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COMPREHENSIVE MOLECULAR EVALUATION OF ERCC5 RS1047768 T>C GENE VARIATION AND ITS ASSOCIATION WITH PREDISPOSITION AND CLINICOPATHOLOGICAL CHARACTERISTICS OF BREAST CANCER

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ABSTRACT

Breast cancer is a genetically diverse disease that is affected by genetic variations such as polymorphisms of DNA repair genes. The case-control study examined the relationship between ERCC5 T>C (rs1047768) and breast cancer risk and clinicopathological features in a Saudi cohort. One hundred Saudi women who had primary breast cancer and 100 healthy age-matched controls were included. ARM-PCR was used to complete genotyping and distribution of genotype in controls was in accordance with HardyWeinberg equilibrium. The TC and CC genotypes were more common in patients compared to controls (45% and 15% vs. 35% and 8%), and the frequency of the C allele was greater in patients (0.37 vs. 0.25). Under codominant, dominant and allelic models, significant associations with the risk of breast cancer were found. Moreover, the association of tumor stage, histological grade, estrogen receptor status, progesterone receptor status, HER2 status and distant metastasis with the association of rs1047768 were significant, whereas age and treatment status were not. These results indicate the possibility of breast cancer susceptibility in this population with ERCC5 rs1047768 T>C and potentially tumor characteristics that are more aggressive. Functional validation and larger studies should be done to validate its clinical relevance.

KEYWORDS: Breast cancer, ERCC5, rs1047768, single nucleotide polymorphism, DNA repair, nucleotide excision repair, genetic susceptibility, clinicopathological features, Saudi cohort.

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women globally and continues to pose a significant clinical and public health challenge, despite improvements in screening, molecular subtyping, and targeted treatments [1]. It is a complex disease that involves the interaction of hormonal, environmental, lifestyle, and genetic factors. While some inherited breast cancer can be attributed to high-penetrance pathogenic mutations in BRCA1, BRCA2, TP53 and PALB2 genes, most cases arise in the absence of these mutations and are likely the result of low- to moderate-penetrance variants that modulate genome stability, cell-cycle control and DNA repair [2,3]. As a result, common genetic variants in DNA repair genes have emerged as potential candidates to explain individual differences in the susceptibility to breast cancer and its clinicopathological features.

Genomic stability is maintained by DNA repair pathways that eliminate DNA lesions from becoming mutations. In particular, nucleotide excision repair (NER) is critical because it excises bulky, helix-distorting DNA lesions induced by ultraviolet light, chemical carcinogens, reactive oxygen species and certain DNA-damaging anti-cancer treatments [4,5]. NER involves lesion recognition, unwinding of the damaged DNA, incision on both sides of the lesion, excision of the damaged oligonucleotide, repair synthesis, and ligation. Impairment of NER can lead to an increased accumulation of mutations and genomic instability, which are key features of cancer development [3]. This is important in the genesis of breast cancers, as the mammary epithelium can be exposed to oxidative damage, estrogen-derived genotoxins, replication stress and other environmental DNA damaging insults.

Excision Repair Cross-Complementation Group 5 (ERCC5) gene, also known as XPG, is a structure-specific endonuclease required for NER. ERCC5 acts as a molecular "scissor" that makes the 3′ incision at the damaged DNA strand, and ERCC1-XPF makes the 5′ incision, allowing excision of the damaged DNA fragment and repair of the damaged strand [4,6]. In addition to its role as a catalytic incision enzyme, ERCC5 also stabilises the repair complex through its interaction with other NER proteins (e.g., TFIIH, XPA and RPA) suggesting it has both a catalytic and structural role in the coordination of repair [5]. ERCC5 has also been shown to be involved in transcription-coupled NER that repairs lesions that stall RNA polymerase II, further contributing to its role in RNA transcription fidelity and cellular homeostasis [4,7].

The critical role of ERCC5 in biology is also highlighted by rare genetic repair diseases. Germline mutations in ERCC5 cause xeroderma pigmentosum complementation group G and can also cause combined xeroderma pigmentosum/Cockayne syndrome, which results in impaired NER, severe sensitivity to sunlight, abnormalities in neurodevelopment, premature ageing and high risk of cancer [8-10]. These phenotypes indicate that ERCC5 plays a vital role in genome protection. In sporadic cancer, however, the impact will tend to be less dramatic: common ERCC5 polymorphism can also have an effect on DNA repair, cancer susceptibility or even tumor progression without a classical DNA repair disorder.

Among the ERCC5 polymorphisms that were tested, the rs1047768 T>C (also known as T335C or His46His) is of particular interest. Although rs1047768 is a synonymous polymorphism that does not alter the amino acid sequence, synonymous variants are not considered silent any longer. They are able to change the stability of mRNAs, codon bias, rate of translation, protein structure, splicing, or be linked to other functional variants within the same gene, which affects gene expression or protein activity [11,12]. In a DNA repair gene such as ERCC5, even mild alterations in repair ability may have biological implications, particularly in the long term or during environmental exposures that involve carcinogens. ERCC5 polymorphisms have been reported to be associated with cancer susceptibility, but there is much variation in the direction and strength of association based on cancer type, population and study design. A recent meta-analysis of 47 articles reported that a number of XPG/ERCC5 polymorphisms were linked with cancer susceptibility, with the possible risk of some including the rs1047768 T>C in lung cancer [13]. Recent meta-analyses have also attributed gastrointestinal, respiratory and other cancers to common ERCC5 polymorphisms, and the overall significance of DNA repair gene polymorphisms in cancer susceptibility [14]. ERCC5 rs4771436 and 1047768 genotypes were linked to a higher risk in Chinese in lung cancer [15]. In gastric cancer, several studies and meta-analysis have evaluated ERCC5 variants, including rs751402 and rs2296147, with associations with populations reported [16,17]. These reports indicate that genetic, environmental factors and population subgroup may alter the impact of the ERCC5 polymorphisms. Limited but biologically plausible evidence exists on the rs1047768 in breast cancer. ERCC5 rs1047768 was also linked to the risk of breast cancer in one Pakistani case-control study, and the heterozygous genotype was a risk factor [18]. This indicates that the ability of rs1047768 to alter the risk of breast cancer among non-Europeans is possible. Variants of ERCC5 have been reported by other studies of breast cancer that have also reported a role of NER gene variants in predisposing to breast cancer, although there has been inconsistency [19,20]. This can be anticipated in studies where there are variations in allele frequencies, linkage disequilibrium, sample size, environmental risks, and proportions of tumor subtypes.

In addition to its cancer susceptibility, there are potential pharmacogenetic implications of rs1047768. The platinum-based drugs introduce lesions that are repaired by NER to a certain degree; therefore, genetic variation in NER genes may influence the sensitivity to the drug. A meta-analysis observed that Chinese patients who were carriers of the C allele of the rs1047768 had higher sensitivity to platinum-based chemotherapy, suggesting that the variant can influence the process of platinum-induced DNA damage [21]. However, a prospective cohort study of non-small cell lung cancer was that ERCC5 rs751402 and rs1047768 did not significantly influence outcomes after platinum-based chemotherapy indicating that the effect size of the two markers is setting specific and requires confirmation in individual cancers and populations [22]. Further population-specific analyses are required for Arab populations where there are few reports of ERCC5 polymorphisms. This is significant since breast cancer in this population is frequently reported at a young age and with relatively poor clinicopathological features compared to many Western populations [23]. In addition, the genetic background and allele frequency may vary between Arab populations and other South Asian, East Asian, European and African populations. Recent studies from Northwest Iran and Saudi Arabia also indicate that evaluating cancer-associated genetic variants in their native genetic backgrounds rather than non-regional data is warranted in the region, including variation in DNA repair genes [17,24].

Considering the role of ERCC5 in NER, the potential functional impact of rs1047768, and the lack of data on Arab breast cancer populations, the present study aimed to evaluate the association between ERCC5 rs1047768 T>C and breast cancer risk, and to determine its impact on clinicopathological characteristics.

METHOD:

Study Population

This case–control study included 100 Saudi women with primary breast cancer and 100 age- and gender-matched healthy controls recruited from the general community. All the control participants were cancer-free and were not related to the patients.

Inclusion and Exclusion Criteria

The criteria of eligibility were Saudi women whose primary breast cancer was clinically verified, diagnosed through radiological, histopathological and clinical results. Patients that had undergone previous treatment such as radiotherapy, chemotherapy or hormone therapy were also used to represent real-life clinical presentation. Patients were not included when diagnosed with more than one form of cancer, those with history of other major malignancies, and non-Saudi nationals or failed to adhere to the study procedures.

The control group was composed of healthy Saudi women who were recruited among people who visit King Fahd Special Hospital in Tabuk, Saudi Arabia, to have a regular health check-up. Each participant has been enrolled by filling out a structured questionnaire and by giving an informed consent. The qualified controls were women aged 40 years and above

and with no history of cancer. The subjects were not included in case they had family history of breast cancer, were not Saudi nationals and were younger than 40 years.

Ethical Approval
The local ethics committee of the University of Tabuk approved the study (Approval No. UT-115-13-2020). All participants were provided with an informed consent written before sample collection, which is also in line with the ethical standards.

Sample Size Justification
The number of participants to include in the study was calculated based on one of the prevalence studies standard formulas: $N = Z^2 * P(1-P) / e^2$. N is the size of the sample required, Z is the Z-score of a 95% confidence level (1.96), P is the prevalence that is expected (which is 0.5 at no prior information so as to maximize the sample size), and e is the margin of error (assigned a 0.1). On this calculation, 96 participants per group were the minimum sample size, rounded to 100 per group and control.

Genomic DNA Extraction
Whole blood samples were used to obtain genomic DNA using a Qiagen DNA extraction kit (Cat No. 69506, Hilden, Germany), following the protocol of the manufacturer. The DNA was extracted and dissolved in nuclease-free water and it was kept at 4C until it was used. The purity and quality of DNA were determined by spectrophotometric measurements of DNA at 260 and 280 nm, where A260/A280 ratio was 1.83-1.99 which indicated the presence of high quality and purity DNA to be used in downstream analysis.

ERCC5 rs1047768 Genotyping through ARMS-PCR.
ERCC5 rs1047768 TC polymorphism was genotyped as the amplification-refractory mutation system polymerase chain reaction (ARMS-PCR) in a tetra-primer format. Primer3 (version 0.4.0) was used to design primers. PCR reactions were carried out using a final volume of 25 0.25 50 pmol of each primer, 10 0.25 50 pmol of GoTaq Green Master Mix (Promega, Madison, WI, USA). A gradient PCR approach was used to optimize the annealing temperature. Thermocycling conditions included an initial denaturation at 95 °C for 10 minutes, followed by 35 cycles of denaturation at 95 °C for 35 seconds, annealing at 70 °C for 45 seconds, and extension at 72 °C for 45 seconds. A final extension step was performed at 72 °C for 10 minutes, followed by storage at 4 °C. Primers Fo and Ro amplified a 219 bp fragment as an internal control. Primers Fo/RI amplified a 125 bp fragment corresponding to the mutant (C) allele, while primers FI/Ro amplified a 149 bp fragment corresponding to the wild-type (T) allele.

Table 1. Primers used for ARMS-PCR genotyping of ERCC5 rs1047768 T>C

Gene	Sequence	Allele	Product Size	Tm
ERCC5 -FO	5′-GTCTGTTTCTTCAATAGTGGAGCATCCC-3′		219 bp	70°C
ERCC5 -RO	5′-GATGAAGAGAAAAATCCCGGAGTTTTTT-3′			
ERCC5 -FI	5′-CACTTAAAGGAGTCCGGGATCGCAAT-3′	T-allele	149 bp	
ERCC5 -RI	5′-GAAGATGAGGATTTTCTATTGAGTTCACG-3′	C-allele	125 bp	

Statistical Analysis
Statistical analysis was performed using SPSS version 16.0 (Chicago, IL, USA). Hardy–Weinberg equilibrium (HWE) was assessed using the chi-square (χ^2) goodness-of-fit test. Continuous variables were analyzed using Student's t-test or analysis of variance (ANOVA), while categorical variables were compared using the chi-square test. The association between ERCC5 rs1047768 genotypes and breast cancer risk was evaluated using unconditional logistic regression. Adjusted odds ratios (ORs) and 95% confidence intervals (CI) were determined, adjusting the covariates, and the control group was used as the reference.

RESULTS
Demographic and Clinicopathological Features.
Table 2 presents the baseline clinicopathological features of the 100 breast cancer patients. All cases had complete clinical data. Patients were categorized by age into two groups: ≥40 years (n = 65, 65%) and <40 years (n = 35, 35%). In terms of disease stage, 30 patients (30%) were diagnosed at an early stage (stages I–II) and the largest number of patients (n = 70, 70%) had advanced disease (stages III IV). Histopathological grading demonstrated that 10, 30 and 60 percent were grade I, grade II, and grade III, respectively, which is a high-grade tumor predominant. Regarding receptor status, 60% of patients were estrogen receptor (ER)-positive, 70% progesterone receptor (PR)-positive and 43% HER2-positive. In a quarter of patients distant metastasis was noted. In terms of treatment, 32 percent were given Herceptin, and 62 percent were given tamoxifen.

Table 2. Baseline clinicopathological features of breast cancer patients (n = 100)

Parameters	Category	n (%)
Age (years)	>40	65 (65%)
	<40	35 (35%)
Breast cancer stage	Early (I–II)	30 (30%)
	Advanced (III–IV)	70 (70%)
Histopathological grades	Grade I	10 (10%)
	Grade II	30 (30%)
	Grade III	60 (60%)
Estrogen receptor (ES)	Positive	60 (60%)
	Negative	40 (40%)
Progesterone receptor (PR)	Positive	70 (70%)
	Negative	30 (30%)
Her2/neu status	Positive	43 (43%)
	Negative	57 (57%)
Distant metastasis	Positive	25 (25%)
	Negative	75 (75%)
Herceptin treatment	Yes	32 (32%)
	No	68 (68%)
Tamoxifen treatment	Yes	62 (62%)
	No	38 (38%)

Genotyping Quality and HardyWeinberg Equilibrium

ERCC5 T:C genotype distribution at the control group was in agreement with Hardy-Weinberg equilibrium (0.62 0.430), which means that the expected genetic proportions were not violated. To confirm the accuracy of genotyping 10 percent of the control samples were re-analyzed randomly, showing a concordance rate of more than 99 percent.

Genotype and Allele Distribution.

The ERCC5 T>C genotypes at the position of 1047768 were significantly different among the breast cancer patients and controls ($p = 0.041$) as demonstrated in Table 3. The TT, TC, and CC genotypes were 40, 45, and 15 percent, respectively, among patients versus 57, 35, and 8 percent, respectively in the controls. Moreover, the frequency of C alleles was found to be more prevalent in patients compared to controls (0.37 vs. 0.25), which might indicate its relation to the predisposition of breast cancer.

Table 3. Genotype and allele frequency of ERCC5 rs1047768 T:C in breast cancer patients and controls.

Group	n	TT n (%)	TC n (%)	CC n (%)	T allele frequency	C allele frequency	χ^2	p-value
Breast cancer	100	40 (40%)	45 (45%)	15 (15%)	0.63	0.37	6.36	0.041
Controls	100	57 (57%)	35 (35%)	8 (8%)	0.75	0.25	—	—

Linkage of ERCC5 rs1047768 with Breast Cancer Risk.

Multivariate analysis revealed the existence of significant relationships among ERCC5 genotypes of the genotype of ERCC5 rs1047768 and the risk of breast cancer under various genetic models (Table 4). In the codominant model, the TC genotype was associated with increased risk (OR = 1.83, 95% CI: 1.01–3.33, $p = 0.047$), and the CC genotype showed a stronger association (OR = 2.67, 95% CI: 1.03–6.89, $p = 0.042$), compared with the TT genotype. In the dominant model, carriers with at least one C allele (CT+CC) were at a high risk when compared to the carriers with TT (OR = 1.98, 95% CI: 1.133.49, $p = 0.016$). The recessive model (CC vs. CT+TT), in turn, did not give a statistically significant association ($p = 0.126$). The allelic model showed that the C allele had a significant impact on raising the risk of breast cancer (OR = 1.75, 95% CI: 1.14-2.69, $p = 0.010$). In the overdominant model there was no significant association ($p = 0.149$).

Table 4. Correlation of T to C genotypes of ERCC5 rs1047768 variants with breast cancer risk using various genetic models.

Genetic Model	Genotypes	Controls (n)	Cases (n)	OR (95% CI)	RR (95% CI)	p-Value
Codominant	TT	57	40	1 (reference)	1 (reference)	
	TC	35	45	1.83 (1.0067 to 3.3344)	1.34 (0.9958 to 1.8117)	0.047

	CC	08	15	2.67 (1.0348 to 6.8987)	1.68 (0.9422 to 3.0293)	0.042
Dominant	TT	57	40	1 (reference)	1 (reference)	
	TC + CC	43	60	1.98 (1.1325 to 3.4909)	1.40 (1.0611 to 1.8672)	0.016
Recessive	TC + TT	92	85	1 (reference)	1 (reference)	
	CC	08	15	2.02(0.8191 to 5.0283)	1.49 (0.8390 to 2.6617)	0.126
Allelic	T	149	125	1(reference)	1(reference)	
	C	51	75	1.75 (1.1427 to 2.6890)	1.34 (1.0590 to 1.7043)	0.010
Overdominant	TT + CC	65	55	1 (reference)	1 (reference)	
	TC	35	45	1.51 (0.8599 to 2.6849)	1.23 (0.9190 to 1.6680)	0.149

Note: OR, odds ratio; RR, risk ratio; CI, confidence interval. The reference group (Ref.) was used for comparison in each genetic model. Associations were evaluated using logistic regression analysis.

Correlation with Clinicopathological Features.

Table 5 shows the association of the ERCC5 rs1047768 genotypes and the clinicopathology features. There was no significant correlation with age ($p = 0.895$). Nevertheless, the polymorphism was significantly correlated with tumor stage ($p = 0.002$), and distant metastasis ($p = 0.001$). The histopathological grade was also significantly correlated (0.016) meaning a potential association with tumor differentiation. Furthermore, ERCC5 rs1047768 was significantly associated with receptor status, including ER ($p = 0.002$), PR ($p = 0.022$), and HER2 ($p = 0.038$). Conversely, treatment variables, such as the use of Herceptin ($p = 0.132$) and tamoxifen ($p = 0.882$) did not demonstrate any significant associations.

Table 5. Gene-association correlating clinicopathological features with TC genotypes of ERCC5 rs1047768 in breast cancer (n = 100).

Parameter	Category	n (%)	TT (n)	TC (n)	CC (n)	χ^2	df	p-value
Age (years)	≥ 40	65 (65%)	26	30	9	0.22	2	0.895
	< 40	35 (35%)	14	15	6			
Stage	Early (I–II)	30 (30%)	8	12	10	11.75	2	0.002
	Advanced (III–IV)	70 (70%)	32	33	5			
Histopathological grade	Grade I–II	40 (40%)	13	16	11	8.25	2	0.016
	Grade III	60 (60%)	27	29	4			
Estrogen receptor (ER)	Positive	60 (60%)	25	32	3	12.42	2	0.002
	Negative	40 (40%)	15	13	12			
Progesterone receptor (PR)	Positive	70 (70%)	30	34	6	7.57	2	0.022
	Negative	30 (30%)	10	11	9			
HER2/neu status	Positive	43 (43%)	11	24	8	6.53	2	0.038
	Negative	57 (57%)	29	21	7			
Distant metastasis	Positive	25 (25%)	10	6	9	13.06	2	0.001
	Negative	75 (75%)	30	39	6			
Herceptin treatment	Yes	32 (32%)	10	14	8	4.05	2	0.132
	No	68 (68%)	30	31	7			
Tamoxifen treatment	Yes	62 (62%)	26	27	9	0.25	2	0.882
	No	38 (38%)	14	18	6			

DISCUSSION

This study presents population-specific data that support the association of ERCC5 rs1047768 T>C with breast cancer risk and clinical phenotypes of importance. C allele and variant genotypes were more common in the patients than in the controls and the TT, TC and CC genotypes were found to be 40%, 45% and 15% among the BC patients compared to the 57%, 35% and 8% patients, respectively. C allele was also more prevalent among patients compared to controls (0.37 vs. 0.25), which suggests that it is a possible susceptibility allele in this cohort. Moreover, high correlations with tumor stage,

histological grade, ER, PR, HER2 status, and distant metastasis suggest that this variant can also be correlated with tumor phenotype and disease aggressiveness. These findings extend the relevance of rs1047768 beyond disease incidence; however, the observed clinicopathological associations require confirmation in larger cohorts.

The biological plausibility of this association is due to the fact that ERCC5/XPG is a significant component of the NER pathway that defends cells against bulky DNA damages, and enables them to maintain the integrity of the genome [4–6]. Although rs1047768 is a synonymous mutation, synonymous mutations may however influence gene regulation, mRNA stability, splicing, translation efficiency or may be linked to other functional variants [11,12]. Therefore, the correlation that we found between the C allele in our study may be the result of small but biologically significant effects on the ability to repair DNA breakages that can result in breast carcinogenesis. Though functional studies are yet to be undertaken to validate that whether or not, rs1047768 has a direct impact on either the expression or repair activity in the case of ERCC5.

The genetic results were reproducible in a number of analytical models. Genotype distribution of controls was in accordance with Hardy-Weinberg equilibrium and genotyping accuracy was more than 99% which helps to support the reliability of the data. The codominant model showed increased breast cancer risk for both TC (OR = 1.83, 95% CI: 1.0067–3.3344, p = 0.047) and CC genotypes (OR = 2.67, 95% CI: 1.0348–6.8987, p = 0.042) compared with TT. Similarly, the dominant model showed increased susceptibility among C-allele carriers (OR = 1.98, 95% CI: 1.1325–3.4909, p = 0.016), while the allelic model confirmed a significant association with the C allele (OR = 1.75, 95% CI: 1.1427–2.6890, p = 0.010). Together, these findings suggest a stable trend of allele-associated risk, but the small size of the sample of CC carriers must be considered when estimating the strength of the effect. These findings were consistent with the prior data which has linked ERCC5 variation to cancer susceptibility. The meta-analytic and pooled studies have shown that there is a correlation between ERCC5 polymorphism and the risk of cancer, but the direction and strength of the effect depend on the type of cancer, ethnicity, and genetic model [13,14]. To be more precise, the present results are consistent with a Pakistani case-control study that demonstrated the correlation of ERCC5 rs1047768 with the risk of breast cancer, particularly, with the heterozygous genotype [18]. Prior research on the impact of ERCC5 polymorphisms in breast cancer has produced inconsistent findings [19,20], likely because of differences in sample size, allele frequencies, ancestry, environmental exposures, and differences in tumor subtype makeup. In this respect, our data provide important evidence on an underrepresented Saudi cohort.

Besides susceptibility, the correlation between the rs1047768 and clinicopathological variables is clinically significant. The polymorphism was significantly associated with tumor stage ($p < 0.002$), distant metastasis ($p < 0.001$), histological grade ($p < 0.016$), ER status ($p < 0.002$), PR status ($p < 0.022$), and HER2 status ($p < 0.038$). This result indicates that the ERCC5 difference may be linked to the tumor biology and not necessarily the cancer incidence. Its correlation with high stage and metastasis is consistent with the idea that a low capacity of repairing DNA may play a role in promoting genomic instability, which causes tumor progression, tumor invasion, and tumor dissemination [3]. This cohort had 70% of the patients with advanced stage disease and 60% with grade III tumours which underscores the possible importance of identifying genetic markers that relate to aggressive presentation. However, no recurrence and/or survival and longitudinal results were studied, hence, the rs1047768 cannot be considered a confirmed prognostic biomarker yet.

The associations with ER, PR, and HER2 status are also noteworthy. Receptor status indicates various biological pathways and plays a huge role in the prognosis and treatment options. The fact that ERCC5 polymorphism is associated with receptor status allows it to be possible that DNA repair capacity can interact with hormones and growth factors signaling pathways to dictate tumor phenotype. Previous studies revealed that malfunctions of DNA repair mechanisms can affect estrogen receptor signalling and endocrine therapy responsiveness [25]. In turn, the correlation of rs1047768 with tumor features defined by receptors might indicate significant interactions between receptor-repair interaction and the biology of breast cancer subtypes. This interpretation however remains hypothesis-generating lacking molecular subtype classification or pathway level analysis.

No association was found to exist between the age and treatment factors like Herceptin and tamoxifen use and the rs1047768. This means that the polymorphism was not correlated with the status of the treatment in this cohort. Nevertheless, the status of treatment is not similar to that of treatment response and no conclusion can be drawn about the effectiveness of treatment, resistance, recurrence, or survival. This inconsistency is critical because pharmacogenetic studies have shown that in some settings, the response to platinum-based chemotherapy might depend on the presence of the rs1047768 although the findings have varied across tumor types and populations [21,22]. The context of the population makes this study relevant. The Arab and Saudi data concerning polymorphism in ERCC5 of breast cancer are limited despite the possibility of differences in the allele frequencies, linkage disequilibrium, consanguinity, exposure to environmental factors, and clinicopathological index. Breast cancer in the Middle East is usually diagnosed at a younger age, and has relatively aggressive features as compared to most of the western cohorts [23]. Therefore, it is important to determine the polymorphism of DNA repair in the local population compared to generalization using non-regional data [17,24].

CONCLUSION

This research proposes that the ERCC5 rs1047768 T>C could be linked to high risk of breast cancer and selected clinicopathological characteristics such as tumor stage, histological grade, receptor status, HER2 status, distant metastasis. These results indicate the possible applicability of NER gene variation in the biology of breast cancer, especially among underrepresented groups. However, before rs1047768 can be used in clinical risk assessment, or as a prognostic tool, validation in larger multicenter cohorts is required, along with functional studies and longitudinal outcome data..

SEthics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki revised in 2013 and approved by the ethics committee of the University of Tabuk (protocol code UT-115-13-2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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