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ERCC1 C118T POLYMORPHISM HAS PREDICTIVE RISK VALUE FOR BREAST CANCER IN PATIENTS RECEIVED PLATINUM-BASED CHEMOTHERAPY AS THE ADJUVANT TREATMENT

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ABSTRACT
We conducted a cohort study to investigate the role of 118 single-nucleotide polymorphisms of the excision repair cross complimentary group 1 (ERCC1) gene polymorphism in risk of breast cancer in Iraqi women. A total of 44 patients with breast cancer diagnosed participated in this study. ERCC1 rs11615 were genotyped. Individuals with the ERCC1 rs11615 CT genotype and the T allele showed a significant risk to breast cancer compared to the wild-type genotype. In conclusion, this study reports that the ERCC1 rs11615 CT polymorphism can be used as a prognostic marker to determine the risk of breast cancer patients treated with platinum base chemotherapy.

KEYWORDS:

INTRODUCTION
Platinum-based Chemotherapy regimens is considered the standard treatment for advanced cancer.[1] However, the response rate to platinum-based chemotherapy is approximately 20% and drug resistance and lack of effective therapies result in poor prognosis for patients with cancer.[2]

The nucleotide excision repair (NER) pathway is the most versatile DNA repair mechanism and is responsible for removing a wide variety of DNA lesions.[3] Excision repair cross-complimentary group 1 (ERCC1) is a major component of the NER pathway and plays an important role in repairing intrastrand crosslinks in DNA.[4]

The correlation between the ERCC1 polymorphism and cancer has been reported in several studies.[5, 6, 7] However, the results are conflicting. Therefore, we conducted study to investigate the role of 118 common single-nucleotide polymorphisms (SNPs) of the ERCC1 gene polymorphism in response to chemotherapy and clinical outcomes of patients cancer.

MATERIAL AND METHODS
Patient eligibility
Between January 2015 and November at the same year, 44 patients with breast cancer who received diagnosis of cancer from Oncology Teaching Hospitals /Medical City campus and Al -Amel National Hospital for Tumors /Baghdad, 31 apparently healthy subjects which regard as a control group. These subjects were taken from the people and the hospital's staff. A total of 44 patients were willing to participate in our study. All the patients signed the informed consents and the ethics approval was obtained from ethics committee of the Hospitals. All patients received platinum-based chemotherapy at least two cycles of treatments.

Genotyping
All study participants were asked to provide 2 mL venous blood, which was stored at -23°C until use, with EDTA used as an anticoagulant. Genomic DNA was extracted using the Relia Prep Blood gDNA Miniprep System (Promega/USA) according to manufacturer instructions. gDNA were verified by 1.0% agarose gel electrophoresis. PCR was conducted in a 20-µL reaction volume containing 250 ng genomic DNA. The PCR reaction started at 94°C for 3 min, followed with 40 cycles of 94°C for 30 s, the annealing temperature was reduced to 60°C for 1min.

Statistical analysis
Statistical analysis was conducted using SPSS® version 13.0 (SPSS Inc.; Chicago, IL, USA) for Windows. Categorical variables were expressed as the number of subjects (%). The correlation between ERCC1 118 polymorphisms and risk of breast cancer was assessed using odds ratios and their corresponding 95% confidence intervals (CIs). $P < 0.05$ was considered to be statistically significant.

RESULTS

The wild type C/C was found in 34.09% (n=15) of the patients and the results demonstrate 83.87 % (n=26) in the control. The difference was statically significant, P=0.0001; the odd ratio was 0.099 (95% CI =0.03-0.31). The heterozygous genotype C/T was found in 61.36% (n=27) of the patients and 9.67% (n=3) in the control. The difference was statically significant, P=0.0001; the odd ratio was 14.82 (95% CI =3.89-56.40). The mutant homozygous genotype T/T was 4.54% (n=2) of the patients and 6.45 % (n=2) in the control. The difference was statically significant, P=0.71; the odd ratio was 0.69 (95% CI =0.09-5.18).

The results found that mutant heterozygous C/T 118 SNP in *ercc1* was significantly associated with greater risk of breast cancer.

An allele frequency was calculated according Hardy-Weinberg equilibrium.

The allele C was found in 64.77% (n=57) of the breast cancer patients and the results demonstrate 88.71% (n=55) in the control. The allele T was found in 35.23% (n=31) of the lung cancer patients and the results demonstrate 11.29% (n=7) in the control. The difference between C and T alleles was statically significant, P=0.001; the odd ratio was 4.27 (95% CI =1.73-10.51).

Table 1: Association between breast cancer cases and control in ERCC1 118 polymorphism

Genotype	Patients		Control		p-value	Odd ratio	95%CI
	No	%	No	%			
CC	15	34.09	26	83.87	0.000	0.09	0.03-0.311
CT	27	61.36	3	9.67	0.000	14.82	3.89-56.40
TT	2	4.54	2	6.45	0.71	0.69	0.09-5.18
C	57	64.77	55	88.71	0.001	4.27	1.73-10.51
T	31	35.23	7	11.29			

DISCUSSION

In this study, we investigated the associations between common, potentially functional genetic variants ERCC1 Asn118Asn and the risk of breast cancer in a Iraqi women with breast cancer. We found that ERCC1 Asn118Asn seemed to be.

Associated with increased risk of breast cancer. These results are consistent with many previous studies. In a study were found an association between ercc1 codon 118 C>T polymorphism and breast cancer risk[8,9], in the another study they found an association between ERCC1 codon 118 C>T polymorphism and the outcome of chemotherapy in Asian patients with colorectal cancer.[10]

Decreased efficiency of DNA repair is considered as a crucial role in carcinogenesis as such defects accelerate genetic instability and the rate of genetic.[11] As genes in the NER pathway, ERCC1 is essential to the repair of DNA adducts in breast cancer. For example, a multitude of studies have focused on the relationship between ERCC1 polymorphisms and the risk in breast cancer patients.[12]

Zaanan et al, 2014 have revealed that ERCC1 rs11615 genotypes are associated with the clinical outcome of gastric or colorectal cancer patients who receive platinum-based chemotherapy.[13] Genetic polymorphism may affect structure, function, stability and folding of proteins and may be related to the effect of chemotherapy in cancer patients. ERCC1 rs11615 C to T, in the NER pathway, is associated with its decreased expression levels mRNA, and functional consequences in the repair of platinum induced DNA lesions.[14] The polymorphisms of this gene could alter DNA repair capacity, so it was biologically plausible to assume that the ERCC1 and polymorphisms might have functional significance in breast cancer.[15] The present study investigated the associations of the ERCC1 Asn118Asn polymorphisms with risk of breast cancer in the Iraqi women. The ERCC1 Asn118Asn T allele appeared to be the risk allele for developing breast cancer, which was more frequent in cases than in controls. The precise mechanism for the positive association of the ERCC1 Asn118Asn polymorphism remains unclear, as there are no direct functional data available for this polymorphism.

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