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Effect of *CYP3A4* Genetic Polymorphism on Clinical Response of Tamoxifen in Postmenopausal Iraqi Women with Breast Cancer

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Abstract

Breast cancer is the leading cause of death and is the most frequent disease among women. Tamoxifen is an antiestrogen used to treat breast cancer. It may completely halt the disease's progression in high-risk individuals and lower the risk of death and recurrence in premenopausal and postmenopausal women. Variations in tamoxifen responsiveness between individuals may be attributed to polymorphisms in the primary metabolizing enzyme CYP3A4. The wild genotype (GG) of rs35599367 was found to be the most common in 100 female breast cancer patients who were hormone receptor positive and taking tamoxifen, according to the study. This genetic variation may have a significant impact, as the GG genotype is strongly linked to significantly lower levels of CA15.3 and estrogen. Therefore, the results of this study imply that *CYP3A4* variations may be a useful predictor of a patient's prognosis and response to tamoxifen.
Keywords: CA 15.3, *CYP3A4* Polymorphism, Estradiol, Tamoxifen.

Introduction

Among women, breast cancer claims the largest number of cancers diagnoses and related deaths [(1) (2)]. It is recognized as a diverse illness that includes estrogen receptor α (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. Those who are ER-positive (ER +ve) account for 70% of breast cancer patients. Addressing ERs via antidotes offers a sensible method of combatting ER + ve breast cancer [(3)]. Medicines like tamoxifen (TAM), which slow breast carcinoma, are applicable to high-risk individuals [(4)]. For over thirty years, TAM has been a trusted method of treating estrogen-receptor-positive breast cancer, effectively aiding in the treatment of both early and metastatic breast cancer cases [(5)]. Women across several age ranges benefit from TAM, as it has been shown to substantially reduce mortality and relapse rates in both premenopausal and postmenopausal women affected by breast cancer. An impressive statistic from [(6,7)] shows that TAM is capable of reducing the 15-year risks of breast cancer recurrence and death by about a third in early-stage applications. Despite TAM's success, it is still common for 30 – 50 % of those receiving the treatment to exhibit a lack of response, which may indicate gene variations [(8)].

Previously our team had suggested that CYP2D6 strongly associated with survival and TAM response [(9)]. In our pursuit of knowledge regarding the TAM metabolizing enzyme cytochrome p450 family 3 subfamily A member 4 (CYP3A4) 's genetic variants, we have discovered their correlation with the diverse clinical responses manifested in those undergoing TAM treatments. TAM is a prodrug that is metabolized by CYP2D6 and, to a lesser extent, CYP3A4 in the liver, resulting in the active metabolites 4-hydroxytamoxifen and endoxifen, which have a significantly higher affinity for endogenous receptors than TAM. The rate-limiting enzyme in the metabolism of tamoxifen is believed to be CYP2D6, but other CYP enzymes, especially CYP3A4, may also play a significant role in determining tamoxifen metabolism and may contribute to interindividual variability in serum concentration, which may then affect the action on the ER and the response to treatment [(10, 11, 12)]. Both

CYP2D6 and *CYP3A4* polymorphisms are significant predictors of a patient's endoxifen level and the possible benefit of tamoxifen therapy in the future [13]. That being said, not much is known about the clinical implications of *CYP3A4* polymorphism. The *CYP3A4*22* allele, however, has reportedly been shown to be a functional of CYP3*A* allele, which occurs in the Caucasian population with a frequency of 5-7%, has been associated with decreased CYP3A4 activity [10 - 14]. As a result, there is a chance that the metabolizing enzyme's genetic variations have varying degrees of correlation with the clinical results seen in TAM-treated patients [14]. As far as we are aware, no studies have been done on how *CYP3A4*22* polymorphisms affect TAM response in Iraqi populations. This study aimed to identify the *CYP3A4*22* G>A (rs35599367) genetic polymorphism in a sample of Iraqi women with breast cancer and to explore the effect of the selected SNP in the study on TAM response.

Patients and Methods

Patients

This cross-sectional observational study was conducted in November 2022 to April 2023 at Imam Al-Hussein Medical City and Imam AL-Hassan AL-Mujtaba Teaching Hospital / Oncology Center in Kerbala. Tamoxifen 20 mg/day has been the standard adjuvant therapy for 100 female breast cancer patients with hormone receptor positive estrogen receptor and/or progesterone receptor, aged 45 years and above, for at least 4 months. Before starting tamoxifen treatment, all patients had previously finished all primary surgery, radiation, and adjuvant chemotherapy. The study was approved by the College of Pharmacy's Scientific and Ethical Committee at the University of Kerbala. Following an explanation of the study's purpose and design, each patient signed an informed consent form. Patients who began taking TAM concurrently with adjuvant radiation therapy, chemotherapy, or both (or both) or who were receiving other adjuvant endocrine therapies were excluded. Patients with a history of gastrointestinal disorders or surgery that may have affected the absorption of TAM, as well as concurrent medications that induce or inhibit CYP2D6 and CYP3A4, were excluded from the study. We categorized the study patients into two groups: responders and non-responders, based on their plasma levels of estradiol (E2) and cancer antigen tumor marker (CA15.3). The classification was determined through careful analyses of individual patient data, taking into account the specific cutoff values for E2 and CA15.3 values referred to the normal kit values that used in the measurements. Patients with levels above a certain threshold were considered non-responders, while those below were responders. This grouping method allowed to study how treatment outcomes varied based on hormone and tumor marker profiles. Threshold value for estradiol plasma level of postmenopausal women according to the utilized kit was: 32.2 pg./ml, and for tumor marker CA15.3 level was: 32.4 U/ml.

Clinical data collection

Some clinical data, including age, weight, family history, number of children, use of contraception, and existence of side effects, were collected directly from patients during treatment. The date of the diagnosis of breast cancer, the site (left breast, right breast, bilateral), the stage, the immunohistochemical status (ER, PR, HER2), the surgery, the chemotherapy, the radiation, the length of time on tamoxifen therapy, and other information were also taken from the medical records of the consenting female patients.

Blood sample collection

Each female participant in the study gave about 5 ml of venous blood, of which 2 ml was put in an EDTA tube for genetic testing. The remaining (3 ml) was put in a gel tube, allowed to clot for 15 minutes, and then centrifuged for 10 minutes at 5000 rpm to separate the serum used to measure biochemical parameters like CA15.3 and E2.

Genotyping

This study includes one SNP of (rs35599367) in the gene *CYP3A4*, which is involved in the metabolism of TAM, according to genotyping. The DNA extraction was done at the University of Kerbela- College of Pharmacy's Laboratory of Molecular Biology. Using the AddPrep Genomic DNA Extraction Kit (Korea), genomic DNA was isolated. Spectrophotometry was used to determine the DNA content, and before being used, purified DNA was kept at -20 °C. The *CYP3A4* gene's rs35599367 was found using the amplification refractory mutation system polymerase chain reaction (ARMS-PCR) technique in the current study. This SNP's specific primers are listed in Table 1. The PCR mixture was prepared in a microcentrifuge tube by adding 25 µl of smart mix (SolGent/Korea), two µl of each primer, five µl of DNA, and nuclease-free water to bring the volume to 50 µl. The 32 cycles in the PCR amplification program are as follows: a 30-second denaturation at 95°C, a 30-second anneal at 61°C, a 1-minute extension at 72°C, and a 5-minute extension at 72˚C. The initial denaturation lasts for three minutes at 95°C. UV trans-illuminator was used to view the amplified segments that had been separated by a gel electrophoresis apparatus using 1.5% agarose gel and ethidium bromide stain. Using a DNA ladder (100–1500 base pair (bp)), the molecular weights of the bands were ascertained after DNA bands were captured on camera with a UV trans illuminator.

Biochemical analysis

The instrument used for serum determination of CA15.3 and E2 is DIRUI CM – 180 Chemiluminescence Immunoassay Analyzer. The quantitative determination of CA 15.3 and E2 in

human serum in vitro by the chemiluminescence immunoassay (CLIA) ([15]. Reference range for estradiol level in postmenopausal female < 32.2 pg/ml, and for tumor marker CA15.3 level <32.4 U/ml.

Statistical Analysis

The statistical package for social sciences (SPSS) version 26 was used to analyze the participant data that was entered into an electronic database. The biochemical results are normally distributed and displayed as mean ± SD, while the genotyping results are expressed as a percentage. ANOVA was utilized as a single factor to compare the biochemical parameters between the genotypes that were detected; a P-value of less than 0.05 was deemed significant. While nominal (categorical) variables are represented by frequency (number of participants) and proportion (percentage) in descriptive statistics, scale variables are presented as mean and standard deviation (SD). Measurement of the relationship between categorical variables was done using the Chi-Square test. In cases where the Chi-Square test was not applicable, Fisher's Exact test was utilized as a backup.

Table 1. Primers sequences of *CYP3A4*22* (G>A) (rs35599367) genetic polymorphism [16]

Primers	Primer sequence (5 '->3 ')	Primer size (bp)	Product size (bp)
I-F allele G	GATGCAGCTGGCCCTACG	18	215
I-R allele A	AGTGTCTCCATCACACCCAGT	21	297
O-F	AGGGGTCTTGTGGATTGTTGA	21	474
O-R	CACCTGTCTTGAGCCCCTTAG	21	474
I-F: Inner Forward, I-R: Inner Reverse, O-F: Outer Forward, O-R: Outer Revers			

Results

Characterization of the study's patients

Demographic data of a total 100 women with breast cancer were presented in the Table 2. The patients were categorized based on age (45 - 49, 50-54, 55-59, 60-65), body mass index (Underweight, Healthy weight, Overweight, Obesity), duration of tamoxifen treatment was defined according to months, and duration of the disease (6-30, 31-54, 55-78, 79-102, 103-126, 127-150, 174-198 months).

Table 2. Description of demographic characteristics of the studied patients (n=100)

Variables	(N), %
Age (Years)	
45-49	(61), 61
50-54	(27), 27
55-59	(6), 6
60-65	(6), 6
BMI (Kg/m2)	
Underweight	(1), 1
Healthy weight	(7), 7
Overweight	(35), 35
Obesity	(57), 57
Duration of tamoxifen (months)	
4-18	(53), 53
19-33	(15), 15
34-48	(15), 15
49-63	(4), 4
64-78	(4), 4
79-93	(8), 8
94-108	(1), 1
Duration of disease (months)	
6-30	(53), 53
31-54	(18), 18
55-78	(14), 14
79-102	(6), 6
103-126	(5), 5
127-150	(2), 2
174-198	(2), 2
N refers to the number of patients, % refer to percent of the population	

Overview of clinical characteristics of the study patients

Key demographic and clinical characteristics of breast cancer females' patients were demonstrated in the Table 3 as percentages for each variable. The family history, 53% of patients have no family history, while 47% have a positive family history. Contraceptive use shows 42% using contraceptives and 58% not using them. Regarding the number of births, 73% of patients have had 1-5 children, 14% are nulliparous, and 13% have 6-8 children. The site of breast tumors is predominantly left-sided (51%), followed by right-sided (46%) and bilateral (3%). Breastfeeding practices vary, with 54% practicing breastfeeding, 22% mixed feeding, and 10% not breastfeeding. Surgical interventions include 39% undergoing breast-conserving surgery, 53% undergoing mastectomy, 2% having both mastectomy and breast-conserving surgery, and 6% having no surgical interruption.

The majority receive chemotherapy (94%) and radiotherapy (80%). Immunohistochemical testing for HER-2 reveals 70% negative and 30% positive results, with additional information on estrogen receptor (ER) and progesterone receptor (PR) status. Cancer stage distribution includes 14% at Stage I, 67% at Stage II, and 19% at Stage III. Recurrence is observed in 5% of cases.

Table 3. Description of demographic and disease characteristics of the studied patients (n=100)

Variables			Percentage
Family history %	No		53
	Yes		47
Contraceptive use %	Yes		42
	No		58
Number of births%	Nulliparity		14
	1-5 child		73
	6-8 children		13
Site of breast tumor%	Left		51
	Right		46
	Bilateral		3
Breast feeding%	Mix		22
	No		10
	Yes		54
	Nulliparity		14
Type of surgery%	Breast conserving		39
	Mastectomy		53
	Mastectomy and breast conserving		2
	No surgical interruption		6
Use of chemotherapy%	Yes		94
	No		6
Use of radiotherapy%	Yes		80
	No		20
Immunohistochemical test	Human epidermal growth factor receptor2 (HER-2)	Negative	70
		Positive	30
	Positive for both ER/PR		92
	ER positive /PR negative		6
	ER negative/PR positive		2
Cancer stage%	I		14
	II		67
	III		19
Recurrence	Yes		5
	No		95

Results are presented as percentages. HER2 stands for Human epidermal growth factor receptor 2.

Genetic analysis

The amplification result of *CYP3A4* gene, specifically *CYP3A4*22* (G>A) (rs35599367), displayed a clear band with a molecular size of 215 base pairs (bp) and 297 bp, as depicted in Figure 1. The determination of amplicon size was accomplished by comparing it with a DNA ladder ranging from 100 to 1500 bp. In Figure 1. we present the results of ARMS-PCR analysis for the genetic polymorphism of *CYP3A4*22* (G>A) (rs35599367)

within current study. Lane M signifies a DNA ladder (100-1500 bp). Lanes 7, 9, 10, 11, 12, 14, 16, 17, 18, and 19 exhibit GG genotype (wild type) homozygous individuals, displaying a distinct 215 bp band. Lanes 1, 2, 4, 6, 13, 15, and 20 represent AA genotype (mutant) homozygous individuals, characterized by a 297 bp band. Lanes 3, 5, 8, and 21 denote GA genotype (heterozygous) individuals, displaying both 215 bp and 297 bp bands. Electrophoresis was conducted at 45 volts.

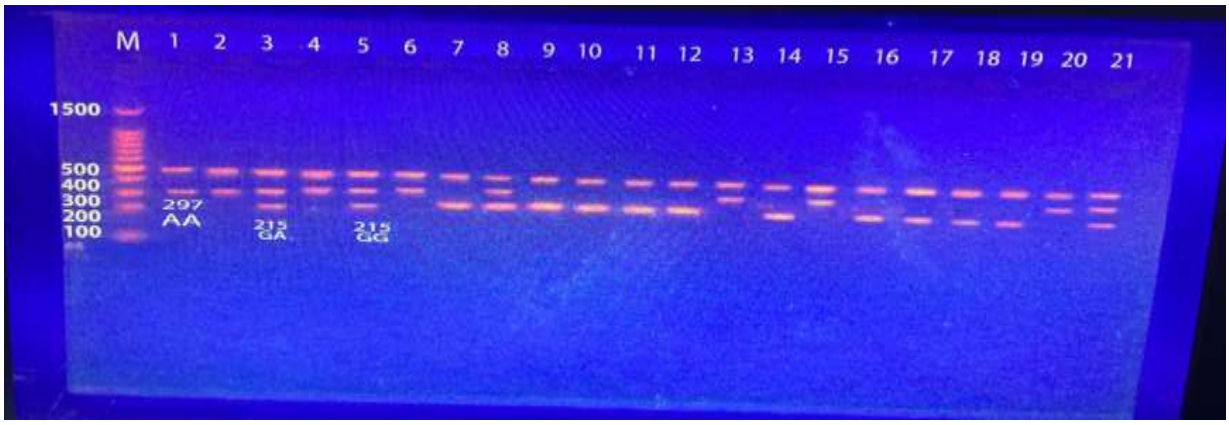

Figure 1. Polymorphism analysis of CYP3A4*22 (G>A) (rs35599367) using ARMS-PCR

CYP3A4*22 rs35599367 genotype distribution analysis and Hardy-Weinberg equilibrium assessment

In the current study of 100 individuals, we examined the genotype and allele frequencies of the *CYP3A4*22* gene single nucleotide polymorphism (SNP) as in Table 4. The observed genetic variation analysis revealed three genotypes (GG, GA, and AA), with GG being the most prevalent (39%), followed by AA (35%) and GA (26%). The data was presented both in numbers (frequency) and as percentages, allowing for an understanding of the relative distribution of each genotype within the sample.

Table 4. Distribution of *CYP3A4*22* (G>A) (rs35599367) gene SNP in breast cancer patients (n=100)

Gene SNP	Genotype	(N), %
*CYP3A4*22*	GG	(39), 39
	GA	(26), 26
	AA	(35), 35
Data presented by numbers and percentage.		

The genotype distribution in the studied patients along with statistical analyses assessing Hardy-Weinberg equilibrium were explored. Figure2 demonstrates the percentage of individuals with the genotypes GG, GA, and AA, and it compares the observed genotype frequencies with the expected frequencies under Hardy-Weinberg equilibrium. The Fischer exact test is applied for each genotype (GG, GA, AA), with the resulting p-values provided, and statistical significance is indicated by asterisks (*** denotes $p < 0.001$).

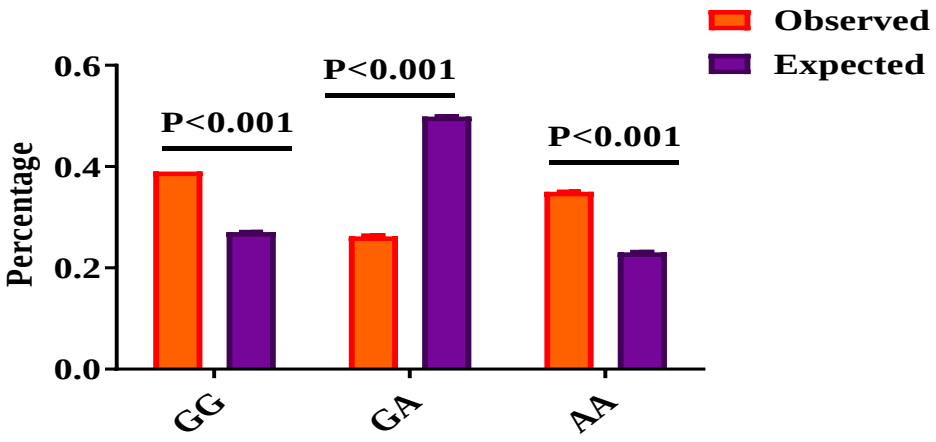

Figure 2. Represent the distribution and percentage of observed (obs.) individuals having CYP3A4*22 rs35599367 verse the expected (exp.) under Hardy–Weinberg equilibrium.

Exploring the influence of CYP3A4*22 SNP on laboratory parameters in breast cancer patients

Table 5 presents information on the parameters (Estradiol and CA 15.3) in relation to the *CYP3A4*22* gene variant, categorized by different genotypes (GG, GA, AA). The Mean±SD values represent the mean and standard deviation for each parameter within each genotype group. Tukey's Multiple Comparison Test is then applied to assess the significance of differences between genotypes. The Mean Diff. column indicates the mean difference between the compared groups, and the p-values in the "Significant P < 0.05" column determine if the differences are statistically significant. The "95% CI of diff" provides the 95% confidence interval for the mean difference. We found the mean difference of estradiol between GG and GA is not significant (p = 0.7330), while the mean difference between GG and AA is -12.95 with a p-value of 0.0916. Similarly, CA 15.3 shows significant mean differences between certain genotype pairs.

Table 5. Genotype-dependent effects of Tamoxifen on laboratory parameters in breast cancer patients: *CYP3A4*22* SNP analysis

Parameters	*CYP3A4*22* Mean±SD			Tukey's Multiple Comparison Test	Mean Diff.	P < 0.05	95% CI of diff
	GG n=30	GA n=26	AA n=35				
Estradiol Pg/ml	18.63±15.18	20.07±17.44	31.59±43.48	GG vs GA	-1.437	0.7330	-18.95 to 16.07
				GG vs AA	-12.95	0.0916	-29.36 to 3.449
				GA vs AA	-11.52	0.2282	-29.91 to 6.877
CA 15-3 U/ml	21.41±10.14	19.75±10.36	30.16±21.14	GG vs GA	1.658	0.5313	-7.304 to 10.62
				GG vs AA	-8.759	0.0132*	-17.34 to -0.1780
				GA vs AA	-10.42	0.0122*	-19.91 to -0.9190
*Denoted to the significant difference, CI rerefers to confident interval, mean Diff refers to mean differences							

Defined of study's patients into responders and non-responders based on normalization with estradiol and CA15.3 plasma levels.

We categorized the study patients into responders and non-responders based on the normalization with estradiol and CA15.3 plasma levels, as mentioned earlier in the materials and methods section. Table 6 refers to the genotypes GG, GA, and AA that considered for each biomarker, indicating the number of responders and non-responders within these genotype groups. For instance, in the case of estradiol levels and the GG genotype, there are 31 responders and 8 non-responders among a total of 39 individuals. The same categorization is applied to CA15.3 levels, providing insights into the distribution of patient responses across different genetic profiles.

Table 6. Cross-tabulation of *CYP3A4* genotype response according to serum estradiol and CA15.3 levels

Biomarker	Genotype	Responders, n	Non- Responder, n	Total
Estradiol level	GG	31	8	39
	GA	17	9	26
	AA	24	11	35
CA15.3 level	GG	30	9	39
	GA	19	7	26
	AA	24	11	35

Discussion

TAM is an effective drug for the treatment of hormonal positive breast cancer patients. However, about 20%–30% of those patients may develop relapse [17]. The Previous study provided evidence that allelic variations in *CYP3A4* enzyme highly affect response to tamoxifen by modulating the metabolism of tamoxifen into its pharmacologically active metabolite endoxifen [18]. Although *CYP3A4* polymorphisms has been investigated in many studies in the western countries, the results of its role on tamoxifen concentrations as well as its impact on the clinical

outcomes of the treated patients are conflicting and still not clear [19]. In this cohort study, we investigated the prognostic and predictive role(s) of *CYP3A4* polymorphism in metastatic and/or locally recurrent inoperable breast cancer patients from Iraq undergoing TAM treatment. Understanding the impact of genetic factors is crucial for identifying patients who may not respond to TAM, guiding alternative therapeutic modalities.

Demographic, clinical characteristics and breast cancer features of the study patients

The demographic and clinical characteristics data of 100 women with breast cancer disease that categorized according to a variety of variables including age, BMI, duration of disease and duration of TAM treatment/months. Clinical parameters were presented as percentages for each variable, we noticed a predominant percentage of patients have no family history of breast cancer, and a significant proportion of patients have had 1-5 children. The site of breast tumors is predominantly left-sided and a significant percentage of patients practiced breastfeeding. In terms of treatment, a noteworthy of patients underwent breast-conserving surgery, and the majority received chemotherapy and radiotherapy. HER-2 testing demonstrated a variation results with highly percentage revealed negative incomes. The distribution of cancer stages includes Stage I, Stage II, and Stage III, and relapse was observed in small percentage of the cases. The idea of collecting the descriptive data in this cohort study is to cluster factors that contribute to our understanding of shared genetic and environmental influences on breast cancer risk. For instance, Family history plays a crucial role that influence the risk of developing breast cancer. Females with family history of a first degree female relative diagnosed with breast cancer, her risk approximately doubles. This risk is even higher when more close relatives have breast cancer, or if a relative developed breast cancer under the age of 50 [20]. Aging is another factor that plays an important fact that enhance breast cancer development [21]. Many studies have suggested that obesity is associated with an increased risk of breast cancer recurrence and cancer death [22]. Previously, scientists have found that women who were assigned to receive about 5 years of adjuvant treatment with tamoxifen had a lower risk of recurrence in the 15 years after starting treatment. Coming from this evidence, our interest lies to investigate whether the suggested hypothesis could be influenced by genetic variations [23]. In addition, hormonal birth control may slightly increase the risk of breast cancer. Furthermore, studies have recommended that the more times women have given birth, the lower the risk of breast cancer. These evidences have tentative us to explore whether the suggested hypothesis could be impaired by the effect of gene variations [24,25]. Most patients had 1-5 children and breastfed them, which are factors associated with reduced breast cancer risk. However, these factors did not entirely prevent the development of the disease, indicating the influence of other, potentially more impactful, factors. Tumor distribution indicated a higher incidence of left-sided breast cancer, aligning with some existing studies, which may be due to hormonal variations, environmental factors or diagnostic biases [26,27]. Mastectomy, chemotherapy, and radiotherapy were common treatments, suggesting aggressive tumor characteristics. However, most patients had a negative HER2 status and a positive ER/PR status, favorable prognostic factors predicting better therapy response and lower recurrence risk [28]. The majority of patients were in stage II, indicating locally advanced tumors with a good chance of cure but necessitating close follow-up. Although a small percentage experienced recurrence, this reflects the effectiveness of treatment, highlighting the need for long-term follow-up and screening. Hence, these demographic variables serve as essential baseline data for assessing the influence of genetic factors, such as *CYP3A4*22* polymorphism, on TAM resistance in this diverse patient population.

Genetic variation analysis of CYP3A4*22 in breast cancer patients

In the current study, the observed genetic variation analysis revealed three genotypes (GG, GA, and AA), with GG being the most prevalent, which is consistent with the previous study in Iraqi population [16], while mutant genotype (AA) detected in others studies with very low frequency for example in Jordanian patients (2%) and (5%-7%) in Caucasian while Asian and African population below (1%) [29,30]. Deviation from Hardy-Weinberg equilibrium for all genotypes indicated specific factors influencing the genetic distribution of *CYP3A4*22* in this breast cancer patient population. Consistently with previous studies have observed this phenomenon, which emphasizes the importance of investigating the underlying genetic mechanisms and their implications for disease susceptibility and treatment outcomes [31, 32, 33].

Impact on laboratory parameters

The study explored the impact of *CYP3A4*22* SNP on laboratory parameters, including estradiol and CA15.3 levels. The GA and GG genotypes were significantly associated with lower CA15.3 levels, indicating a potential effect of gene variations on tumor marker levels. Estradiol levels were marginally lower in the GG genotype, suggesting a crucial role on hormone levels in a subset of patients. These findings suggest that the GG genotype may be significantly related to specific laboratory parameter variations and could be a key factor in individual responses to treatment and prognosis in breast cancer patients [16, 34, 35]. These findings underscore the importance of examining gene variations in breast cancer patients for tailoring personalized treatment plans. Understanding the

impact of genetic variations on laboratory parameters can provide valuable insights into disease aggressiveness, hormone receptor status, treatment decisions, and survival rates [36, 37, 38].

Defined of study patients into responders and non-responders based on normalization with estradiol and CA15.3 plasma levels.

We divided patients into two groups responders and non-responders based on the normalization with estradiol and CA15.3 plasma levels and their genotypes (GG, GA, AA). In case of estradiol plasma levels and the GG genotype, there are 31 responders and 8 non-responders among a total of 39 individuals. This means that a significant majority of individuals with the GG genotype responded to the treatment when considering estradiol levels. Similarly, applied to the plasma CA15.3 plasma levels, which allows researchers to understand how different genetic profiles might influence the response to treatment. interestingly, our data align with previous findings in which scientists suggested that genetic variations can significantly influence how patients respond to treatments [39, 40]. This specifically true in the field of oncology, where the effectiveness of cancer treatment including chemotherapy can vary greatly depending on the patient's genetic background. Furthermore, studies have shown that patients with different certain genotypes may respond differently to treatment [41]. for instance, patients with high concentration of CA15.3 before treatment and certain genotypes had poor prognoses and pathological response. More studies have shown that elevated CA15.3 post-treatment correlation with other factors such as lympho-vascular invasion and HER2 status, predicted a reduced disease-free survival [42, 43, 44].

Conclusion

The data of this study underscores the crucial role of genetic variations, in particular the *CYP3A4*22* polymorphism in estradiol positive breast cancer women underwent TAM therapy. *CYP3A4*22* has shown as a significant factor influencing treatment efficacy and clinical parameters. By characterizing patients according on genotype variations and clinical markers such as CA15-3 and estradiol levels, we can make treatment plans more proficiently, improving personal medicine and prognosis. Therefore, more research should employee to understand the complex relationship between genetics and cancer outcomes, which may translate into personalized clinical practice.

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Conflicts of Interest

There is no conflict of interests to mention.

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Ethics Statements

This study was conducted following ethical guidelines to ensure participants protection. We got the consent from all the participants were fully informed about the study's purpose, procedure and benefits. Participants were voluntary and they could withdraw from the study at any time without restrictions or penalty. All the participants data were anonymized and securely storing in password protected files accessible only to the research team. The study was approved by the Kerbala University/College of Pharmacy/Scientific and Ethical Committee (Approval#2022HU4 on November 2022)

Author Contribution

Arjwan Fouad Hussain: conceptualizing, methodology, data collection, formal analyses and writing original draft. Shaima Jabbar: formal analyses, writing and visualizing. Amal Umran Mosa: methodology, supervision and editing. Ahmed Salih Sahib: supervision, data collection and methodology. Jamal Ali Ashoor: methodology, resources and editing. Karrar Kadhim Mohsin: resources, methodology and data collection.

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تأثير تعدد الاشكال الجينية ل *CYP3A4* على الاستجابة السريرية للتاموكسفين لدى النساء العراقيات المصابات بـ سرطان الثدي بعد انقطاع الطمث

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الخلاصة

سرطان الثدي هو المرض الأكثر شيوعا وهو السبب الرئيسي للوفيات بين النساء. تاموكسيفين هواحد مضادات الاستروجين المستخدمة لعلاج سرطان الثدي. الذي قد يمنع تمامًا تطور المرض لدى الأفراد ذات المخاطر العالية ويقلل من خطر الوفاة والانتكاس لدى النساء قبل انقطاع الطمث وبعد انقطاع الطمث. قد تعزى الاختلافات في استجابة عقار تاموكسيفين بين الأفراد إلى تعدد الأشكال الجينية في إنزيم الاستقلاب الأولي CYP3A4. ووفقاً للدراسة، فقد وجد أن النمط الجيني متماثل الزيجة الطبيعي(GG)للمتغير الجيني ٣٥٥٩٩٣٦٧ هو الأكثر شيوعاً في ١٠٠ مريضة بسرطان الثدي اللاتي كانت مستقبلات الهرمون لديهن إيجابية ويتناولن عقار تاموكسيفين. يُلاحظ ارتباطًا معنويًا بين النمط الجيني GG ومستويات CA15.3 والاستراديول المنخفضة بشكل ملحوظ، مما يشير إلى التأثير المحتمل لهذا التباين الجيني على المعايير المختبرية. ولذلك، فإن نتائج هذه الدراسة تشير إلى أن اختلافات *CYP3A4* قد تكون مؤشرا مفيدا للتوقعات والاستجابة الدوائية للتاموكسيفين للمرضى.

لكلمات المفتاحية: دلالة الورم CA15.3، التعدد الجيني ل *CYP3A4*، استراديول، تاموكسيفي