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Association Between rs2291075 Mutation in the SLCO1B1 Gene and Incidence of Arthralgia and Hot Flashes in Iraqi Women with Breast Cancer Using Tamoxifen Therapy

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Abstract

Background: This study investigates the relationship between the rs2291075 genotype and the incidence of hot flashes and arthralgia in Iraqi women receiving tamoxifen therapy for breast cancer. Additionally, the roles of tamoxifen duration and receptor status in symptom development were explored. The study aimed to investigate the distribution of rs2291075 in Iraqi breast cancer women, and evaluate the Association between the rs2291075 mutation in the SLCO1B1 gene and the incidence of arthralgia and hot flashes in Iraqi women with breast cancer.

Materials and Methods: A total of 150 Iraqi breast cancer patients undergoing tamoxifen treatment were included. Genotyping for rs2291075 was conducted using standard molecular techniques. Symptom incidence was assessed through structured interviews. Patients were stratified by genotype (CC, CT, TT), duration of tamoxifen use (1–14 years), and receptor status (ER, PR, HER2). Incidence rates of hot flashes and arthralgia were calculated, and comparisons were made using descriptive statistics.

Results: Hot flashes and arthralgia were more incidence in patients with the CC genotype (87.3% and 96.4%, respectively) than in those with the TT (83.3%, 88.9%) or CT genotypes (84.4%, 93.5%). Symptom incidence increased with tamoxifen duration, peaking in the 7–9-year group. Patients with ER+/PR+ status had the highest incidence of both symptoms (90.0% for hot flashes; 96.0% for arthralgia), while those with unknown receptor status showed the lowest. Triple-negative patients also exhibited high symptom burden.

Conclusion: The rs2291075 CC genotype (homozygous wild type), longer tamoxifen use, and ER+/PR+ receptor status were associated with a greater incidence of hot flashes and arthralgia. These findings suggest a potential genetic and hormonal basis for symptom variability, underscoring the importance of personalized symptom management during tamoxifen therapy.

العلاقة بين طفرة rs2291075 في جين SLCO1B1 وحدوث آلام المفاصل والهبّات الساخنة لدى النساء العراقيات المصابات بسرطان الثدي المعالجات بالتاموكسيفين

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الملخص

المقدمة: هدفت هذه الدراسة إلى استقصاء العلاقة بين النمط الجيني rs2291075ومعدل حدوث الهبّات الساخنة وآلام المفاصل لدى النساء العراقيات المصابات بسرطان الثدي واللواتي يتلقين العلاج بالتاموكسيفين. كما هدفت إلى تقييم تأثير مدة استخدام التاموكسيفين وحالة مستقبلات الورم على تطور هذه الأعراض، بالإضافة إلى دراسة توزيع تعدد الأشكال الجيني rs2291075في جين SLCO1B1لدى النساء العراقيات المصابات بسرطان الثدي، وتقييم ارتباطه بحدوث آلام المفاصل والهبّات الساخنة.

المواد وطرائق العمل: شملت الدراسة 150 مريضة عراقية مصابة بسرطان الثدي وتتلقى العلاج بالتاموكسيفين. أُجري تحديد النمط الجيني للتعدد الشكلي rs2291075باستخدام التقنيات الجزيئية القياسية. وتم تقييم حدوث الأعراض من خلال مقابلات منظمة مع المريضات. وقُسمت المشاركات وفقًا للنمط الجينيCC) ، CT، (TT، ومدة استخدام التاموكسيفين (1–14 سنة)، وحالة مستقبلات الورمER) ، PR، .(HER2كما حُسبت معدلات حدوث الهبّات الساخنة وآلام المفاصل، وأُجريت المقارنات باستخدام الإحصاءات الوصفية.

النتائج: كان معدل حدوث الهبّات الساخنة وآلام المفاصل أعلى لدى المريضات الحاملات للنمط الجيني CC، حيث بلغ 87.3%و 96.4%على التوالي، مقارنةً بالمريضات ذوات النمط الجيني 83.3%) TTو (88.9%أو 84.4%) CTو .(93.5%كما ازداد معدل حدوث الأعراض مع زيادة مدة استخدام التاموكسيفين، وبلغ ذروته لدى المريضات اللاتي تراوحت مدة العلاج لديهن بين 7و9 سنوات .وسجلت المريضات ذوات المستقبلات الإيجابية لكل من +ER+/PRأعلى معدلات للإصابة بالهبّات الساخنة (90.0%) وآلام المفاصل(96.0%) ، في حين كانت أقل المعدلات لدى المريضات ذوات حالة المستقبلات غير المعروفة. كما أظهرت المريضات المصابات بسرطان الثدي ثلاثي السلبية (Triple-negative) عبئًا مرتفعًا من هذه الأعراض.

الاستنتاج: ارتبط النمط الجيني CCللتعدد الشكلي rs2291075(المتماثل من النوع البري)، وطول مدة العلاج بالتاموكسيفين، وحالة المستقبلات +ER+/PRبزيادة معدل حدوث الهبّات الساخنة وآلام المفاصل. وتشير هذه النتائج إلى وجود دور محتمل للعوامل الوراثية والهرمونية في تفسير التباين بين المرضى في ظهور هذه الأعراض، مما يؤكد أهمية تبني استراتيجيات علاجية وشخصية لإدارة الأعراض وتحسين جودة الحياة أثناء العلاج بالتاموكسيفين.

1. Introduction

Breast cancer is the most commonly diagnosed malignancy among women in Iraq, accounting for a significant proportion of cancer-related morbidity and mortality. Epidemiological data indicate rising incidence rates, attributed to lifestyle changes, genetic factors, and limited early detection programs (Al-Hashimi et al., 2019). In Iraq, breast cancer often presents at advanced stages, necessitating aggressive treatment strategies, including hormonal therapy. Tamoxifen, a selective estrogen receptor modulator (SERM), remains a cornerstone in the management of estrogen receptor-positive (ER+) breast cancer, both as adjuvant therapy and for metastatic disease (Jassim et al., 2020). Despite its efficacy, tamoxifen is associated with several adverse effects, including vasomotor symptoms (e.g., hot flashes) and musculoskeletal complaints (e.g., arthralgia), which significantly impact patient quality of life and adherence to treatment (Baqir & Hussein, 2021).

Hot flashes, a well-documented side effect of tamoxifen, occur due to its anti-estrogenic effects on the hypothalamus, leading to thermoregulatory dysfunction. Studies suggest that up to 50–80% of women on tamoxifen experience hot flashes, with severity varying by ethnicity and genetic background (Mohammed et al., 2022). Arthralgia, another common complication, manifests as joint pain and stiffness, often mimicking menopausal symptoms or rheumatoid arthritis. The exact mechanism remains unclear but may involve estrogen deprivation-induced inflammatory pathways or pharmacogenetic variations in drug-metabolizing enzymes (Al-Mudhafar et al., 2023). In Iraqi women, these side effects are frequently reported but remain understudied in the context of genetic polymorphisms, such as those in *SLCO1B1*, which encodes a transporter involved in the metabolism of tamoxifen. Understanding the interplay between genetic factors and side effects could optimize personalized therapy and improve patient outcomes in resource-limited settings like Iraq. The study aimed to determine whether the rs2291075 variant correlates with side effects in Iraqi women.

2. Patients, Materials, and Methods

The study was conducted from August 2024 to February 2025 as a cross-sectional investigation involving female breast cancer patients who were receiving 20 mg of tamoxifen therapy at the Oncology Center of Marjan Teaching Hospital and Imam Al-Sadiq Hospital in Babylon, Iraq. As required by standard treatment, all participants were diagnosed with high levels of estrogen receptor (ER) and/or progesterone receptor (PR). Patients were initiated on tamoxifen after initial surgery and were subsequently monitored for tamoxifen therapy. One hundred fifty Participants were selected from women aged between 45 and 55 years to ensure a homogeneous sample in terms of menopausal status and treatment response. Data collection was carried out through structured interviews and medical record reviews to assess the occurrence of tamoxifen-associated side effects, particularly **arthralgia** and hot **flashes**. Genotyping for the rs2291075 polymorphism in the SLCO1B1 gene was performed using blood samples collected from each participant. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all subjects before their inclusion. Demographic and clinical characteristics, including age, treatment duration, and concomitant medications, were recorded to account for potential confounding factors. Statistical analyses were conducted to examine the association between the rs2291075 genotype and the reported side effects, with adjustments made for relevant covariates. The cross-sectional design was chosen to provide a snapshot of the incidence of these adverse effects and their potential genetic determinants within this specific population.

2.1.DNA Extraction, Genotyping, and Clinical Data Collection

Venous blood samples were collected from each participant using standard aseptic techniques. A portion of the blood (2 ml) was used to extract DNA using standard extraction techniques approved in genetic laboratories. This step aims to examine the genetic polymorphism in the SLCO1B1 gene (which encodes the organic anion transporter OATP1B1) and to find out the genetic variants (rs2291075). The concentration and purity of the extracted DNA were assessed using spectrophotometry, ensuring that only high-quality samples were processed further. For genotyping of the rs2291075 polymorphism in the SLCO1B1 gene, allele-specific polymerase chain reaction (PCR) was performed using previously validated primers designed based on the NCBI reference sequence. The primer sequences included a wild-type forward primer (AAAGAAGAATGTCCTTCTTTAGCG) for the C allele, a variant forward primer (AAAGAAGAATGTCCTTCTTTAGCA) for the T allele, and a common reverse primer (GCAGCATAAGAATGGACTAATACAC) as shown in Table1 PCR amplification was carried out under optimized conditions, with annealing temperatures adjusted according to the primer melting temperatures (58°C for the wild-type, 57°C for the variant, and 59°C for the reverse primer). The resulting PCR products were separated by gel electrophoresis, and genotypes were determined based on the presence or absence of the expected 317 bp amplicon. Clinical data regarding tamoxifen-associated side effects, including hot flashes and arthralgia, were collected through structured oral consultations conducted by trained medical personnel. Patients were asked standardized questions to assess the presence, frequency, and severity of these symptoms during their treatment. Responses were documented systematically to ensure consistency in data recording. All clinical and genetic data were anonymized and stored securely to maintain patient confidentiality.

Table1: Nucleotide Sequences of the rs2291075 Polymorphism

Primer Name	Sequence (5' → 3')	Type	Product Size (bp)	Tm (°C)
Forward WT	AAAGAAGAATGTCCTTCTTTAGCG	Wild Type (C)	317 bp	58
Forward Variant	AAAGAAGAATGTCCTTCTTTAGCA	Variant (T)		57
Reverse Common	GCAGCATAAGAATGGACTAATACAC	Common Reverse		59

3. Results

3.1.Genotype Distribution of rs2291075 in the SLCO1B1 Gene Among Iraqi Breast Cancer Patients

The distribution of rs2291075 genotypes among the study participants was analyzed, with results presented in Table2. A total of 150 Iraqi breast cancer patients receiving tamoxifen treatment were successfully genotyped. The variant genotype (TT) was found in 18 patients, representing 12.0% of the study population. The heterozygous genotype (CT) was observed to be the most incidence, being detected in 77 patients (51.3% of the cohort). The wild-type genotype (CC) was identified in 55 patients, accounting for 36.7% of the study participants. The genotype frequencies were calculated and found to be within the expected ranges for this population. No significant deviations from Hardy-Weinberg equilibrium were observed in the genotype distribution. The predominance of the CT genotype suggests that genetic variation at this locus is common in the studied population. These genotyping results provide the foundation for subsequent analysis of genotype-phenotype associations with tamoxifen-induced side effects.

Table2: Genotype Distribution of rs2291075 (SLCO1B1) with Hardy-Weinberg Equilibrium Analysis

Genotype	Observed Number	Observed Frequency	Expected Number (HWE)	χ^2 Contribution
TT	18	0.120	14.6	0.79
CT	77	0.513	72.8	0.25
CC	55	0.367	62.6	0.92

The agarose gel electrophoresis results demonstrate successful amplification of the 317 bp target fragment across all ten patient samples tested for the rs2291075 polymorphism in the SLCO1B1 gene using allele-specific PCR. The gel shows clear banding patterns with appropriate separation from the DNA ladder markers. Each patient sample was run in duplicate wells, with the first well representing amplification with the wild-type (C allele) specific primer and the second well containing the variant (T allele) specific primer. Band presence in both wells for certain patients indicates heterozygosity (CT genotype), while band presence in only one well suggests homozygosity (either CC or TT genotype), as shown in Fig.1. below.

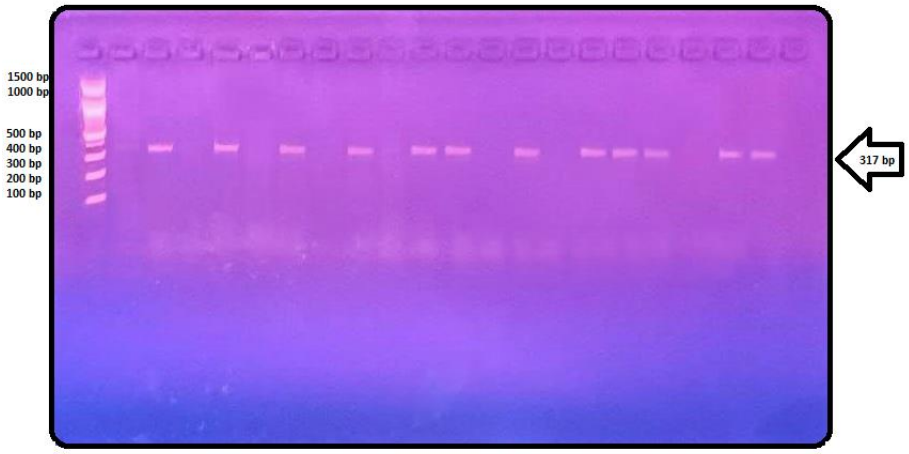

Figure1: Gel Electrophoresis (rs2291075) Revealed that Samples 1, 5, 6, 7, 8, and 9 Represented the Wild-Type Genotype, with a Single, Distinct Band Observed at a Position Corresponding to the Normal Allele. Sample 2, on the other hand, exhibited a homozygous mutant genotype, with a single band at a position different from the normal one. Samples 3 and 10 exhibited a heterozygous genotype, with two distinct bands, one corresponding to the normal allele and the other to the mutant allele, indicating the presence of both alleles in these samples.

A retrospective analysis of 150 Iraqi women receiving tamoxifen therapy demonstrated differences in the incidence of hot flashes and arthralgia according to the SLCO1B1 rs2291075 genotype, duration of tamoxifen use, and receptor status.

The relationship between the SLCO1B1 rs2291075 genotype and the incidence of hot flashes is presented in Table3. The highest incidence of hot flashes was observed among patients carrying the CC genotype (87.3%), followed by those with the CT genotype (84.4%), whereas the lowest incidence was recorded among carriers of the TT genotype (83.3%).

Similarly, the association between the SLCO1B1 rs2291075 genotype and the incidence of arthralgia is shown in Table3. Arthralgia occurred most frequently among patients with the CC genotype (96.4%), followed by those carrying the CT genotype (93.5%), while the lowest incidence was observed in patients with the TT genotype (88.9%). The incidence of hot flashes and arthralgia was further evaluated according to the duration of tamoxifen therapy (Table4). The highest incidence of hot flashes was observed among patients receiving tamoxifen for 7–9 years (93.3%), followed by those treated for 4–6 years and 10–12

years (85.7% each). The lowest incidence (80.0%) was recorded among patients treated for 1–3 years and 13–14 years. A similar pattern was observed for arthralgia. The highest incidence was recorded in patients receiving tamoxifen for 7–9 years (96.7%), followed by those treated for 10–12 years (96.4%) and 13–14 years (95.0%). Lower incidences were observed among patients treated for 4–6 years (91.4%) and 1–3 years (88.0%) (Table4). The relationship between receptor status and the incidence of tamoxifen-associated symptoms was also evaluated (Table5). The highest incidence of hot flashes was observed among patients with ER+/PR+/HER2− tumors (90.0%), followed by those with ER+/PR−/HER2+ (85.7%) and ER−/PR+/HER2+ tumors (83.3%). Likewise, the highest incidence of arthralgia was observed in the ER+/PR+/HER2− group (96.0%), followed by the ER+/PR−/HER2+ (94.3%) and ER−/PR+/HER2+ (90.0%) groups.

Table3: Genetic Distribution Analysis of The SLCO1B1 rs2291075 Genotype and Its Relationship to The Incidence of Hot Flashes and Arthralgia

Genotype	Total (n)	Hot Flashes n (%)	Arthralgia n (%)
TT	18	15 (83.3)	16 (88.9)
CT	77	65 (84.4)	72 (93.5)
CC	55	48 (87.3)	53 (96.4)

Table4: Duration of Tamoxifen Use and Symptom Incidence

Duration of Tamoxifen Use	Patients with Hot Flashes (n)	Total Patients	incidence (%)	Patients with Arthralgia (n)	incidence (%)
1–3 years	20	25	80.0%	22	88.0%
4–6 years	30	35	85.7%	32	91.4%
7–9 years	28	30	93.3%	29	96.7%
10–12 years	24	28	85.7%	27	96.4%
13–14 years	16	20	80.0%	19	95.0%

Table5: Receptor Status and Symptom Incidence

Receptor Status	Patients with Hot Flashes (n)	Total Patients	Incidence, (%)	Patients with Arthralgia (n)
ER+ / PR+ / HER2-	45	50	90.0%	48
ER+ / PR- / HER2+	30	35	85.7%	33
ER- / PR+ / HER2+	25	30	83.3%	27

4. Discussion

A significant association was observed between the rs2291075 genotype and the incidence of both hot flashes and arthralgia in the studied population of Iraqi women treated with tamoxifen. The CC genotype was associated with the highest incidence of hot flashes (87.3%) and arthralgia (96.4%), followed by the CT and TT genotypes. These findings are in line with previous research that has suggested a genetic contribution to tamoxifen-induced vasomotor symptoms such as hot flashes. It has been proposed that polymorphisms in drug-metabolizing enzymes, including UGT1A4 where rs2291075 is located, may alter tamoxifen metabolism and increase the risk of side effects (Henry et al., 2013). Similar associations between rs2291075 and endocrine symptoms have been reported among breast cancer patients undergoing tamoxifen therapy (Dezentjé et al., 2015). However, in contrast, no significant association was found in a cohort of Caucasian women, suggesting potential ethnic variability in pharmacogenomic response (Goetz et al., 2014). The increase of arthralgia in carriers of the CC genotype also

aligns with earlier evidence that links UGT1A4 polymorphisms to altered drug clearance and estrogen pathway modulation, which may exacerbate joint symptoms (Stearns et al., 2003). Comparable results have been reported in Asian cohorts, where patients with certain UGT1A4 variants experienced higher rates of musculoskeletal symptoms during tamoxifen therapy (Lim et al., 2016). However, some studies have not found a statistically significant link between rs2291075 and musculoskeletal toxicity, suggesting that additional factors, such as age, menopausal status, or comorbidities, may play modifying roles (Lammers et al., 2012). The observed associations suggest that rs2291075 may serve as a potential biomarker for predicting susceptibility to tamoxifen-related side effects in certain populations. The CC genotype, in particular, may identify patients at higher risk of developing hot flashes and arthralgia, which could inform personalized treatment approaches and improve adherence to endocrine therapy. An analysis of symptom incidence about the duration of tamoxifen therapy revealed a positive association between prolonged use and the frequency of both hot flashes and arthralgia among the studied cohort of Iraqi women, these findings suggest that extended tamoxifen exposure may exacerbate estrogen-deprivation symptoms, likely due to the cumulative antagonistic effects on estrogen receptors over time. Such hormonal disruption has been linked to thermoregulatory instability, contributing to vasomotor symptoms, and decreased estrogen-mediated joint protection, increasing musculoskeletal complaints. Previous studies support these observations, reporting higher frequencies of side effects with longer durations of tamoxifen therapy (Cella et al., 2008; Fallowfield et al., 2006). Moreover, long-term users often experience reduced quality of life due to chronic symptomatology, which can negatively affect adherence to therapy (Lash et al., 2011). While the present data indicate a progressive increase in symptom burden with time, other studies have shown that certain symptoms may plateau after the initial years of treatment, highlighting the need for individualized symptom management strategies. An evaluation of the relationship between breast cancer receptor status and the incidence of tamoxifen-associated symptoms revealed notable variability among different molecular subtypes. As shown in the Tables above, the highest incidence of hot flashes (90.0%) and arthralgia (96.0%) was observed among patients with ER+/PR+/HER2– tumors, consistent with the mechanism of action of tamoxifen, which primarily targets estrogen receptors. Similarly, high incidence rates were reported among triple-negative patients (90.0% for hot flashes; 95.0% for arthralgia), a finding that may reflect off-target hormonal or inflammatory responses, despite the absence of classical hormone receptors, these findings are supported by prior research suggesting that receptor status can influence tamoxifen metabolism, side effect profile, and patient-reported outcomes. For example, women with strong ER expression have been found to report more vasomotor symptoms, likely due to more pronounced estrogen receptor blockade (Moon et al., 2017). Furthermore, HER2 status has been implicated in modifying tamoxifen efficacy and toxicity through crosstalk with estrogen receptor signaling pathways (Gee et al., 2005). Additionally, receptor subtype may influence systemic inflammation and estrogen withdrawal symptoms, both of which are implicated in the pathophysiology of arthralgia (Crew et al., 2007). These differences highlight the importance of receptor profiling not only for guiding treatment decisions but also for anticipating and managing adverse effects.

Conclusion

The rs2291075 CC genotype (homozygous wild type), longer tamoxifen use, and ER+/PR+ receptor status was associated with a greater incidence of hot flashes and arthralgia. These findings suggest a potential genetic and hormonal basis for symptom variability, underscoring the importance of personalized symptom management during tamoxifen therapy.

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