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GENETIC POLYMORPHISM OF SULT1A1 IN IRAQI BREAST CANCER WOMEN ON TAMOXIFEN

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Abstract

Background

Sulfotransferase enzyme SULT1A1 responsible for sulfation of active tamoxifen metabolites and formation of inactive ingredients that losing their pharmacological activity.

The objective of this study is to identify SULT1A1 genetic polymorphisms in Iraqi breast cancer women and their effects on tamoxifen treatment response.

Patients and methods venous blood taken from each participated women used for assessment of genotyping for both SNP of SULT1A1 gene rs6839 and rs9282861

Results indicated that for rs6839, the wild type TT is the predominant genotype compared to mutant TC and CC type, however for rs9282861 the homozygous mutant TT is the predominant genotype in comparison to the mutant CT and wild type CC. Among the several genetic variations of the SULT1A1 gene, the results showed a high incidence of joint pain with a low recurrence rate.

Conclusion in this cross-sectional study, we observed that in Iraqi women with breast cancer, the wild type of rs6839 was more common than the mutant version, and vice versa for rs9282861. However, these findings had only a small impact on side effects and recurrence among the patients. Large sample size is necessary to evaluate the true significance of the current findings and their potential impact on the prognoses of breast cancer patients.

Keywords Tamoxifen, SULT1A1 gene, side effects, recurrence

Introduction

Breast cancer is a major public health issue all over the world. In the United States, data collected in 2022 estimated a higher incidence of breast cancer 287,850 new cases (compromising 31% of all cancer types) compared to lung cancer 118,830 case (13%), despite the fact that lung cancer mortality is 21% (of all cancer deaths) overcoming breast cancer mortality 15% (1). In 2019, the most prevalent cancer among Iraqis is breast cancer (19.8 % of top ten cancer types), followed by Bronchus and Lung cancer (7.9 %), while cancer-related deaths are due to bronchus and lungs (16%), breast (11.3%), and leukemia (8.6%) (2).

Numerous risk factors may contribute to breast cancer include genetic predisposition, early menarche, late menopause, low parity, oral contraceptives and long-term hormone replacement

therapy (HRT), high breast density, a history of atypical hyperplasia and ionising radiation, obesity, and modern life style factors such as diet, cigarette smoking, and alcohol consumption (3).

Estrogen receptor positive (ER+) breast cancer account for approximately 75% of all breast cancers diagnosed. its expression in breast tumors may predict a favorable response to hormone therapy, which inhibits the effect of estrogen on breast cancer cells (4).

Tamoxifen is commonly used to treat women with estrogen receptor (ER)-positive breast cancer. Tamoxifen is a prodrug extensively metabolized by the cytochrome P450 enzyme system into 4-hydroxy tamoxifen and N-desmethyl-tamoxifen, which is then further metabolized to 4-hydroxy-N-desmethyl-tamoxifen (endoxifen), the most potent metabolite (5). Phase II drug metabolizing enzymes, including sulfotransferases (SULTs) and UDP-glucuronosyltransferases (UGTs), proceed the metabolic conversions to even more hydrophilic forms, facilitating excretion (6).

The thermostable phenol sulfotransferase SULT1A1 has been shown to be the primary enzyme responsible for the sulfation of tamoxifen. SULT1A1 primarily catalyzes the conversion of 4-OHTAM into inactive 4-OHTAM sulfate and endoxifen into inactive endoxifen sulfate (7)(8).

The variation in sulfonation capacity may be important not only in determining an individual's response to xenobiotics, but also to suggest the roles of SULT polymorphism in disease susceptibility (9).

Two SULT1A1 SNP has been studied, rs6839 (902T>C), was discovered in the 3′-untranslated region of the SULT1A1 gene. This SNP is linked to lower SULT1A1 enzymatic activity (8). Also a genetic polymorphism in exon 7 of the SULT1A1 gene rs9282861 (638C>T) causes an amino acid shift from arginine to histidine at the conserved position 213 of the protein (Arg213His) (10).

The purpose of this study was to investigate the frequency genotypes of SULT1A1 SNPs and to see how SULT1A1 gene polymorphism affected the therapeutic efficacy of tamoxifen in women with breast cancer.

Patients and methods

This cross-sectional observational study was carried out at the Oncology Center in Kerbala at Imam AL-Hussein Medical City in Iraq during the period (November 2021-Sepember 2022). A total of 100 female patients with hormone receptor (estrogen and/or progesterone) positive breast cancer treated with tamoxifen (20 mg) once daily for at least 3 months (nolvadex®), aged 45-65 years were enrolled in this study. The study was approved by ethical and scientific committee of college of pharmacy at Kerbala University, and each participant was given a written informed consent form and questioner for their participation.

The exclusion criteria included women taking tamoxifen therapy concomitantly with other adjuvant endocrine therapies, adjuvant chemotherapy or radiotherapy (or both), or taken drugs that induce or inhibit CYP2D6 such as fluoxetine. Pregnant or lactating women and females with history of thromboembolic events (deep vein thrombosis, pulmonary embolism) excluded from this study.

Clinical data collection

Some clinical information was collected from patients themselves while they were receiving treatment, such as age, weight, height, academic achievement, workplace, marital status, family history menopausal status and breast feeding. Another information taken from patient's medical records in the center which include date of diagnosis, site and type of breast cancer, stage and grade, dose, duration and time of tamoxifen.

Sample collection

Two ml of venous blood were collected from each female was kept in an EDTA tube for the genetic assay.

DNA extraction and Genotyping

The genomic DNA was extracted from a whole blood sample using a commercially available kit the favorprep mini kit (Favorgen/Taiwan) according to manufacturer's instruction. Genotyping of SULT1A1 gene involved in the metabolism of tamoxifen was accomplished using amplification refractory mutation system PCR (ARMS PCR) with specific primers for rs6839 (902T>C) and rs9282861 (638C>T) synthesized by using primer BLAST software and purchased from Macrogen/Korea as lyophilized product to evaluate the major alleles.

To prepare for PCR reaction, each primer dissolved by adding specific volumes of nuclease free water to obtain a stock solution with a concentration of 100 pmol/ µl. after that, a diluted work solution was made by adding 90 µl of nuclease free water to 10 µl of each stock solution. This work solution was kept at -20 until use.

The PCR mixture was prepared in a microcentrifuge tube by adding 12.5 µl of green master mix (Promega/USA), 0.5 µl of inner forward and reverse primers,1.5 µl of outer forward and reverse primers, 4 µl of DNA and the volume was brought to 25 µl with 4.5 µl of nuclease free water. Amplified segments were separated by gel electrophoresis apparatus using agarose gel 1.5% and ethidium bromide stain and observed under ultraviolet (UV) trans-illuminator. Tables 1-6 show primer sequences and PCR program for each SNPs.

Table (1): Primers sequences of rs 6839 (902T>C) and their primer size

Primers	Primers Sequence (5'-> 3')	Primer size (bp)	Product size (bp)
I-F	GCACACTCCCTCTGCAGTGCCT	22	T allele: 189 C allele: 136
I-R	AGCTGTGAGAGGGGCTCCTTGG	22	
O-F	CAGCCTCCAAATTGCTGGGATTACA	25	Two outer primers: 283
O-R	GGATGAGACTCCAGCTTTGCTCCC	24	
Inner Forward, I-R: Inner Reverse, O-F: Outer Forward, O-R: Outer Reverse			

Table (2): Primers sequences of rs 9282861 (638C>T) and their primer size

Primers	Primers Sequence (5'-> 3')	Primer size (bp)	Product size (bp)
I-F	GGTCTCCTCTGGCAGGGCGT	20	T allele: 191 C allele: 147
I-R	AAAAGATCCTGGAGTTTGTGGGTCG	25	
O-F	GGGAGATGCTGTGGTCCATGAAC	23	Two outer primers: 293
O-R	AGGAGTTGGCTCTGCAGGGTTTCT	24	
I-F: Inner Forward, I-R: Inner Reverse, O-F: Outer Forward, O-R: Outer Reverse			

Table (3): The volumes of nuclease free water added to each primer to obtain 100 pmol/µl concentration.

Primers		Volume of nuclease free water added (µl)
rs 6839 T > C	**rs9282861 C > T**	
I-F	I-F	250
I-R	I-R	250
O-F	O-F	250
O-R	O-R	250

Table (4): PCR mixture for genotyping of SULT1A1 rs 6839 T > C and rs 9282861 C > T

Component	Volume (µl)
Inner forward primer	0.5
Inner reverse primer	0.5
Outer Forward primer	1.5
Outer Reverse primer	1.5
DNA template	4
Nuclease free water	4.5
Green Master mix	12.5
Total	25

Table 5: PCR program for SULT1A1 gene rs 6839 (902T>C)

Steps	Temperatures (°C)	minute/second	Cycle
Initial denaturation	94	05:00	1
Denaturation	94	00:35	35

Annealing	62	00:30	
Extension	72	01:00	
Final extension	72	07:00	1

Table 6: PCR program for SULT1A1 gene rs9282861 (638C>T)

Steps	Temperatures (°C)	minute/second	Cycle
Initial denaturation	94	05:00	1
Denaturation	94	00:35	35
Annealing	60	00:30	
Extension	72	01:00	
Final extension	72	07:00	1

Statistical Analysis

The data of participants were converted into a computerized database, revised for errors or inconsistencies, and then managed, processed, and analysed by using the statistical package for social sciences (SPSS) version 28, IBM, US.

Scale variables presented in mean, standard deviation (SD), while descriptive statistics for nominal (categorical) variables represented as frequency (number of participants) and proportion (percentage). Chi-Square test was used to measure the association between categorical variables. Fisher's Exact test was used as an alternative when the chi square was inapplicable.

Finally, results and findings were presented in tables and or figures with an explanatory paragraph for each table or figure.

Results

Descriptive and demographic data

The studied population included100 female patients with breast cancer. The mean age was 51year ± 4.85 (range 45-65) (table1). The majority of participants were married (93%). The women with known family history of BC were (44%) in corresponding to (56%) had no family history. Over half of women (55%) have right side breast cancer compared to (45%) who had cancer in left side. Lymph node involved in (64%) of patient and absent in the others. Patients have both ER+/PR+ was (98%) and only (2%) were ER+/PR-, with higher percentage of HER2 + (67%) compared with HER2 - (33%). The percentage of patients who undergo previous surgery, radiotherapy and chemotherapy were (94%), (79%) and (91%) respectively. A high proportion of participants (76%) reported joint pain with no recurrence (97 %).

Table 7: Description of the Demographic and laboratory characteristics of the study patients

Variables			**Statistical values**
Age (Years) mean ±SD			51.08 ± 4.85
BMI (Kg/m^2) mean ±SD			28.30 ± 5.57
Duration of tamoxifen (Years) mean ±SD			3.41 ± 2.36
Duration of disease (Years) mean ±SD			4.18 ± 2.5
Marital status (%)	Married		93
	Single		7
Family History (%)	Yes		44
	No		56
Breast cancer Side (%)	Left breast		45
	Right breast		55
Lymph node Involvement (%)	Yes		64
	No		36
Surgery (%)	Yes		94
	No		6
Chemotherapy (%)	Yes		91
	No		9
Radiotherapy (%)	Yes		79
	No		21
Immunohistochemical tests (%)	HER2	Negative	67
		Positive	33
	Positive for both ER/PR		98
	ER positive /PR negative		2
Side effects (%)	Hot flashes		13
	Joint pain		76
	Both (Hot flashes & Joint pain)		9
	endometrial hyperplasia		2
Recurrence (%)	Yes		7
	No		93

Genetic Analysis

The detected SULT1A1 genotypes in Iraqi breast cancer females

Table 8 shows the frequency and percentage of rs 6839 genotypes detected in breast cancer patients. The wild genotype (TT) was found to be the most frequent genotype in 100 Iraqi women with breast cancer (54%), followed by the homozygous mutant genotype (CC) (29%), and the heterozygous genotype (TC) (17%).

Table (8): The frequency and percentage of SULT1A1 gene rs 6839 detected in breast cancer Patients

Genotype	Group n=100	Frequency	%
rs 6839	TT (wild)	54	54%
	TC (heterozygous)	17	17%
	CC (homozygous)	29	29%
Data Presented by numbers and percentage			

Table 9 shows the frequency and percentage of rs 9282861 genotypes detected in breast cancer patients. The homozygous mutant genotype (TT) was found to be the most frequent genotype in 100 Iraqi women with breast cancer (41%), followed by the wild genotype (CC) (38%), and the heterozygous genotype (CT) (21%).

Table (9): The frequency and percentage of SULT1A1 gene rs 9282861 detected in breast cancer Patients

Genotype	Group n=100	Frequency	%
rs 9282861	CC (Wild)	38	38%
	CT (heterozygous)	21	21%
	TT (homozygous)	41	41%
Data Presented by numbers and percentage			

The observed and expected SULT1A1 genotype distribution of the tested variants among the 100 Iraqi breast cancer females according to Hardy–Weinberg equilibrium.

The result of comparison between observed and anticipated values for SNP with rs 6839 in the tested population were shown in figure (1), and table (10). The distribution and percentage of individuals having rs 6839 differ from those expected under Hardy–Weinberg equilibrium {number of observed vs expected were: TT (54, 39.1); CC (29, 14.1); TC (17, 46.9) (goodness-of-fit χ^2 for rs 6839 40.526, $P < 0.001$) and therefore it was statistically significant.

Table (10): Hardy–Weinberg equilibrium for rs 6839 genotype in patients

Genotype n=100	Frequency%	Alleles		Hardy–Weinberg equilibrium test χ^2
		T	C	
TT (Homozygous wild type)	54	0.625	0.375	40.619
TC	17			P < 0.001 [S]

(Heterozygous mutant type)				
CC (Homozygous mutant type)	29			

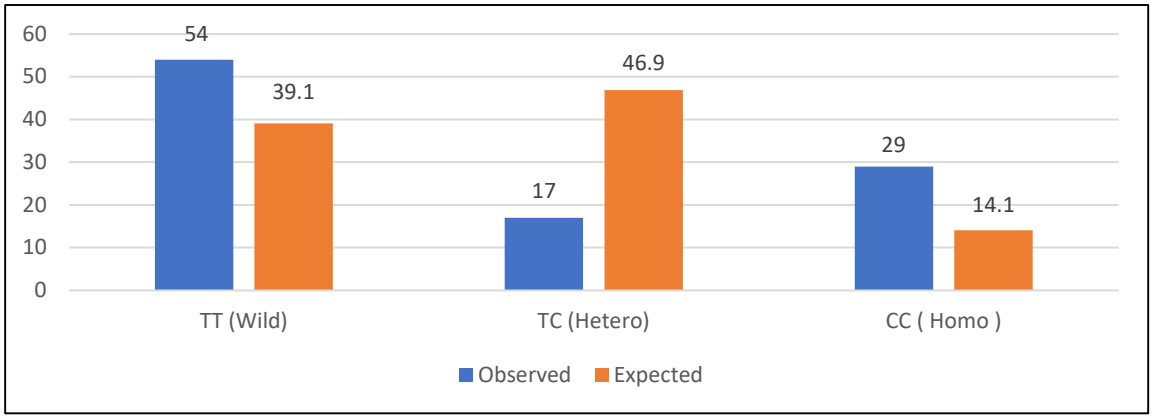

Figure (1): Observed (Obs.) vs expected (Exp.) genotype frequencies % of rs 6839 among individuals' sample

The result of comparison between observed and anticipated values for SNP with rs 9282861 in the tested population were shown in figure (2), and table (11). The distribution and percentage of individuals having rs 9282861 differ from those expected under Hardy–Weinberg equilibrium {number of observed vs expected were: CC (38, 23.5); TT (41, 26.5); CT (21, 50) (goodness-of-fit χ^2 for rs 9282861 33.595, $P < 0.001$) and therefore it was statistically significant.

Table (11): Hardy–Weinberg equilibrium for rs 9282861 genotype in patients

Genotypes n=100	**Frequency%**	**Alleles**		**Hardy–Weinberg equilibrium χ^2 test**
		T	**C**	
CC (Homozygous wild type)	38	0.515	0.485	33.595 P < 0.001 [S]
CT (Heterozygous mutant type)	21			
TT (Homozygous mutant type)	41			

rs 9282861 among individuals' sample

Figure (2): Observed (Obs.) vs expected (Exp.) genotype frequencies % of rs 9282861 among individuals' sample

Group		Recurrence		P Value
		No	Yes	
Age Group	44 - 49 yr.	44	1	0.025*
	50 – 55 yr.	32	6	
	56 - 65 yr.	17	0	
BMI group	Obese	57	4	0.828
	Non-obese	36	3	
Duration of Treatment	≤5 Years	75	6	0.742
	>5 Years	18	1	
Duration of Diagnosis	≤5 Years	66	4	0.441
	>5 Years	27	3	

Table (12): Association of side effects with demographic data

Group		Hot flashes	Joint pain	Both	Endometrial hyperplasia	P Value
Age Group	44 - 49 yr.	5	33	7	0	0.252
	50 - 55 yr.	6	29	1	2	
	56 - 65 yr.	2	14	1	0	
BMI group	Obese	7	48	5	1	0.887
	Non-Obese	6	28	4	1	
Duration of Treatment	≤5 Years	10	62	7	2	0.876
	>5 Years	3	14	2	0	
Duration of Diagnosis	≤5 Years	8	53	7	2	0.668
	>5 Years	5	23	2	0	

Table (13): Association of recurrences with demographic data

Table (14) Difference between side effect and recurrence in rs 6839 SNP

Demographic parameters		Genotype n=100			P value
		TT n=54	TC n=17	CC n=29	
Side effect	Hot flashes	5	1	7	0.21
	Joint pain	44	14	18	
	Both (Hot flashes & Joint pain)	3	2	4	
	Endometrial hyperplasia	2	0	0	
Recurrence	Yes	3	1	3	0.70
	No	51	16	26	
Results are presented as mean ± SD, n= number of subjects and percentage, P value < 0.05 considered significant					

Table (15) Difference between side effect and recurrence in rs 9282861 SNP

Demographic parameters		Genotype n=100			P value
		CC n=38	CT n=21	TT n=41	
Side effect	Hot flashes	2	6	5	0.19
	Joint pain	31	13	32	
	Both (Hot flashes & Joint pain)	4	1	4	
	Endometrial hyperplasia	1	1	0	
Recurrence	Yes	4	2	1	0.32
	No	34	19	40	
Results are presented as mean ± SD, n= number of subjects and percentage, P value < 0.05 considered significant					

Discussion

Tamoxifen is a standard endocrine therapy that act as selective estrogen receptor modulator, prescribed for the treatment of hormone sensitive tumor, early, locally advanced and metastatic breast cancers in pre- and postmenopausal women, ductal carcinoma in situ, and as primary chemoprevention in high-risk women. It can be used as neo- or adjuvant therapy, with lymph node negative/positive (11). Because many tamoxifen-metabolizing enzymes are polymorphic, genetic differences in tamoxifen-related outcomes may account for interindividual or interethnic differences (12).

Sulfotransferase enzymes catalyze the transfer of sulfonate (SO_3^-) from the universal sulfonate donor 3′-phosphoadenosine-5′-phosphosulfate (PAPS) to the hydroxyl or amino group of an acceptor molecule. Sulfonation has generally been considered a detoxification pathway leading to

more water-soluble conjugates and aiding their excretion via the kidneys or bile (13)
The genetic differences in SULT1A1 is of great interest because this enzyme is involved in the metabolism of endo- and xenobiotics, procarcinogen activation/detoxification, and the disposition of several therapeutic agents including acetaminophen, minoxidil, diethylstilbestrol and 4-hydroxy tamoxifen (14).
The SULT1A1-catalyzed sulfation of 4-OH TAM may have a significant impact on the efficacy of tamoxifen therapy because 4-OH TAM has a much higher affinity for binding to the estrogen receptor than the parent compound. As a result, SULT1A1 activity could be an important indicator of tamoxifen therapeutic efficacy, and modification of SULT1A1 activity by genetic and/or environmental factors may influence treatment outcomes (15).
Among the 200 Egyptians genotyped for SULT1A1, the genotype distribution and alleles frequency for rs9282861 were CC (149), CT (48), and TT (3), with 0.865 and 0.135 for the C and T alleles, respectively (16).
In the 97 Japanese participants with rs9282861, the frequency distribution of high activity allele (CC) was 78 and low activity alleles were 19, p value >0.037 associated with SULT1A1 activity. While 3′-UTR rs 6839 SNP were not associated with enzymatic activity (p value >0.05) (17).

The genotype distribution of 97 normal snap-frozen liver specimens from the United States was obtained. For rs 6839, the allele frequencies for wild TT (35), mutant TC (43), and CC (19) were supplied, whereas for rs 9282861, the allele frequencies for wild CC (37), mutant CT (40), and TT (20) were given (8).
Previous research by Yu et al. (18) and Sanchez et al. (8) confirmed that lower enzymatic activity of SULT1A1 in the presence of the rs 6839 SNP would result in higher concentrations of endoxifen and 4-OH TAM due to their lower elimination. According to these findings, the low activity group (CC genotype) had a lower risk of relapse than the medium (TC) and high activity groups (TT). Despite the fact that only a few patients relapsed in our study, they were evenly distributed between (CC genotype) and (TT genotype).
The findings of Tengström et al. (10), a study of 412 Finnish breast cancer patients in which 65 patients received adjuvant tamoxifen, are comparable to our findings regarding the fact that risk of recurrence was more prominent in genotypes CC and CT and less prominent in those with the genotype TT. This supports the idea that the homozygous TT variant genotype of SULT1A1 rs9282861 may have a functional consequence of decreased enzymatic activity and thermostability that may result in slower removal of 4-OH-TAM, extending its duration of action and enhancing survival.
Nowell et al. (15) and Wegman et al. (19) found that homozygous (mutant TT genotype) had a worse outcome in tamoxifen-treated breast cancer patients than both homozygous (wild CC genotype) and heterozygous (mutant CT genotype) SULT1A1 carriers of rs9282861. However, Consequently, the effect of SULT1A1 and clinical outcome among tamoxifen-treated patients is still unclear. It is hypothesized that hepatic sulfation of 4-OH TAM, followed by kidney reabsorption and further desulfation by steroid sulfatase expressed in breast tumors, would slow

the rate of clearance of 4-OH TAM and result in higher levels of circulating metabolite in individuals with higher activity SULT1A1 alleles. Furthermore, the presence of SULT1A1 in breast tumors, in conjunction with steroid sulfatase, may result in the cycling of 4-OH TAM between sulfated and non-sulfated forms within the cancerous cell. thus, extending the duration of action of active 4-OH TAM.

In a systematic and meta-analysis study based on ethnicity, Mohammad et al. (20) discovered that the SULT1A1 Arg213His (rs9282861) polymorphism increased breast cancer risk in Asians but not in Caucasians. The studies included were published between 2000 and 2013. There were twelve studies of Caucasian descendants and eight studies of Asian descendants among those. These studies were carried out in the United States, Austria, India, Korea, Sweden, Germany, Finland, China, Taiwan, Russia, and Italy. Although Iraq is considered to be part of the Asian continent, we found no difference in cancer risk or relapse between polymorphisms in our study.

Wang et al. (21) performed a meta-analysis of 14 published case–control studies find no significant association of the Arg213His (rs9282861) polymorphism with breast cancer risk. However, further ethnic population analysis revealed a significant association of the variant homozygote TT with a 2.27-fold increased risk of breast cancer in Asian population compared with subjects carrying CC genotype.

Joint pain and arthralgia are among the most common side effects seen in our research in patients receiving tamoxifen or aromatase inhibitors (AIs) for prolonged time periods as adjuvant hormonal treatment and have a negative impact on their quality of daily life. It is possible that younger patients have a higher frequency of arthralgia than their older counterparts due to the acute reduction of sex hormones caused by hormonal treatment (22). Previous studies revealed that the majority of Iraqi women in Kerbala who had breast cancer reported arthralgia while receiving hormonal therapy using the aromatase inhibitor anastrzole (23) (24).

Estrogen receptors can be found in joint cartilage, subchondral bone, and synovium. Estrogen has anti-inflammatory and immunosuppressive properties. In vitro studies have shown that acute estrogen withdrawal activates the nuclear factor κB transcription factor, which then increases the production of proinflammatory cytokines, eventually leading to tissue destruction. Estrogen receptors can also be found in the limbic system and the dorsal root ganglion. In the central nervous system, estrogens inhibit pain signaling (25).

Genotype distribution for both SULT1A1 SNPs rs6839 and rs9282861 were not in Hardy-Weinberg equilibrium (χ^2=40.619 and 33.595, respectively, with significant p value < 0.001), this may be attributable to the small sample size which may not accurately reflect the whole population.

Conclusion

In summary, we noticed that the rs6839 wild type was more prevalent than the mutant type in our study of breast cancer in Iraqi women, whereas the rs9282861 mutant type was more prevalent than the wild type. According to this study, the likelihood of recurrence and adverse effects are not significantly impacted. Therefore, further large scale, population-based association studies are required to asses real relevance of the present findings and their potential influence on the

treatment outcomes of breast cancer patients.

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