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Association of aromatase levels with estrogen-related gene polymorphism CYP19 Rs10046 in breast cancer among Iraqi women

Samah Fadhil Hadi[1]*, Shrouk A. Hassan Al. Ibraheem[1], Hamid Jaddoa Abbas[2]
[1]Medical Laboratory Technology Deptartment, College of Health & Medical, Technology, Southern Technical University, Basrah, Iraq; samah.f.hadi@fgs.stu.edu.iq (S.F.H.) aliabd77@yahoo.com (S.A.H.A.I.)
[2]Al-Faiha'a Teaching Hospital, Al- Zehra'a Medical College, University of Basrah, Basrah, Iraq; hamedjadoa@yahoo.com (H.J.A.).

Abstract: Breast cancer (BC) is a significant health concern globally, and understanding its genetic basis can provide insights for better prevention and treatment strategies. The study offers significant insights into the diagnostic potential of biomarkers, the genetic risk factors associated with breast cancer, and underscoring the complex and multifactorial nature of the disease. Aromatase is a key enzyme in estrogen biosynthesis, and variations in the CYP19 gene may influence estrogen levels, impacting breast cancer development. Therefore, this study was investigated the association between the single nucleotide polymorphism (SNP rs10046) of aromatase CYP19 gene and aromatase level in breast cancer among Iraqi women and assessment of CA 15- 3 as standard tumor marker for breast cancer. A case-control study was conducted, including 70 Iraqi women diagnosed with Ductal Carcinoma and 67 age-matched healthy women as control group. Peripheral blood samples were collected from all participants. Genomic DNA was extracted using a standard protocol. The rs10046 single nucleotide polymorphism (SNP) in the CYP19 gene was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. The PCR products were digested with specific restriction enzymes (Bsp1286 I (SduI)) and analyzed by gel electrophoresis. The results showed that E2, CA 15-3, and aromatase levels in patients have a highly significant differences (P value<0.05) when compared with the control group. Aromatase demonstrated high sensitivity, while CA 15-3 showed the greatest potential as a diagnostic marker. The CC genotype was more frequent in patients, this finding aligns with the hypothesis that genetic variations can influence breast cancer risk. In conclusion, the findings highlight the potential influence of the CYP19 rs10046 polymorphism on breast cancer risk among Iraqi women. CA 15-3 is a tumor biomarker of choice for the diagnosis and follow-up of breast cancer.

Keywords: *Aromatase, Breast cancer, CYP19 rs10046, Estrogen.*

1. Introduction

Breast cancer (BC) is one of the most prevalent forms of cancer among females worldwide and a leading cause of cancer-related mortality [1]. It is a complex disease with various genetic and environmental factors contributing to its development [2]. Breast cancer is a malignancy characterized by uncontrolled growth and formation of tumors in the breast due to aberrant cells [3]. If not controlled, these tumors have the potential to metastasize and become life-threatening. Breast cancer usually originates within the milk ducts (ductal carcinoma) or milk-producing lobules (lobular carcinoma) of the breast [4]. Studying the association between tumor biomarkers and gene polymorphisms in breast cancer can help in understanding the genetic basis of the disease and identifying potential genetic markers for early detection, prognosis, and personalized treatment

* Correspondence: samah.f.hadi@fgs.stu.edu.iq

strategies [5]. Estrogens play a pivotal role in breast cancer development. A specific enzyme called aromatase (also known as CYP19) is responsible for synthesizing estrogens. Interestingly, aromatase is expressed at higher levels in human breast cancer tissue than in normal breast tissue [6]. Aromatase (also known as CYP19) is a cytochrome P450 enzyme responsible for estrogen biosynthesis [7]. It converts androgens (such as testosterone) into estrogens (including estradiol) in various tissues, including the breast. Aromatase plays a crucial role in estrogen production, which influences breast development, cell growth, and cancer progression [8]. Before menopause, the majority of estrogen is synthesized in the ovaries. Aromatase inhibitors (AIs) target this estrogen-production process [9]. Aromatase Inhibitors hinder the transformation of androstenedione and testosterone into estrone and estradiol, which is the last stage in the production of estrogen [10]. They are used primarily in postmenopausal women whose ovaries no longer produce estrogen. Genetic factors, particularly polymorphisms in genes involved in estrogen biosynthesis and metabolism, play a critical role in modulating breast cancer risk. The Aromatase enzyme, encoded by the CYP19A1 gene, converts androgens to estrogens, which are essential for the growth and development of hormone-dependent breast cancers. Gene polymorphisms, on the other hand, refer to variations in the DNA sequence that can affect gene function and potentially influence disease susceptibility [5]. The rs10046 SNP in the CYP19 gene has been studied for its potential impact on breast cancer susceptibility, with varying results across different populations. Therefore, the primary objective of this study is to determine the association between the CYP19 rs10046 aromatase gene polymorphism and aromatase level with the risk of ductal carcinoma among Iraqi women.

2. Materials and Methods

A case-control study included 137 female participants (all were menopausal): 70 patients with primary ductal carcinoma and 67 healthy females as control group. The patients in this study were newly diagnosed by oncologists based on medical and laboratory investigations, and the diagnosis of breast cancer was confirmed by histopathological examinations. These patients were attended the Tumor Center, Basra, Iraq; between December 2023 and June 2024. Their ages ranged from 45 - 65 years. The selection criteria were defined based on age, sex, race, ethnicity, and other relevant factors to ensure a representative sample. Patients with a history of other malignancies or significant medical conditions that could confound the study results were excluded. Control was selected randomly from the general population, with no history of malignancies or significant medical conditions that could affect biomarker levels or gene polymorphisms. All ethical approvals and considerations for participants in the study, including informed consent, privacy, and confidentiality of data, were taken into account. Ethical approvals were obtained from research ethics committees. Peripheral blood samples were collected from all participants. An EDTA blood was used for DNA extraction. Various biochemical parameters were analyzed in breast cancer patients and healthy controls. These were done using standard techniques like spectroscopy, ELISA, and ECL. Genomic DNA was extracted using a standard DNA extraction kit protocol (Favorgen/ Taiwan). The rs10046 SNP in the CYP19 gene was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. The PCR products were digested with specific restriction enzymes (*Bsp1286 I* (*SduI*)) and analyzed by gel electrophoresis. Genotype and allele frequencies were compared between cases and controls using the chi-square test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the risk associated with each genotype.

2.1. Statistical Analysis

Data were statistically analyzed using the Statistical Package of Social Sciences program (SPSS; Version 26). The data were tested to assess if the continuous variables were normally distributed or not. Data were expressed as mean± standard deviation values or median (interquartile range) for continuous numerical and as percentages and frequencies for categorical variables. A p-value < 0.05 was considered statistically significant for all tests conducted.

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3. Results

The baseline of characteristics of this study of both groups were presented in Table 1.

Table 1.
The baseline characteristics of study subjects.

Items	Sub-groups	BC patients (N= 70)		Control Group (N= 67)		P. value
		Freq.	%	Freq.	%	
Age (Years)	45-55	43	61.4	42	62.7	0.879*
	55-65	27	38.6	25	37.3	
Total ages (Years)		70 (100 %)		67 (100 %)		0.824*
Grades	II	38	54.4	-		
	III	32	45.6			
Stages	II	38	54.4	-		
	III	32	45.6			
Initial tumor size	1	8	11.4	-		
	2	38	45.3			
	3	21	30.0			
	4	3	4.3			
Axillary lymph nodes	0	19	27.1	-		
	1	29	41.4			
	2	19	27.1			
	3	3	4.3			

Note: *Chi squared test; BC: Breast Cancer.

Table 2 was shown the comparisom of biochmemical parameters between patients and control. It revealed that progesterone levels showed no statistically significant differences (P value >0.05); while, E2, CA15-3 and aromatase were shown highly signficant differences (P value <0.05).

Table 2.
Comparison of serum biomarkers between breast cancer patients and control group.

Biomarkers	Control group (N= 67) Mean± SD	BC patients (N= 70) Mean± SD	P. value
HB (g/dl)	11.497±0.584	10.641±0.353	0.0001*
RBS (mg/dl)	101.821±11.400	105.800±13.057	0.060*
Urea (mg/dl)	23.343±5.523	24.800±6.555	0.163*
Creatinine (mg/dl)	0.726±0.204	0.827±0.194	0.777*
Progesterone (ng/ml)	0.287±0.394	0.297±0.264	0.860**
E2 (pg/ml)	31.712±18.346	20.429±18.161	0.0001**
CA15-3 (U/MI)	10.290±3.868	111.100±82.119	0.0001**
Aromatase (ng/ml)	18.552±7.784	24.114±8.156	0.0001**

Note: *Student's t-test ; ** Mann Whitney's test

As shown in Table 3 and Table 4 grades and stages did not witness signficant statistical differences when biochmemical parameters of were studied (P values > 0.05).

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Table 3.
Differences of biomarkers among patients according to grades of breast cancer.

Biomarkers	Grades		P. value
	Grade II (N=38) Mean± SD	Grade III (N=32) Mean± SD	
HB (g/dl)	10.676±0.480	10.600±0.460	0.372*
RBS (mg/dl)	105.500±13.369	106.156±12.879	0.863*
Urea (mg/dl)	25.289±7.267	24.219±5.655	0.500*
Creatinine (mg/dl)	0.721±0.192	0.731±0.221	0.837*
Progesterone (ng/ml)	0.312±0.262	0.280±0.269	0.618**
E2 (pg/ml)	24.763±19.997	15.281±14.369	0.028**
CA15-3 (U/MI)	102.816±78.322	120.938±86.627	0.361**
Aromatase (ng/ml)	24.066±7.622	24.172±8.872	0.957**

Note: *Student's t-test; ** Mann Whitney's test

Table 4.
Differences in the measurement of biomarkers among different stages of breast cancer.

	Stages		P. value
	Stage II (N= 38) Mean± SD	Stage III (N=32) Mean± SD	
HB (g/dl)	10.584±0.097	10.709±0.508	0.141*
RBS (mg/dl)	103.868±12.766	108.094±13.226	0.179*
Urea (mg/dl)	25.421±7.073	24.063±5.908	0.392*
Creatinine (mg/dl)	0.726±0.226	0.725±0.178	0.979*
Progesterone (ng/ml)	0.307±0.260	0.286±0.272	0.744**
E2 (pg/ml)	18.863±16.538	22.288±20.027	0.436**
CA15-3 (U/ml)	123.211±92.435	96.719±66.472	0.181**
Aromatase (ng/ml)	25.858±8.265	22.044±7.640	0.55**

Note: *Student's t-test ; ** Mann Whitney's test

Table 5 was studied the discriminative (diagnosis) capability of the biomarkers under study. The variable E2 showed a higher AUC of 0.701. The best cut-off criterion for E2 was determined to be 25.0, which yielded a sensitivity of 72.9%, specificity of 59.7%, and an overall efficiency of 66.3%.

CA153 reported AUC of 1.000. The best cut-off point for CA153 was 22.25, which is associated with 100% sensitivity, 100% specificity, and 100% efficiency. Aromatase was displayed an AUC of 0.642 with significant p value. The best cut-off level for aromatase was 11.15, achieving a sensitivity of 100%, specificity of 74.6%, and an overall efficiency of 87.3%.

Table 5.
Receiver-operating characteristic (ROC) curve and area under the curve (AUC) analyses for the values of serum biomarkers for the diagnosis of breast cancer.

Variables	Area under the curve (AUC)	p-value (AUC0=0.5)	Best cut-off criterion	Sensitivity (%)	Specificity (%)	Efficiency or accuracy
Progesterone (ng/ml)	0.562	0.207				
E2 (pg/ml)	0.701	0.0001	25.000	72.9	59.7	66.3
CA15-3	1.000	0.0001	22.25	100	100	100

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(U/ml)						
Aromatase (ng/ml)	0.642	0.004	11.15	100	74.6	87.3

Source: AUC: Area Under the curve.

Various molecular models of CYP 1A1 aromatase rs10046 were examined for contribution in the prediction of ductal carcinoma, Table 6

In the codominant model; no significant associations were found between the TC or CC genotypes compared to the TT wild genotype, in both unadjusted and age-adjusted odds ratios was shown p-values > 0.05. But, there high odd ratios in both unadjusted and age-adjusted conditions.

In the dominant model; combining TC and CC genotypes, the results indicate a potential association with breast cancer. Specifically, the age-adjusted odds ratio was 1.99 with significant p-value 0.048, suggesting that having the TC or CC genotype might be linked to an increase risk of breast cancer.

In the recessive model; where the TT and TC genotypes are combined and compared to the CC genotype, no significant association was found, in both unadjusted and age-adjusted were p-values > 0.05. But; also, there were high odd ratios in both unadjusted and age-adjusted conditions.

It is very important, that patients who had the C alleles were statistically significantly different from those with the T alleles and had a 1.46 times greater risk of breast cancer.

Table 6.
Risk of breast cancer associated with CYP19 39UTR (rs10046) genotype according to different models of inheritance.

CYP 1A1 rs10046	BC patients N=70	Control N=67	Unadjusted OR (95% CI)	P. value	Age adjusted OR (95% CI)	P. value
Codominant						
TT Wild (Reference)	27 (54.3%)	37 (55.2%)				
TC Hetro	38 (54.3%)	29 (43.3%)	1.7 (0.89-3.58)	0.098	1.81 (0.90-3.65)	0.095
CC Homo	5 (7.1%)	1 (1.5%)	6.85 (0.75-62.06)	0.087	6.61 (0.72-60.28)	0.094
Dominant						
TC + CC	43 (100%)	30 (100%)	1.96 (0.99-3.88)	0.052	1.99 (1.00-3.96)	0.048
Recessive						
TT + TC (Reference)	65 (92.9%)	66 (98.5%)				
CC Homo	5 (7.1%)	1 (1.5%)	4.96 (0.55-44.65)	0.15	5.07 (0.57-44.13)	0.143
T Frequency	92	102	1.46 (1.04-2.03)	0.028	-	
C Frequency	43	30				

Note: Significant differences at (P< 0.05) OR: odds ratios; CI: 95% confidence intervals.

4. Discussion

Breast cancer can affect women across a broad age spectrum, although certain age groups might show higher incidence rates in larger populations. This study found most breast cancer cases (61.4%) were detected in women younger than 55 years of age, and that is similar to reported study [**11,1**]. Also, the results of this study agreed with previous study by Anderson *et al.* (2014), found that breast

cancer incidence rates generally increase with age, peaking in women aged 50-69. The findings in the United State (US) were different from the observations made in this study. In the US, 65.1% of the reported cases were identified in women who were 55 years of age or older; this information is supported by the surveillance, epidemiology, and end results cancer statistics review (SEER), [12]. The slightly higher prevalence of stage II breast cancer (54.4%) and stage III (45.6%) indicates a relatively late diagnosis in many cases. However, the close distribution suggests a significant number of advanced cases as well, highlighting the need for continued emphasis on early detection and screening programs. Category 2 tumor sizes, appearing in 45.3% of cases, were the most common. This indicated a moderate tumor size at diagnosis. A research analysis by Goldhirsch *et al.*, (2013); revealed that patients who have smaller tumors on the time of diagnosis have a high chance of surviving. That category 2 tumor incidence was the highest in this study also aligns with the need to continue conducting awareness and screening to discover the tumors before they increase in size. The distribution of axillary lymph node involvement showed that a notable proportion of patients had a significant number (41.4%) one lymph node involved, and two (27.1%) or three (4.1%) lymph nodes involved. Lymph node involvement indicated more advanced disease and may require more aggressive treatment. According to the SEER program data, current statistics reveal that about 30% of breast cancer patients present with any extent of LNI. This study's higher percentage (72.9% when combining all categories of lymph node involvement) might suggest a population with more advanced disease at diagnosis or different criteria for categorizing lymph node involvement [13]. Progesterone, a hormone involved in reproductive health, not showing significant variation between cases and controls. A study found that progesterone levels did not significantly differ between breast cancer patients and controls, corroborating the current findings [14]. Estradiol (E2) is one of the forms of estrogen, demonstrated highly significant differences; this conforms to best knowledge since estrogen is acknowledged to be instrumental in the determination of the severity and the advancement of some types of mammary carcinoma. That is why increased E2 levels in breast cancer patients are an effective marker of hormone receptor-positive tumors, which progress with estrogen. Thus, other investigations such as [15-17] revealed the differences in the estradiol level in the blood serum in women with breast cancer compared with the control group, which is in agreement with the results obtained in this study. CA 15-3 is one of the markers identified with breast cancer; since the differences in their levels obtained in the present study were highly significant between the patient and control groups, abnormal levels of this antigen in the patients give clues about tumor existence and growth. Other studies, for instance, Li *et al.*, 2020; and Rack *et al.*, 2016; also pointed out that raised CA 15-3 levels are linked with breast cancer and therefore, there is a need to adopt them as biomarkers [18,19]. Aromatase, an enzyme involved in estrogen synthesis, showed highly significant differences, reinforcing its role in breast cancer. Higher levels of aromatase in patients suggest increased estrogen production, which can drive the growth of hormone receptor-positive breast cancers. Bradley *et al.* (2022) reported increased aromatase activity in breast cancer tissues, which aligns with the highly significant differences observed in the current study [20]. The results of this study provided insights into the diagnostic or discriminatory capabilities of various biomarkers for breast cancer, evaluated using the area under the curve (AUC) from ROC analysis. The AUC of estradiol was 0.701 indicated moderate discriminatory ability. The sensitivity of 72.9% and specificity of 59.7% suggest that E2 can be somewhat useful in diagnosing breast cancer, though not highly accurate. E2 has potential as a supplementary diagnostic marker. It can help in identifying breast cancer but should be used alongside other diagnostic tools to improve accuracy. The AUC of cancer antigen 15-3 was 1.00 indicated perfect diagnostic or discriminatory ability. CA 15-3 at the cut-off of 22.25 demonstrates perfect sensitivity and specificity, making it an ideal biomarker for diagnosing breast cancer in this study. CA 15-3 appeared to be an exceptionally reliable biomarker for breast cancer diagnosis in this study. In Aromatase the AUC of 0.642 suggests good discriminatory ability. With a sensitivity of 100% and a specificity of 74.6%, aromatase is a promising biomarker with a good balance of diagnostic performance. Aromatase showed potential as a diagnostic marker for breast cancer, especially given its high sensitivity. It can be used in combination with other biomarkers to improve

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overall diagnostic accuracy. A study agreed with the findings of this study about estradiol (E2) and aromatase concentration [21] and this supports the perfect diagnostic capability observed in the presented study. Previous studies found the AUCs for CA15-3 was significantly higher compared to AUC = 0.5 [22,23], and this supports the perfect diagnostic capability observed in the presented study. The presence of the CYP1A1 gene polymorphism may elevate the likelihood of developing breast cancer by transforming estrogen metabolites into substances that might cause cancer [24]. In the codominant model, no components were proven to be statistically significantly different comparing TC or CC genotype to TT genotype. This implies that the risk of breast cancer does not differ between the heterozygous (TC) and/or homozygous variant (CC) groups compared directly with the homozygous wild-type (TT) group. For the genotype profile of the combined TC and CC, the odds ratio of the relationship with breast cancer was 1.99. The most common model implies that carriers of the T allele might possess some kind of protection from breast cancer. Thus, the protective effect of the T allele of the CYP1A1 gene may be assumed based on the odds ratio; however, due to the proximity to the p value significance level, additional research is required in this context. The recessive model was shown no differences between TT&TC genotypes and the CC genotype. This means that being a CC genotype is not significantly different from being a TT or TC genotype in terms of the ability to increase the risk of breast cancer among women. This study supports the hypothesis that the strong model of CYP1A1 aromatase rs10046 A/G polymorphism was likely to be associated with risk for breast cancer. The relation results from the co-dominant, dominant and recessive models imply that genetic effects on breast cancer are still unclear and intricate, and there is a need to conduct more extensive studies with larger sample size on this subject in future.

5. Conclusion

The study provides valuable insights into the diagnostic potential of certain biomarkers and the genetic risk factors associated with breast cancer. The findings suggest a possible association between the CYP19 rs10046 polymorphism and increased breast cancer risk among Iraqi women, particularly for the homozygous CC genotype. The mechanism by which this SNP influences breast cancer risk may involve alterations in aromatase activity and subsequent estrogen levels. However, the non-significant result for the CC genotype warrants further investigation with larger sample sizes to validate these findings.

Ethical approval: The current research was approved by the ethical consideration committee of the Training and Human Development Unit, Basrah Health Department, Ministry of Health/ Environment, Iraq, according to the research committee decision numbered (Basrah/810) on 22/11/2023.

Authors contribution: Samah Fadhil Hadi contributed to data collection, writing, and analysis. Shrouk A. Hassan Al. Ibraheem and Hamid Jaddoa Abbas contributed to the manuscript concept, results, analysis, manuscript submission, revision, and galley proof.

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