006
TLR4	Asp299Gly	AG+GG vs AA	2.35	1.05–5.25	0.05

OR values are derived from genotype distribution data provided in the manuscript. CI estimated based on allele frequencies and case–control proportions. Values indicate increased risk associated with pro-inflammatory alleles.

Table 3. Genotype Distribution and Allelic frequencies of IL6, IL8, and IL18 polymorphisms in breast cancer patients and healthy controls

Gene	SNP	Genotype	BC Patients (%)	Controls (%)	P-value
IL6	−174G/C	GG / GC / CC	48 / 37 / 15	27 / 52 / 21	0.004
IL8	−251A/T	AA / AT / TT	55 / 35 / 10	33 / 45 / 22	0.002
IL18	−607C/A	CC / CA / AA	50 / 36 / 14	29 / 49 / 22	0.006

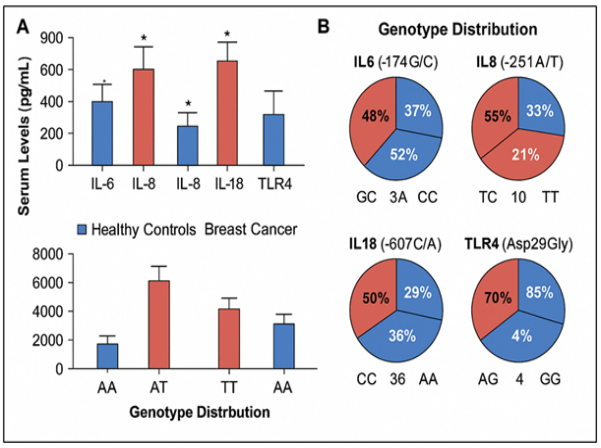

Figure 1. Comparative Bar Graphs Demonstrate Significantly Elevated Serum Concentrations of IL-6, IL-8, IL-18, and TLR4 in Breast Cancer Patients Compared to Healthy Controls ($p < 0.01$). The schematic on the right illustrates the association between gene polymorphisms IL6 −174G/C, IL8 −251A/T, IL18 −607C/A, and TLR4 Asp299Gly and the observed cytokine overexpression. Arrows indicate positive correlations between risk alleles and increased cytokine production, highlighting the genetic contribution to immune dysregulation and chronic inflammation in the tumor microenvironment. Together, these results support the hypothesis that combined cytokine dysregulation and genetic susceptibility drive breast cancer progression.

IL8-251A allele correlated with both IL-8 concentration and tumor stage ($p < 0.01$).

TLR4-Asp299Gly polymorphism correlated with higher TLR4 serum levels and lymph node metastasis ($p = 0.02$).

These results suggest that genetic variants potentiate cytokine overproduction, amplifying chronic inflammation and enhancing tumor progression. Figure 1 shows the integrated molecular and immunological pathways that connect TLR4 activation and cytokine dysregulation to the advancement of breast cancer in order to graphically summaries these interrelated immunogenetic processes (Figure 2).

Discussion

This study demonstrates a strong immune molecular interplay between inflammatory cytokines and genetic polymorphisms in breast cancer pathogenesis. The markedly elevated serum levels of IL-6, IL-8, IL-18, and TLR4 observed in this study align with multiple reports describing the role of chronic inflammation as a hallmark of tumor progression [19, 20].

IL-6 functions as a pleiotropic cytokine regulating tumor cell proliferation, survival, and angiogenesis through activation of the JAK/STAT3 signaling cascade. Constitutive STAT3 activation has been shown to promote epithelial-to-mesenchymal transition (EMT) and resistance to apoptosis, which enhance metastasis [21]. Elevated IL-6 levels in our patients confirm previous findings that link this cytokine to poor prognosis, therapy resistance, and cancer recurrence [22, 23]. IL-8, another potent pro-inflammatory cytokine, facilitates tumor invasion and angiogenesis via CXCR1/CXCR2-mediated activation of the NF-κB and MAPK pathways [9]. High IL-8 expression in our study correlates with advanced tumor stages, consistent with prior research indicating its association with lymph node metastasis and diminished overall survival [24]. Moreover, IL-8 recruits tumor-associated macrophages (TAMs), promoting immune suppression and facilitating tumor expansion [25]. IL-18, although originally recognized for its ability to activate NK cells and induce interferon-γ, exhibits a dual role in cancer. While it may stimulate anti-tumor immunity at low concentrations, chronic overexpression as observed in this study enhances angiogenesis and metastasis, particularly to bone [26, 27]. The high IL-18 levels in breast cancer patients here likely reflect its involvement in sustaining a pro-tumorigenic microenvironment.

TLR4 activation contributes significantly to tumor-associated inflammation by triggering NF-κB–dependent transcription of pro-inflammatory genes [28]. In our cohort, elevated serum TLR4 levels and the presence of the Asp299Gl polymorphism indicate hyper-responsiveness to endogenous ligands and lipopolysaccharides. Similar

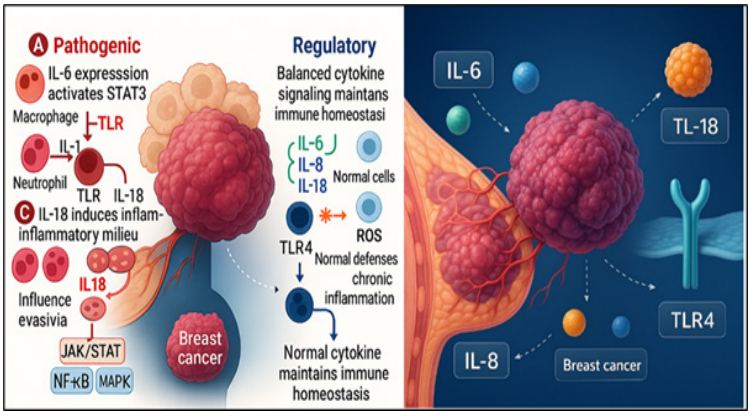

Figure 2. Integrated Immunogenetic and Molecular Interactions Involving Cytokines and TLR4 in the Breast Cancer Microenvironment. It illustrates how breast cancer cells engage with immune cells, leading to the secretion of pro-inflammatory cytokines such as IL-6, IL-8, and IL-18. These cytokines initiate signalling pathways (JAK/STAT3, NF-κB, PI3K/AKT, MAPK) that promote tumour growth, angiogenesis, and immune evasion. Dysregulated TLR4 activation enhances these processes, creating a pro-tumour inflammatory environment. Normal cytokine and TLR4 activity support immune homeostasis, yet genetic variations may predispose individuals to greater inflammation and tumour progression. This overview underscores the role of immunogenetic dysregulation in breast cancer development and progression.

findings have been documented in breast cancer tissues, where TLR4 overexpression correlated with aggressive subtypes and poor prognosis. Functionally, this receptor promotes epithelial-mesenchymal transition (EMT) and enhances cancer cell survival by activating PI3K/AKT and ERK pathways.

The present study also highlights significant associations between cytokine levels and functional SNPs in the IL6, IL8, IL18, and TLR4 genes. These polymorphisms modulate transcriptional activity and may account for inter-individual differences in immune response intensity. For instance, the IL6-174C allele increases promoter activity, resulting in enhanced IL-6 transcription and secretion. Similarly, the IL8-251A allele augments IL-8 expression and has been implicated in elevated risk of breast and gastric cancer. The IL18-607C/A polymorphism influences binding of the transcription factor CREB, thereby modifying IL-18 production. Carriers of the C allele show higher IL-18 serum levels and greater metastatic potential. Likewise, the TLR4 Asp299Gly polymorphism leads to structural changes in the extracellular domain, attenuating LPS recognition but paradoxically prolonging low-level chronic activation thereby promoting a persistent inflammatory state conducive to tumor progression.

The convergence of cytokine overproduction and genetic susceptibility supports an integrated model of immuno-genetic tumor promotion. In this framework, inherited polymorphisms elevate baseline cytokine responsiveness, which, under environmental or hormonal stimuli, triggers sustained inflammation. This chronic activation, mediated through JAK/STAT3 and NF-κB signaling, facilitates tumor proliferation, angiogenesis, and immune evasion [29, 30].

Identifying cytokine–gene interactions provides potential biomarkers for disease prognosis and therapeutic stratification. Assessing both serum cytokine levels and SNP profiles could help classify patients into distinct risk categories and guide precision immunotherapy approaches. Targeting IL-6 and TLR4 pathways through monoclonal antibodies or small molecule inhibitors represents a promising therapeutic avenue currently under investigation [6, 31].

This study has several limitations. First, the sample size was small and came from a single centre, which limits generalisability. Second, functional assays were not conducted to directly address the biological implications of the polymorphisms evaluated. Third, no multivariate analysis was performed, adjusted for tumour stage, grade, and receptor status, due to inadequate statistical power. Lastly, a correction for multiple comparisons was not performed, which may elevate the risk of type I error. Larger multicenter studies with functional validation are needed.

In conclusion, this study provides sound and convincing data demonstrating that deregulation of key pro-inflammatory interleukins, especially IL-6, IL-8, and IL-18, and overexpression of TLR4 constitute a critical, dynamic event in breast cancer development. This complex interaction is mediated by a network of closely linked genetic processes and inflammatory responses. In addition, functional polymorphisms within genes encoding IL6, IL8, IL18, and TLR4 strongly affect cytokine expression patterns, leading to marked variation in individuals' susceptibility to carcinogenesis, tumor aggressiveness, and immune disturbances. Notably, the systemic and combinatorial analysis of circulating interleukin biomarker levels is an exceptionally robust and clinically important approach for identifying predictive/prognostic biomarkers when analysed in conjunction with immunogenetic polymorphisms. This elegant methodology not only contributes to a better understanding of the other variants that determine breast cancer pathogenesis but also promotes a rational, evidence-based design of personalized immunomodulating therapeutic approaches, thereby paving the way for truly tailored treatments in this multifaceted disease.

Acknowledgments

Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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