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Association of Interleukin-6 Gene Polymorphisms (rs1800796 and rs2069840) with Breast Cancer Susceptibility in an Iraqi Female Population

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Abstract

Background: Breast cancer is a significant and growing health concern among women in Iraq. Although the role of inflammation in carcinogenesis has been established, the influence of specific genetic factors, such as polymorphisms in the pro-inflammatory cytokine Interleukin-6 (IL-6), remains under-investigated in this population.

Objective: This study aimed to invesstigate the association between two IL-6 gene polymorphisms, rs1800796 and rs2069840, and the risk of developing breast cancer in a cohort of Iraqi women.

Material and Methods: A case-control study was conducted with 50 female patientsdignosed with breast cancer and 50 healthy female controls. Genotyping for the rs1800796 and rs2069840 polymorphisms was performed using Tetra-ARMS PCR technique. Statistical analysis was carried out using chi-squared tests to assess the association between genotypes, alleles, and breast cancer risk.

Results: The rs1800796 polymorphism has been strongly associated with breast cancer risk, with the GC genotype (odds ratio = 2.55), the CC genotype (odds ratio = 3.52), and the C allele (odds ratio = 1.82) all being associated with an increased risk of breast cancer. Similarly, for the rs2069840 polymorphism, the GC genotype (odds ratio = 2.70), the CC genotype (odds ratio = 3.52), and the C allele (odds ratio = 2.26) were strongly associated with an increased risk of breast cancer.

Conclusion: the finding suggestThat IL-6 gene polymorphisms rs1800796 and rs2069840 were significant risk factors associated with breast cancer susceptibility in the studied Iraqi female population. These findings underscore the role of genetic inflammatory markers in breast cancer etiology and suggest population-specific genetic risk profiles.

Keywords: Breast Neoplasms; Genetic Polymorphism; Interleukin-6; Risk Factors.

Introduction

Breast cancer represents a significant and escalating global health challenge. It is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide. According to the most recent GLOBOCAN 2022 estimates, approximately 2.3 million new cases were diagnosed and nearly 670,000 deaths were attributed to the disease, making it the most prevalent cancer in 157 of 185 countries(1,2). While high-income countries have historically borne the largest burden, incidence rates are rapidly increasing in many low- and middle-income nations owing to shifts in lifestyle, reproductive patterns, and environmental factors. The Middle East, including Iraq, is experiencing a notable increase in the incidence of breast cancer. Breast cancer is the most common malignancy among women in Iraq, with age-standardized incidence rates showing a significant upward trend in recent years, rising from 36.6 per 100,000 in 2012 to 61.9 per 100,000 in 2022(3,4). This growing public health crisis underscores the urgent need for a deeper understanding of the specific risk factors and molecular drivers that contribute to breast carcinogenesis within this population.

The etiology of breast cancer is profoundly heterogeneous and multifactorial, involving a complex interplay between genetic predisposition, hormonal influences, and environmental exposures. Although high-penetrance germline mutations in genes such as BRCA1 and BRCA2 account for a significant proportion of hereditary cases, they represent only 5-10% of all breast cancers(5). Most cases are sporadic, suggesting that a combination of low-penetrance genetic variants and non-genetic factors contributes to disease development. Among these factors, chronic inflammation has emerged as a critical component in the initiation and progression of numerous malignancies including breast cancer (6). The tumor microenvironment is a complex ecosystem in which cancer cells interact with stromal and immune cells. This interaction is often mediated by a network of signaling molecules, including cytokines, which can create a pro-tumorigenic milieu that fosters cell proliferation, survival, angiogenesis, and metastasis.

Interleukin-6 (IL-6), a pleiotropic proinflammatory cytokine, is a key mediator of this process. Elevated levels of IL-6 in serum and the tumor microenvironment have been consistently linked to poor prognosis and therapy resistance in patients with breast cancer (7). IL-6 exerts its pro-oncogenic effects primarily through activation of the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway. Upon binding to its receptor, IL-6 triggers the phosphorylation and activation of STAT3, which then translocates to the nucleus to regulate the expression of a wide array of target genes involved in cell cycle progression (e.g., Cyclin D1), survival (e.g., Bcl-xL), and invasion(8,9). Constitutive activation of the IL-6/JAK/STAT3 axis is considered a hallmark of many breast cancer subtypes and represents a promising target for therapeutic intervention.

The expression and activity of IL-6 is, in part, genetically controlled. IL-6, located on chromosome 7p21, contains several single-nucleotide polymorphisms (SNPs), particularly within its promoter region, which can influence its transcriptional activity and subsequent protein levels. Variations in IL-6 production owing to these polymorphisms have been associated with susceptibility to a wide range of inflammatory diseases and cancers. Several studies have investigated the association between IL-6 promoter SNPs and breast cancer risk, but the results have often been inconsistent and population dependent(10). This variability highlights the importance of conducting population-specific studies to account for differences in genetic backgrounds, linkage disequilibrium patterns, and gene-environment interactions. Two of the most frequently studied polymorphisms are rs1800796 (-572 G/C) and rs2069840. While some meta-analyses have suggested a link between these SNPs and breast cancer risk, particularly in Asian populations, their significance in Middle Eastern populations, such as Iraq, remains under-investigated(11).

Given the increasing incidence of breast cancer in Iraq and the critical role of IL-6 in its pathogenesis, investigating the contribution of functional IL-6 gene polymorphisms in this specific population is of paramount importance. The use of robust and cost-effective genotyping methods, such as T-ARMS-PCR, allows for efficient screening of these variants in case-control studies(12). Therefore, the aim of the present study was to investigate the association of the IL-6 gene polymorphisms rs1800796 and rs2069840 with the risk of developing breast cancer in a cohort of Iraqi women and to evaluate their potential as genetic risk markers in this population.

Materials and Methods

study population

This study included (50) patients with breast carcinoma and (50) healthy women as controls. All samples were collected at the Diwaniyah General Hospital. Ethical approval was obtained from the relevant committee,andwritten informed consent was obtained from all participants. Demographic data, including age, weight, BMI and place of residence, were collected frommedical records with specialist assistance.Controls were age- and geographically matched healthy women with no history of cancer.. Those less than 18 years of age were excluded.

Sample preparation

Blood samples(5 ml) were collected from patients with BC after confirming clinical diagnosis, and were placed in an EDTA tube containing an anticoagulant to prevent caogulation. Blood was then stored at −80°C.DNA was extracted using the FAVORGEN extraction kit, followed by ethidium bromide staining and 1% agarose gel electrophoresis. The quality and concentration of DNA were assessed under UV illumination.

Genotyping

The rs1800796 and rs2069840 variant genotypes were determined using T-ARMS PCR as previously described(13).Four primers, illustrated in Table (1-1), were designed using Primer 3 toperform polymerase chain reaction (PCR). The reaction mixture was prepared in a

volume of 50µL for each sample in PCR tubes, which included 1µL of primer and 25 µL of the master mix (2× EasyTaq® PCR SuperMix kit).The PCR mixture contained 25 µL master mix, 1 µL of each primer, 5 µL DNA template, and nuclease-free water to complete the final volume. The mixture was thoroughly mixed using anExispin vortex centrifuge. for one minute at 3000 to ensure complete homogeneity. The reaction tubes were then transferred toa PCR thermocycler (Labnet Technology, USA), which included thirty-five cyclesof amplification: denaturation at 95°C for 30 s, annealing at 54°C for (30 sec), and extension at 72°C for (45 s) with a final extension at 72°C for(5 min). Under ultraviolet light, the PCR products were examined using 2% agarose gel electrophoresis with (1µg/ml) ethidium bromide. The product sizes forrs1800796 were 125 bp(G allele), 157 bp (C allele), and 242 bp for the control band, and the product sizes for rs2069840 were 141 bp (G allele), 103 bp (C allele), and 192 bp for the control band.

Table 1: Sequences of primers and product sizes for IL-6 SNPs genotyping

SNP ID rs1800796	**Primer name**	**sequence**	**Product size(bp)**
	FIP	GGCCAGGCAGTTCTACAACAGGCG	125(G allele)
	RIP	TGTTCTGGCTCTCCCTGTGTGG	157(Callele)
	FOP	CTCTAAGTGGGCTGAAGCAGGTGATGA	237(outer)
	ROP	AGTTTCCTCTGACTCCATCGCAGGCC	
rs2069840			
	FIP	TATGTAAATTTCATGAGGAGGCCTAG	141(G allele)
	RIP	TAAACTGCCTTTAAAAAAGCTTGTAG	103 (C allele
	FOP	GTATACATATAGATCCAGGCAGCAAC	192(outer)
	ROP	ACTAATTAAACCTGTGGGAGTTTTAAAC	

Statistical analysis

Statistical analyses were performed using SPSS version 26. The variables ware presented as numbers and percentages. The mean and standard deviation (SD) of the normally distributed variableswere calculated. The chi-square test was used to ascertain the differences between qualitative variables and independent samples. To evaluate the difference between the two groups,an independent sample t-test was used.A p-value of less than 0.05 was considered statistically significant.Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between IL-6 polymorphisms and breast cancer risk.Hardy–Weinberg equilibrium (HWE) was assessed in the control group using an exact test.Fisher's exact test was applied when expected cell counts were less than 5

Result

This table presents a comparative summary of the demographic and clinical characteristics of the 50 BC patients and 50 healthy controls. The analysis reveals a statistically significant difference in the mean BMI between the two groups (28.54 ± 2.76 kg/m² for patients vs. 26.89 ± 3.41 kg/m² for controls; p = 0.010). No significant differences were observed regarding age, residency, weight, or height; however, BMI showed a significant difference

between the two groups. Among these patients, Invasive Ductal Carcinoma (IDC) was the predominant molecular subtype, accounting for 88.0% of cases.

Table 2. Demographic and Baseline Clinical Characteristics of the Study Population

Characteristic	Patients with BC (n=50)	Healthy Controls (n=50)	p-value
Age (years)			
Mean ± SD	50.94 ± 11.7	47.70 ± 10.50	0.150
Range	25 – 76	28 – 72	
< 40, n (%)	9 (18.0%)	10 (20.0%)	0.331
40-49, n (%)	12 (24.0%)	18 (36.0%)	
≥ 50, n (%)	29 (58.0%)	22 (44.0%)	
Residency			
Urban, n (%)	33 (66.0%)	40 (80.0%)	0.115
Rural, n (%)	17 (34.0%)	10 (20.0%)	
Weight (Kg)			
Mean ± SD	73.72 ± 6.08	71.22 ± 7.62	0.073
Range	61 – 88	55 – 90	
Height (cm)			
Mean ± SD	161.20 ± 4.29	163.00 ± 5.76	0.080
Range	155 – 172	156 – 181	
Body mass index (BMI) (kg/m2)			
Mean ± SD	28.54 ± 2.76	26.89 ± 3.41	0.010
Range	22.31– 34.89	20.94–33.46	
Breast cancer molecular subtype			
IDC (Invasive ductal carcinoma), n(%)	44 (88.0 %)	N/A	
ILC (Invasive lobular carcinoma), n(%)	6 (12.0 %)	N/A	

The T-ARMS-PCR method was employed to identify the IL-6 rs1800796 (G/C) polymorphism. This technique allowed for the differentiation of the three genotypes at this specific locus: GG, GC, and CC. A 273bp control band was consistently present across all samples, which confirmed the validity of the experimental procedure. The wild-type homozygous genotype (GG) was characterized by the amplification of a single 125bp product, corresponding to the G allele. In contrast, the homozygous mutant genotype (CC) produced a 157bp amplicon, which is indicative of the C allele. For the heterozygous genotype (GC), the amplification resulted in two distinct products of 125bp and 157bp, representing both the G and C alleles, respectively, as illustrated in Figure 1.

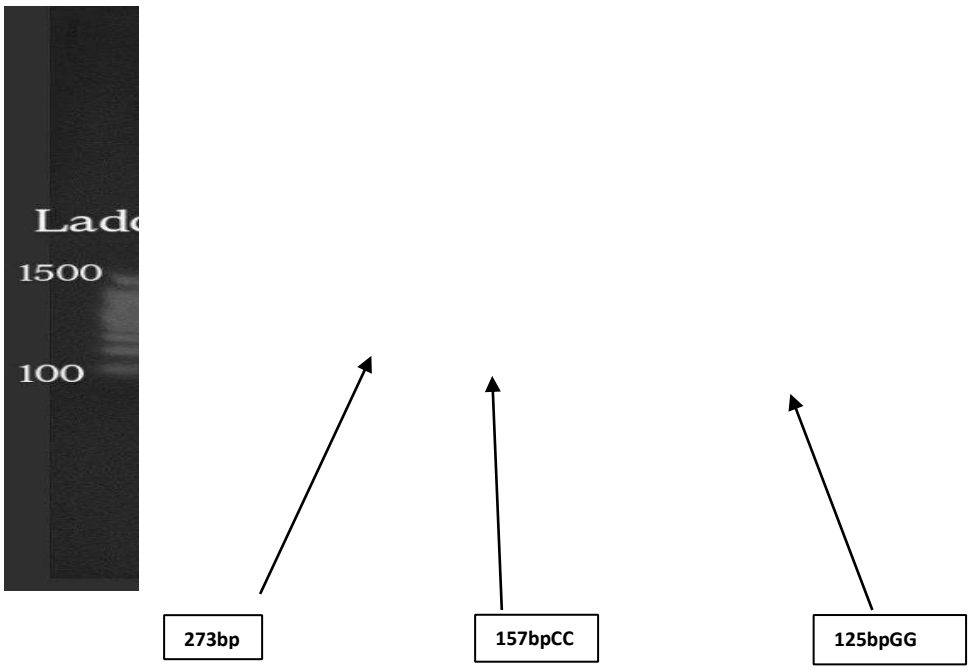

Figure 1 presents the agarose gel electrophoresis results for the T-ARMS-PCR genotyping of the IL-6 rs1800796 G/C polymorphism, with a 100-1500 bp ladder (M) used as a size marker. The analysis revealed three distinct patterns: the GG homozygote (wild-type) is identified by a single 125 bp band (G allele), the CC homozygote (mutant) by a 157 bp band (C allele), and the GC heterozygote by the presence of both bands. A 273 bp internal control product was included in all reactions to validate the amplification process.

This table presents the results of the chi-square (χ^2) test for the HWE for the IL-6 rs1800796 polymorphism. The observed genotype frequencies in the study population in control group were compared with the expected frequencies under HWE. The non-significant p-value (p = 0.348) indicated that the observed genotype distribution did not deviate from the HWE.

Table 3. Hardy-Weinberg Equilibrium Analysis for the IL-6 rs1800796 Polymorphism

Genotypes	observed	expected	$\chi2$	*p*
GG (homozygote reference)	26	23.8	2.112	0.348
GC(Heterozygote)	17	21.4		
CC (Homozygote variant)	7	4.8		

NS: Non-significant at P>0.05; ¥: Chi-square test

This table details the association between IL-6 rs1800796 polymorphism and breast cancer risk. The heterozygous genotype (GC) was significantly associated with an increased risk of breast cancer (OR = 2.55, 95% CI = 1.05-6.17, p = 0.036). In the dominant model, the presence of at least one C allele (CC + GC) conferred a significantly higher risk (p = 0.025). Furthermore, the C allele itself was a significant risk factor (OR = 1.82, 95% CI = 1.02-3.25, p = 0.041).

Table 4. Association of IL-6 rs1800796 Genotypes and Alleles with Breast Cancer Risk

mode	*IL-6 (rs1800796)*	*Patients n* = 50	control n= 50	*P*	OR	95%CI
Co-dominant	CC	10 (20.0%)	7 (14.0 %)	0.119	2.47	0.78-7.86
	G/C	25 (50.0%)	17 (34.0 %)	0.036	2.55	1.05 -6.17
	GG	15 (30.0 %)	26 (52.0%)	Reference		
Dominant	CC+G/C	35 (70.0 %)	24 (48.0 %)	0.025	Reference	
	GG	15 (30.0 %)	26 (52.0%)		0.395	0.17-0.89
Recessive	CC	10 (20.0%)	7 (14.0 %)	0.424	1.54	0.53-4.42
	G/C +GG	40 (80.0%)	43 (86.0%)		Reference	
Alleles	C	45 (45.0%)	31 (31.0%)	0.041	1.82	1.02-3.25
	G	55 (55.0%)	69 (69.0%)		Reference	

¥(: Chi-squartese)S(significant at P> 0.05).

The T-ARMS-PCR technique was utilized to analyze the distribution of the IL-6 (rs2069840) G/C polymorphism, which presents as three genotypes: GG, GC, and CC. As depicted in Figure 2, the wild-type homozygote (GG) yielded a 141 bp amplicon for the G allele, while the mutant homozygote (CC) produced a 103 bp product for the C allele. The heterozygote (GC) was identified by the presence of both the 141 bp and 103 bp amplicons. A 192 bp control band was present in all reactions, confirming successful amplification, and the observed genotype frequencies were found to be in equilibrium with the HWE principle.

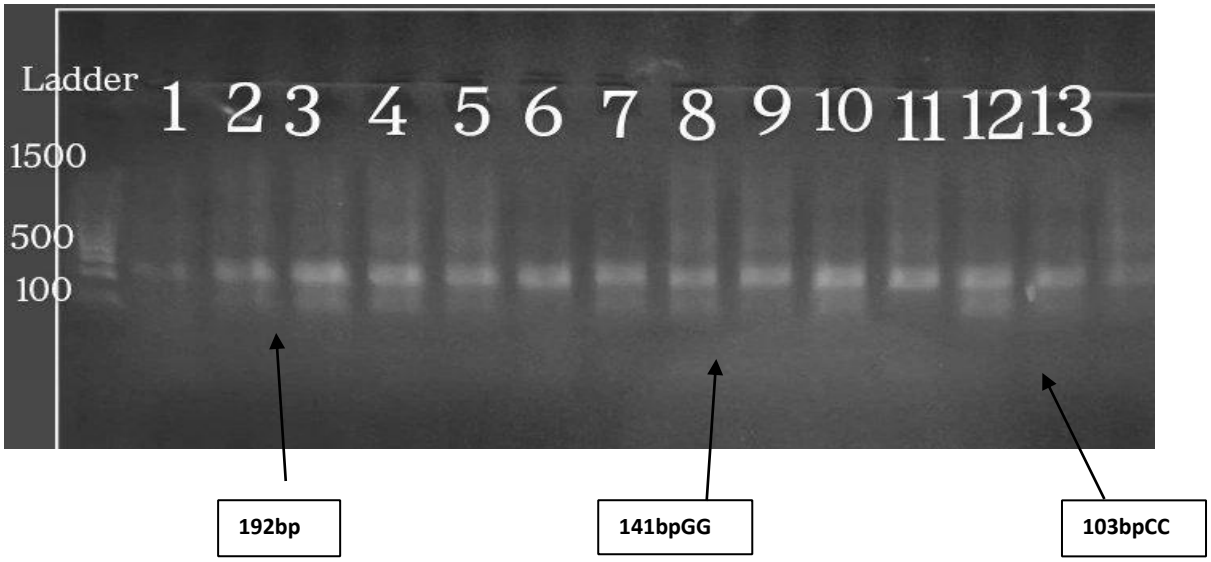

Figure 2 provides an agarose gel electrophoresis analysis of the T-ARMS-PCR products for the IL-6 (rs2069840) G/C polymorphism, benchmarked against a 100-1500 bp DNA ladder (M). The results distinguish the three genotypes: the wild-type homozygote (GG) is indicated by a 141 bp amplicon (G allele), the mutant homozygote (CC) by a 103 bp amplicon (C allele), and the heterozygote (GC) by the presence of both amplicons. The integrity of the PCR is confirmed by a 192 bp internal control product present in each lane.

This table shows the results of the chi-squared (χ^2) test for HWE for the IL-6 rs2069840 polymorphism. The observed genotype frequencies were consistent with the expected frequencies under HWE, as indicated by the non-significant p-value (p = 0.366).

Table 5. Hardy-Weinberg Equilibrium Analysis for the IL-6 rs2069840 Polymorphism

Genotypes	observed	expected	$\chi 2$	*P*
GG(Homozygote reference)	30	28.1	2.009	0.366
GC(Heterozygote)	15	18.8		
CC (Homozygote variant)	5	3.1		

NS(Non-significant at P < 0.05);¥(Chi-square test),

This table presents the association analysis of the IL-6 rs2069840 polymorphism. Both the homozygous variant (CC) and heterozygous (GC) genotypes were significantly associated with an increased risk of breast cancer (OR = 3.52, 95% CI = 1.03-12.04, p = 0.038 and OR = 2.70, 95% CI = 1.12-6.53, p = 0.025, respectively). The dominant model (CC + GC) also showed a significant association with an increased risk (p = 0.009). The C allele was identified as a significant risk factor (OR = 2.26, 95% CI = 1.24-4.13, p = 0.007). Conversely, the GG genotype appeared to have a protective effect (OR = 0.343, 95% CI = 0.15-0.775).

Table 6. Association of IL-6 rs2069840 Genotypes and Alleles with Breast Cancer Risk

Mode	*IL-6 (rs2069840)*	Patients *n* = 50	*Controls n* = 50	*P*	OR	95% CI
Co-dominant	CC	10 (20.0%)	5 (10.0 %)	0.038	3.52	1.03-12.04
	G/C	23 (46.0%)	15 (30.0 %)	0.025	2.70	1.12 -6.53
	GG	17 (34.0 %)	30 (60.0%)	Reference		
Dominant	CC+G/C	33 (66.0 %)	20 (40.0 %)	0.009	Reference	
	GG	17 (34.0 %)	30 (60.0%)		0.343	0.15-0.775
Recessive	CC	10 (20.0%)	5 (10.0 %)	0.161	2.25	0.71-7.14
	G/C +GG	40 (80.0%)	45 (90.0%)		Reference	
Alleles	C	43 (43.0%)	25 (25.0%)	0.007	2.26	1.24-4.129
	G	57 (57.0%)	75 (75.0%)		Reference	

significant at P > 0.05).¥(Chi-square test)

Discussion

The present study investigated the association between two SNPs in IL-6, rs1800796 and rs2069840, and the risk of breast cancer in a cohort of Iraqi women. Our findings indicate that specific genetic variants at these loci are significantly associated with breast cancer susceptibility and corroborate the established clinical and epidemiological risk factors. The discussion will contextualize these findings within the current scientific literature, focusing on the roles of histopathology, metabolic health, and specific contributions of the studied IL-6 polymorphisms.

Consistent with the global epidemiological data, our study identified IDC as the predominant histopathological subtype, accounting for 88.0% of the diagnosed cases. This aligns with reports from numerous international health organizations and clinical studies, which consistently cite IDC as the most common form of invasive breast cancer, comprising

up to 80% of all diagnoses (14,15). The high prevalence of IDC underscores the clinical relevance of our study. Furthermore, our analysis revealed a statistically significant elevation in BMI among breast cancer patients compared to healthy controls (28.54 ± 2.76 vs. 26.89 ± 3.41 kg/m²; p = 0.010). This finding reinforces the well-established link between obesity and increased breast cancer risk, particularly in postmenopausal women(16). Obesity fosters a state of chronic low-grade inflammation, where adipose tissue secretes a range of pro-inflammatory cytokines, including IL-6. This inflammatory tumor microenvironment drives cancer progression by promoting cell proliferation, survival, and angiogenesis through pathways such as JAK/STAT3 signaling(17,18).

Our investigation of the IL-6 promoter polymorphism rs1800796 identified the C allele as a significant risk factor for breast cancer in the Iraqi population. Specifically, the heterozygous GC genotype conferred a 2.55-fold increased risk (OR = 2.55, 95% CI = 1.05–6.17, p = 0.036), and the C allele itself was associated with an OR of 1.82 (95% CI = 1.02–3.25, p = 0.041). This finding is in strong agreement with that of several recent large-scale meta-analyses. For instance, a 2021 meta-analysis by Harun-Or-Roshid et al. encompassing over 115,000 subjects concluded that the rs1800796 polymorphism is significantly associated with overall cancer risk, particularly in Asian populations(11). Similarly, a 2020 meta-analysis by Xu and Wang demonstrated that this polymorphism confers susceptibility to breast cancer(19). More recently, a comprehensive 2026 meta-analysis involving nearly 38,000 participants reported a significant overall association between the rs1800796 C allele and increased breast cancer risk (allelic OR = 1.193, p = 0.046)(20). The consistency of our results with these large-scale analyses, especially those highlighting a pronounced effect in Asian populations, suggests that the pro-inflammatory effects associated with the C allele at this locus are a relevant etiological factor in breast cancer development in Iraqi women.

The most striking finding in our study pertains to the rs2069840 polymorphism. We identified a strong association between the C allele and an increased risk of breast cancer, with significant odds ratios for both CC (OR = 3.52, p = 0.038) and GC (OR = 2.70, p = 0.025) genotypes. The C allele was associated with a 2.26-fold increase in risk (p = 0.007). This result is in direct contrast to a recent large-scale meta-analysis by Azizi et al. (2024), which analyzed 27 articles and concluded that the GC and CC + GC genotypes of rs2069840 play a protective role against breast cancer (OR = 0.89 and OR = 0.91, respectively)(21). This marked discrepancy highlights the complex and potentially population-specific nature of the effect of this polymorphism. While the meta-analysis by Azizi et al. provides a broad overview, our data suggest that in the specific genetic context of the Iraqi population, the C allele at this locus may be linked to a pro-tumorigenic phenotype. This could be due to distinct patterns of linkage disequilibrium with other functional variants or unique gene-environment interactions prevalent in this region. Our findings align with the broader conclusion of a 2021 meta-analysis by Barek et al., which, despite finding no overall cancer risk, noted that rs2069840 may be specifically associated with breast cancer(22). This

conflicting evidence warrants further investigation in larger, well-characterized cohorts from the Middle East to resolve the true effects of this variant.

Limitations

While the findings are significant, this study has some limitations that must be considered. Foremost among these is the relatively small sample size, which may reduce the statistical power of the results and limit their generalizability.

Furthermore, the study did not analyze specific clinical and pathological indicators and their relationship to IL-6 gene polymorphisms, such as

Tumor stage and histological grade.

The status of hormone receptor biomarkers (ER, PR, and HER2).

Finally, given that the study was conducted within a single health center, the results may not accurately reflect the overall demographic diversity of the Iraqi population. Therefore, there is a pressing need for future, larger, multicenter research, including comprehensive clinical characterization, to confirm these conclusions and understand the precise functional role of IL-6 gene polymorphisms in breast cancer susceptibility.

Conclusion

In conclusion, this study provides evidence that IL-6 gene polymorphisms rs1800796 and rs2069840 are significant risk factors for breast cancer in an Iraqi female population. Our findings for rs1800796 are well supported by recent international literature, confirming the role of this proinflammatory variant in breast carcinogenesis. However, our results for rs2069840 challenge the conclusions of a recent meta-analysis and suggest a population-specific risk association, which requires further exploration.

Ethical Approval

The Declaration of Helsinki was adopted as the ethics guide for this research.In addition, ethical approval was obtained from the Ethics Committee of the College of Biotechnology, and all procedures involving human participants adhered to moral principles at the institutional and national levels.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author Contributions:

Conceptualization, NQAA and MAA; methodology, NQAA and MAA; validation, NQAA and MAA; formal analysis, MAA; investigation, NQAA and MAA; resources, NQAA; data curation, MAA; writing – original draft preparation, NQAA and MAA; writing – review and editing, NQAA and MAA; visualization, MAA; supervision, NQAA; project administration, NQAA; funding acquisition, NQAA and MAA.

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