



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

Nabaa Qahtan Abdulhamza Al-Hilali^{1*}, Mohammed Abdulwahab Alaskeri¹

¹Department of Medical Biotechnology, College of Biotechnology, University of Al-Qadisiyah, Qadisiyah, Iraq

Abstract

Introduction: Breast cancer (BC) is a prominent and increasing health issue among women in Iraq. While the significance of inflammation in carcinogenesis is well-established, the impact of particular genetic variables, such as polymorphisms in the pro-inflammatory cytokine Interleukin-6 (IL-6), remains little explored in this group. This research sought to examine the relationship between two IL-6 gene polymorphisms, rs1800796 and rs2069840, and the risk of breast cancer in a cohort of Iraqi women.

Methods: A case-control study was performed with 50 female patients diagnosed with breast cancer and 50 healthy female controls. Genotyping for the rs1800796 and rs2069840 polymorphisms was conducted with the Tetra-ARMS PCR methodology. Chi-squared tests were used for statistical analysis to evaluate the relationship between genotypes, alleles, and breast cancer risk.

Results: The rs1800796 polymorphism has been strongly associated with BC 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 BC. 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 BC.

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

Keywords: Breast neoplasms, Interleukin-6, Gene polymorphisms, Risk factors, Cohort study

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Introduction

Globally, breast cancer (BC) remains a paramount and escalating public health challenge, representing both the most frequently diagnosed malignancy and the leading cause of oncological mortality among the female population. Recent epidemiological data from the GLOBOCAN 2022 database indicate that approximately 2.3 million incident cases were diagnosed worldwide, with the disease claiming nearly 670,000 lives. These figures underscore its status as the predominant malignancy in 157 of the 185 countries evaluated (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 BC. BC 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 notably diverse and multifaceted, encompassing a complex interaction among genetic predisposition, hormonal influences, and environmental exposures. High-penetrance germline mutations in genes such as BRCA1 and BRCA2 contribute to a notable fraction of hereditary cases; however, they constitute merely 5-10% of the total occurrences of breast cancer (5). Most instances appear to be sporadic, indicating that a combination of low-penetrance genetic variants and non-genetic factors plays a role in the development of the disease. Chronic inflammation has been identified as a significant factor in the initiation and progression of various malignancies, including breast cancer (6). The tumor microenvironment constitutes a multifaceted ecosystem wherein cancer cells engage with stromal and immune cells. This interaction is frequently facilitated by a network of signaling molecules, such as cytokines, which can establish a pro-tumorigenic environment that promotes cell proliferation, survival, angiogenesis, and metastasis.

As a pleiotropic proinflammatory cytokine, Interleukin-6 (IL-6) acts as a pivotal mediator in breast oncology. Up-regulated levels of IL-6 within the systemic circulation and the local tumor microenvironment are



*Corresponding Author: Nabaa Qahtan Abdulhamza Al-Hilali, Email: N.Q.Abdulhamza@qu.edu.iq

strongly correlated with unfavorable clinical outcomes and resistance to conventional therapies(7). The pro-tumorigenic functions of IL-6 are chiefly driven by the activation of the JAK/STAT3 signaling cascade. Following ligand-receptor engagement, IL-6 triggers the phosphorylation and subsequent activation of STAT3; this transcription factor then translocates into the nucleus to regulate the transcription of key downstream targets involved in cell cycle progression (such as Cyclin D1), cell survival (such as Bcl-xL), and metastatic invasion (8,9). Consequently, persistent activation of the IL-6/JAK/STAT3 signaling axis represents a hallmark feature across multiple breast cancer subtypes, offering a promising avenue for targeted therapeutic interventions.

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. Numerous studies have explored the relationship between IL-6 promoter SNPs and the risk of breast cancer; however, the findings have frequently shown inconsistency and are influenced by population variations(10). This variability underscores the necessity of performing studies tailored to specific populations in order to address variations 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 BC risk, particularly in Asian populations, their significance in Middle Eastern populations, such as Iraq, remains under-investigated(11).

Given the increasing incidence of BC 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 BC in a cohort of Iraqi women and to evaluate their potential as genetic risk markers in this population.

Materials and Methods

Study Population

A case-control study was conducted involving a total of 100 female participants, equally divided into two groups: a patient group comprising 50 women histopathologically confirmed with breast carcinoma, and a control group consisting of 50 apparently healthy women with no personal or familial history of any malignant disease. All biological specimens and clinical data were obtained

from attendees at Diwaniyah General Hospital during the designated study period. Relevant demographic and anthropometric parameters including age, body weight, height, BMI, and area of residence were systematically extracted from hospital medical records with the guidance of specialist physicians and trained medical staff. The control subjects were carefully selected to match the patient group in terms of age distribution and geographical residence to minimize potential confounding variables. To ensure the homogeneity and validity of the study cohort, strict inclusion and exclusion criteria were applied: specifically, any individual below 18 years of age was excluded from participation, as were women with a prior diagnosis of any other malignancy, those receiving immunosuppressive therapy, or those with chronic inflammatory conditions that could influence the biomarkers under investigation.

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 coagulation. 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.

Genotyping

The rs1800796 and rs2069840 variant genotypes were determined using T-ARMS PCR as previously described(13). Four primers, illustrated in Table 1, were designed using Primer 3 to perform polymerase chain reaction (PCR). The reaction mixture was prepared in a volume of 50 μL for each sample in PCR tubes, which included 1 μL of primer and 25 μL of the master mix ($2\times$ EasyTaq[®] PCR SuperMix kit). The PCR mixture contained 25 μL master mix, 1 μL of each primer, 5 μL DNA template. The mixture was thoroughly mixed using an Exispin vortex centrifuge. For one minute at 3000 to ensure complete homogeneity. The reaction tubes were then transferred to a PCR thermocycler (Labnet Technology, USA), which included thirty-five cycles of amplification. Under ultraviolet light, the PCR products were examined using 2% agarose gel electrophoresis with (1 $\mu\text{g}/\text{ml}$) ethidium bromide. The product sizes for rs1800796 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.

Statistical Analysis

Statistical processing was executed with the SPSS package (v. 26). Data representation involved frequencies and percentages for qualitative parameters, and mean values $\pm$ standard deviations for normally distributed continuous measures. Group comparisons for categorical variables were carried out using the chi-square test. For comparing the means of the two independent

study groups, the independent t-test was selected. The association of IL-6 polymorphisms with breast cancer risk was quantified through OR and 95% CI. A probability value (p) of less than 0.05 was considered statistically significant throughout the analysis. Lastly, an exact test was applied to the control group to verify adherence to the HWE.

Result

The demographic and clinical profiles of the study cohort, comprising 50 patients diagnosed with breast cancer and 50 healthy control subjects, are summarized in Table 1. Comparative analysis revealed a statistically significant divergence in the average BMI between the cohorts ($28.54 \pm 2.76 \text{ kg/m}^2$ versus $26.89 \pm 3.41 \text{ kg/m}^2$, respectively; $P=0.010$). Conversely, no significant differences were observed regarding age, geographical residence, weight, or

height, highlighting BMI as the sole parameter showing a marked intergroup variation. Regarding histopathological classification, invasive ductal carcinoma (IDC) was the predominant subtype, characterizing 88.0% of the patient population (Table 2).

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

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(C allele)
	FOP	CTCTAAGTGGGCTGAAGCAGGTGATGA	237(outer)
	ROP	AGTTTCCTCTGACTCCATCGCAGGCC	
rs2069840			
	FIP	TATGTAAATTTTCATGAGGAGGCCTAG	141(G allele)
	RIP	TAAACTGCCTTTAAAAAGCTTGTAG	103 (C allele)
	FOP	GTATACATATAGATCCAGGCAGCAAC	192(outer)
	ROP	ACTAATAAACCTGTGGGAGTTTAAAC	

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 $\pm$ SD	50.94 $\pm$ 11.7	47.70 $\pm$ 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%)	
$\geq$ 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 $\pm$ SD	73.72 $\pm$ 6.08	71.22 $\pm$ 7.62	0.073
Range	61 – 88	55 – 90	
Height (cm)			
Mean $\pm$ SD	161.20 $\pm$ 4.29	163.00 $\pm$ 5.76	0.080
Range	155 – 172	156 – 181	
BMI (kg/m ²)			
Mean $\pm$ SD	28.54 $\pm$ 2.76	26.89 $\pm$ 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	

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.

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).

The heterozygous genotype (GC) was significantly correlated with an elevated 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) resulted in a markedly increased risk ($P=0.025$). Additionally, the C allele itself was identified as a significant ($OR=1.82$, 95% $CI=1.02-3.25$, $P=0.041$).

The T-ARMS-PCR technique was utilized to analyze the distribution of the IL-6 (rs2069840) G/C polymorphism,

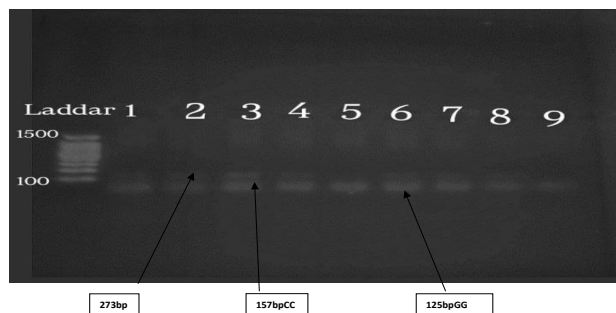


Figure 1. presents the agarose gel electrophoresis results for the T-ARMS-PCR genotyping of the IL-6 rs1800796 G/C polymorphism, with a 100-1500 bp ladder (M) used as a size marker. The analysis revealed three distinct patterns: the GG homozygote (wild-type) is identified by a single 125 bp band (G allele), 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

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.

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).

This table displays the relationship analysis of the IL-6 rs2069840 polymorphism. The CC and GC genotypes were significantly correlated with an elevated risk of BC ($OR=3.52$, 95% $CI=1.03-12.04$, $P=0.038$ and $OR=2.70$, 95% $CI=1.12-6.53$, $P=0.025$, respectively). The predominant model (CC + GC) demonstrated a significant ($P=0.009$). The C allele was recognized as a substantial risk factor ($OR=2.26$, 95% $CI=1.24-4.13$, $P=0.007$). In contrast, the GG genotype had a protective effect ($OR=0.343$, 95% $CI=0.15-0.775$) (Table 6).

Discussion

This research examined the correlation between two SNPs in IL-6, rs1800796 and rs2069840, and the incidence of breast cancer in a cohort of Iraqi women. Our results demonstrate that certain genetic variations at these loci are substantially linked to breast cancer susceptibility and support the recognized 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

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

Genotypes	observed	expected	χ^2	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 $P>0.05$; χ^2 : Chi-square test

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-squar tese)S(significant at $P>0.05$).

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 BC, 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 BC 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 BC risk, particularly in postmenopausal women (16). Obesity induces a condition of persistent low-grade inflammation, characterized by the secretion of several pro-inflammatory cytokines, such as IL-6, from adipose tissue. The inflammatory tumor microenvironment accelerates cancer development by enhancing cell proliferation, survival, and angiogenesis via mechanisms such as JAK/STAT3 signaling (17,18).

Genetic evaluation of the IL-6 promoter polymorphism rs1800796 identified the C allele as a notable susceptibility factor for breast cancer within the Iraqi population. Specifically, individuals carrying the heterozygous GC genotype faced a 2.55-fold increased risk of developing the disease (OR=2.55, 95% CI=1.05–6.17, $P=0.036$), while the C allele overall conferred an odds ratio of

1.82 (OR=1.82, 95% CI=1.02–3.25, $P=0.041$). These observations align closely with findings from several high-power meta-analyses. Notably, a comprehensive meta-analysis pooling data from more than 115,000 subjects demonstrated a significant correlation between the rs1800796 variant and general cancer susceptibility, with a particularly pronounced effect observed in Asian cohorts (11). Similarly, a meta-analysis by Xu and Wang demonstrated that this polymorphism confers susceptibility to BC (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 BC 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 BC 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 BC, 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 meta-analysis, which analyzed 27 articles and concluded that the GC and CC + GC genotypes of rs2069840 play a protective role against BC (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

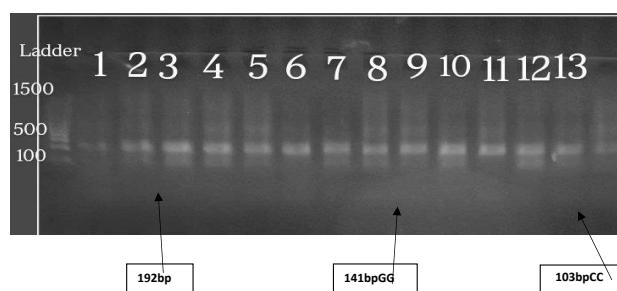


Figure 2. provides an agarose gel electrophoresis analysis of the T-ARMS-PCR products for the IL-6 (rs2069840) G/C polymorphism, benchmarked against a 100-1500 bp DNA ladder (M). The results distinguish the three genotypes: the wild-type homozygote (GG) is indicated by a 141 bp amplicon (G allele), the 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

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

Genotypes	observed	expected	χ^2	P
GG(Homozygote reference)	30	28.1		
GC(Heterozygote)	15	18.8	2.009	0.366
CC (Homozygote variant)	5	3.1		

NS(Non-significant at $P<0.05$); χ^2 (Chi-square test),

Table 6. Genotypes of IL-6 rs2069840 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	

linkage disequilibrium with other functional variants or unique gene-environment interactions prevalent in this region. Our findings align with the broader conclusion of meta-analysis by Barek et al., which, despite finding no overall cancer risk, noted that rs2069840 may be specifically associated with BC (22). This conflicting evidence warrants further investigation in larger, well-characterized cohorts from the Middle East to resolve the true effects of this variant (23-26).

Limitations

While the findings are significant, this study has some limitations that must be considered. The primary concern is the limited sample size, which may diminish the power of statistics of the findings and restrict 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 BC susceptibility.

Conclusion

In conclusion, this study provides evidence that IL-6 gene polymorphisms rs1800796 and rs2069840 are significant risk factors for BC in an Iraqi female population. The 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.

Authors' Contribution

Conceptualization: Nabaa Qahtan Abdulhamza Al-Hilali, Mohammed Abdulwahab Alaskeri
Data curation: Nabaa Qahtan Abdulhamza Al-Hilali, Mohammed Abdulwahab Alaskeri
Formal analysis: Nabaa Qahtan Abdulhamza Al-Hilali,
Funding acquisition: Nabaa Qahtan Abdulhamza Al-Hilali,
Investigation: Nabaa Qahtan Abdulhamza Al-Hilali, Mohammed Abdulwahab Alaskeri
Methodology: Nabaa Qahtan Abdulhamza Al-Hilali, Mohammed Abdulwahab Alaskeri
Project administration: Nabaa Qahtan Abdulhamza Al-Hilali,
Resources: Nabaa Qahtan Abdulhamza Al-Hilali, Mohammed Abdulwahab Alaskeri
Software: Nabaa Qahtan Abdulhamza Al-Hilali, Mohammed Abdulwahab Alaskeri
Supervision: Mohammed Abdulwahab Alaskeri
Visualization: Nabaa Qahtan Abdulhamza Al-Hilali,
Writing – original draft: Nabaa Qahtan Abdulhamza Al-Hilali, Mohammed Abdulwahab Alaskeri
Writing – review & editing: Nabaa Qahtan Abdulhamza Al-Hilali,

Mohammed Abdulwahab Alaskeri ammed

Availability of Data and Materials

There is a fair request that may be made to the corresponding author in order to get the datasets that were created and/or analyzed over the course of the present work.

Competing Interests

None.

Ethical Approval

The Declaration of Helsinki was adopted as the ethics guide for this research. In addition, ethical approval was obtained from the College of Biotechnology (approval references: UAQB-22), and all procedures involving human participants adhered to moral principles at the institutional and national levels.

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