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DNA REPAIR PROTEIN XRCC1 GENETIC VARIATIONS AND THEIR CORRELATION WITH THE RISK OF BREAST CANCER

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ABSTRACT

Background: XRCC1 gene polymorphisms have been associated with hepatocellular carcinoma HCC, lung cancer, pancreatic cancer, and breast cancer. This study aims to examine the association between XRCC1 rs139599857 and rs2293035 polymorphisms and breast cancer. **Methods:** 100 samples were taken from BC patients and healthy individuals. The genotype of the XRCC1 rs (139599857) and (rs2293035) employing allele-specific real-time PCR to identify the samples. **Result:** XRCC1 rs139599857 The genotypes GC and CC were substantially correlated with an elevated risk of BC [OR = 2.98 (2.07 – 7.22), P < 0.001 and OR = 3.11 (0.59 – 9.11), P < 0.001, correspondingly]. Comparable results were noted at the allele level, with carriers of the C allele exhibiting an elevated risk for developing BC [OR = 2.41 (1.64 – 4.01), p< 0.001].The XRCC1 C/T variant genotypes CT and TT were strongly correlated with an elevated risk of BC, with [OR = 3.21 : 2.21 –8.11, P < 0.001) and 3.23 (OR: 1.11 – 7.87, P < 0.001), correspondingly]. Comparable results were noted at the allele level, with carriers of the T allele exhibiting an elevated risk for developing BC [OR = 3.46 (1.53 – 2.88), p < 0.001]. **Conclusion**: In conclusion, XRCC1rs 139599857 the GC genotype and G allele and XRCC1 rs 1395998570 and CT genotype and T allele connected to a higher risk of BC.

KEYWORDS: "Single nucleotide polymorphism", "DNA repair, XRCC, breast cancer BC and Tumor.

1. INTRODUCTION

Globally "breast cancer BC" is the most, prevalent type, of cancer, Numerous risk factors, including as genetic and familial susceptibility, are linked to the occurrence of BC.[1] Its incidence is linked to social-psychological variables, environmental conditions, and poor lifestyle choices. It has been shown that genetic mutations and family history account for 5–10% of breast cancers, while potentially modifiable factors account for 20%–30% of cases.[2] BC first arises in breast cells. A malignant tumor comprises cancer cells capable of infiltrating and destroying adjacent tissue. It might spread throughout the body as well. Occasionally, breast cells experience alterations that impair their ability to proliferate or behave normally, These modifications may result in atypical hyperplasia and cysts, which are benign breast conditions.[3]

Approximately 25% of newly diagnosed cancers in women may be due to breast cancer.[4] By 2025, breast cancer is projected to exceed lung cancer as the predominant cause of cancer incidence globally, with an estimated 2.3 million new cases in women, or 11.7 percent of all cancer cases.[5,6] Approximately two million cases of breast cancer were recorded in the year 2018 .[7] Breast cancer can also affect young women.[8] As of 2021, breast cancer has surpassed lung cancer as the most prevalent cancer diagnosed worldwide, contributing significantly to the burden, particularly among women.[9] BC screening is a useful tool for identifying early-stage cancer and increasing cancer patients' chances of survival.[10],[11] In recent decades, several developed nations have established population-based breast cancer screening programs, leading to a decrease in the incidence of advanced cancer and mortality rates.[12],[13,14] One crucial element in preserving genomic stability is the complex DNA repair system found in the human body.[15,16] By reducing the possible harm brought on by DNA damage, this mechanism maintains the genome's integrity.[17, 18] Oncogenic, transformation can occur as a result of genomic instability caused by abnormalities, such mutations or

deletions in the DNA repair system.[19] One of the essential enzymes of the base excision repair pathway is "X-ray repair cross-complementary" protein 1 (XRCC1).[20] X eroderma, pigment sum protein is one of the key proteins of the nucleotide excision repair pathway and is also known as the excision-repair complex 2.[21] Polymorphisms of the XRCC1 DNA repair genes have been widely studied.[22]

DNA repair is essential for safeguarding the cell's genome against the damage caused by carcinogens or ionizing radiation. Decreased DNA repair capability may elevate the vulnerability to malignancies generated by environmental or occupational factors.[23] The risk genotype of XRCC1 has been contentious, varying across ethnic groups and cancer types. lung cancer research indicated a positive association with the XRCC1.[24-25]

A study of association with multiple XRCC1 forms was conducted with stomach, cancer in the Korean population It has been shown that some individual patterns were linked to stomach cancer[26] We predicted that XRCC1 DNA repair genes could be linked to the onset of breast cancer.

2. MATERIAL AND METHOD

2.1. Study population

This study included 200 samples and they were distributed as follows: The first group comprised 100 samples from healthy adults. The second group comprised 100 samples from women with breast cancer prior to treatment initiation. The samples were collected from Marjan Teaching Hospital in Babylon governorate, from the Oncology Department between 2022 and 2024. The cases were diagnosed using ultrasound, MRI, mammography and biopsy. Diagnosis was also made using marker CA15.3. The study obtained ethical approval from the competent committees in the Ministry of Health and in accordance with the Helsinki principles, as each individual in the study agreed to provide information freely.

2.2. *Sample collection*

Four milliliters of blood samples, were collected from all participants, following with 2 milliliters transferred to EDTA tubes. and DNA was extracted for use in determining the XRCC1 genotype and 2 ml were taken for the CA15.3 test.

2.3. SNP assay of XRCC1 rs(139599857) and (rs2293035) *by Real-time PCR*

Genomic DNA was isolated utilizing the Pure link Genomic DNA Extraction Kits from the USA, adhering to the manufacturer's guidelines provided by Qiagen, The specimens were examined utilizing Taq-Man genotyping test kits with the Applied Bio systems, 7500, Real-time PCR apparatus, Foster City, CA, USA. ,TaqMan, probes have been conjugated with VIC and FAM fluorescent dyes, corresponding to the primer sequence of XRCC1 G/C rs(139599857)and XRCC1 C/T rs2293035 . Reference sequences (GenBank NC_000019.9,)This genetic, variant, is a no synonymous, mutation, resulting from G to C changes in exon 14 of the human XRCC1 gene, causing a glycine (Gly) to alanine (Ala) amino acid substitution. p.Gly506Ala; Forward primer: [5' CAAGTCCCCAGCTGAGAACTGAG -3'] and reverse primer: [5' GCTGTCTCTGCATGCTCACTC -3'] for XRCC1 C/T rs2293035.The sequence, of the forward, primer, is [5 -GAGGAGGATGAGGCCTCTCACAC-3] The reverse primer sequence is [5-TAAGGAGGGAGAGTGGGTGGGT-3. In a 25 µl reaction, the materials included 6.25 µl of nuclease-free water, 1.25 µl of SNP test, and 12.5 µl of Taq-Man master mix, which were mixed and dispensed into each PCR tube. For each unlabeled reaction, 5 µl (10 ng/µl) of genomic DNA template was used, while 5 µl of DNase-free water was included. The solution was carefully agitated and briefly centrifuged. The samples were then introduced into the cycler, and the program was started. Genotype was determined using an Applied Biosystems® 7500 Real-Time PCR Instrument coupled to the TaqMan® Allelic Discrimination Assay.

2.4. Laboratory, examinations

Assessment of the CA15.3 tumor marker. utilizing a gadget The cobas e 411 analyzer It is developed for assay measurements of tumor markers.

2.5. Statical analysis

Statistical analysis was conducted using SPSS 18 program. The genotype distribution of the control group was assessed using Hardy- Hardy-Weinberg equilibrium. The odds ratios (ORs) and 95% CIs (confidence intervals) were computed using the chi-squared test to investigate, the association, between XRCC1, rs139599857 and rs2293035 polymorphisms with breast cancer susceptibility.

Linkage disequilibrium (LD) was evaluated to determine the cumulative impact of the two SNPs on breast cancer incidence using Halo View software <005 indicates a statistically significant difference.

3. *RESULT*

This study involved 200 people, comprising 100 patients, with breast cancer and 100 healthy control subjects.

The demographic information and lab data of patient with healthy control table

Group	control (n=100)	case (n=100)	P' value
Female	100	100	
Age	53.54 ± 5.46	55.45 ± 2.55	2.21
CA15.3U/ml	23.33± 2.3	44.30± 5.23	0.001*

*: Statistically significant at $p \leq 0.05$ p : p value for Case vs Control

The demographic information and lab attributes of study cohorts no significant statistical differences were seen among, the studied, groups for gender and age , indicating appropriate corresponding. Statistically significant differences were observed between BC groups and controls with the CA15.3 test marker.

3.1. Distribution of XRCC1 C/T rs2293035 and G/C rs 139599857 Genotypic and Allelic Frequencies among the Analyzed Cohorts.

Genotypes XRCC1 rs2293035	Control no %	case	X^2	P
CC	74 74%	29 20%	48.65	0.001*
CT	18 18%	60 60%		0.001*
TT	8 8%	11 8%		0.001*
Alleles				
C	168 82%	80 40%	61.54	0.001*
T	32 18%	120 60%		0.001*
XRCC1 rs 139599857				
GG	58 58%	27- 27%	50.21	0.001*
GC	32 32%	57 57%		0.001*
CC	10 10%	14 14%		0.001*
Alleles				
G	170 84%	90 45%	63.71	0.001*
C	30 16%	110 55%		0.001*

*: Statistically significant at $p \leq 0.05$ p: p value for Case vs Control

Prevalence, of the XRCC1 gene genotype (rs2293035) The (C/T,) polymorphism, exhibited a statistically significant, variation across, the examined groups. The CT genotype exhibited greater prevalence. prevalent among breast cancer patients, While the CC was the dominant genotype in the control group $p < 0.001$. The allelic distribution demonstrated a notable elevation of the T allele in the breast cancer, cohort compared, to the control group $p < 0.001$.The genotype frequency of the XRCC1 gene rs(139599857) G/C polymorphism demonstrated a statistically significant difference across the studied groups. The GC genotype was more prevalent, among breast cancer patients, while the GG genotype, was predominant in the control group ,$p < 0.001$, .The allelic distribution demonstrated a significant increase of the C allele in the (BC) cohort compared, to the control group, $p < 0.001$.

3.2. Distribution of observed genotype frequencies and their consistency with Hardy-Weinberg.

	Observed	Expected	χ^2	p
XRCC1 rs 139599857				
Case (n= 100)				
GG	17	22.0	5.865	0.015*
GC	61	51.0		
CC	22	27.0		
Control (n= 100)				
GG	77	75.0	2.75	0.08
GC	18	22.1		
CC	5	3.0		
XRCC1 rs2293035				
case (n= 100)			6.063	0.004*
CC	21	25.0		
CT	63	54.0		
TT	16	21.0		
Control (n= 100)			3.065	0.003*
CC	78	75.0		
CT	19	23.0		

*: Statistically significant at $p \leq 0.05$ p : p value for Case vs Control

The frequencies of the reported G/C genotypes in XRCC1 rs139599857 were elevated in the BC, group relative, to the control group, whilst the frequencies of the observed CT genotypes in XRCC1 rs2293035 were also up in the BC, group compared to the healthy control, group.

3.3. Associations of XRCC1 rs 139599857 and XRCC1 rs2293035 polymorphism with BC.

XRCC1 rs 139599857		
Genotype	OR (CI.95%)	P
GG®	1	
GC	2.98 (2.07 – 7.22)	<0.001*
CC	3.11 (0.59 –9.11)	<0.001*
GC+CC	2.89 (2.12-6.11)	<0.001*
Allele		
G®	1	
C	2.41 (1.64 –4.01)	<0.001*
XRCC1 rs2293035		
Genotype	OR (CI. 95%)	P
CC	1	
CT	3.21 (2.21 – 8.11)	<0.001*
TT	3.23 (1.11 –7.87)	<0.001*
CT+TT	2.65 (2.03-4.89)	<0.001*
Allele		
C®	1	
T	3.46 (1.53 –2.88)	<0.001*

*: Statistically significant at $p \leq 0.05$ p: p value for Case vs Control

The variant genotypes GC and CC were substantially correlated with an elevated risk of BC [OR = 2.98 (2.07 – 7.22), P < 0.001 and OR = 3.11 (0.59 – 9.11), P < 0.001, correspondingly]. Comparable results were noted at the allele level, with carriers of the C allele exhibiting an elevated risk for developing BC [OR = 2.41 (1.64 – 4.01), p< 0.001].The XRCC1 C/T variant genotypes CT and TT were strongly correlated with an elevated risk of BC, with[OR = 3.21 : 2.21 – 8.11, P < 0.001) and 3.23 (OR: 1.11 – 7.87, P < 0.001), correspondingly]. Comparable results were noted at the allele level, with carriers of the T allele exhibiting an elevated risk for developing BC [OR = 3.46 (1.53 – 2.88), p < 0.001].

4. DISCUSSION

Breast cancer continues to be a predominant cause of death from cancer in women.[27] BC, is a worldwide issue, being the most often diagnosed disease in women.[88]

In this study, we investigated the gene XRCC1 We found that it is associated with different types of cancer, and this gene is significantly associated, with the risk of developing BC.

It plays an important role in the formation and progression of gallbladder cancer. Gallbladder cancer is a relatively rare malignant tumor in humans and has a very poor prognosis.[89] Genetic polymorphisms are a risk factor for esophageal cancer.[03]

A slight increase in the risk of prostate cancer was seen in people with two copies of the XPD 312 Assn codon allele. The danger was increased threefold in the presence of two copies, of the XRCC1 399 Gln codon. The findings indicate that diminished DNA repair capability may contribute to Prostate cancer, especially when the functionality of two genes linked to separate DNA repair pathways is compromised.[03]

A study was conducted on the XRCC1 gene polymorphisms in gastric cancer in a Korean population. The results indicated a positive relationship between gastric cancer and genetic polymorphisms.[08]

The research focused on the T allele genotype of the C /T, gene variant (rs2293035) and the C allele genotype of the G /C gene variant (rs139599857) which may correlate, with an elevated risk of hepatocellular carcinoma (HCC).[00]

In a study conducted on an Egyptian population, the XRCC1 polymorphism G/C was found to be associated with an increased risk, of hepatitis C virus-associated hepatocellular carcinoma HCC, [03] A study in China identified an association between XRCC1 genetic variations and the likelihood of developing (HCC).[03]

This study evaluated the significance of the, XRCC1 G/C rs139599857 polymorphism in breast cancer. Our study revealed a statistically significant, difference, in the genotype and allele, frequencies of the XRCC1 G/C rs

139599857 polymorphism among BC, patients. Where the GC, genotype, was more common among BC, patients, while the GG genotype, was more common among controls. The GG genotype of XRCC1 rs 139599857 was correlated with a markedly diminished risk of BC, in patients. The G allele of XRCC1 rs139599857 seems to serve as a, protective, factor, against the onset of BC, in patients.

This study also assessed the impact of the, XRCC1 C/T rs2293035 polymorphism in breast cancer. Our research demonstrated a statistically significant disparity in the, genotype and, allele frequencies, of the XRCC1 C/T rs2293035 polymorphism in breast cancer patients, with the CT genotype being more prevalent among these patients, whereas the CC genotype was more frequent among the controls.. The CC genotype of XRCC1 rs139599857 was linked to a markedly decreased risk of breast cancer in patients. The C allele of XRCC1 rs139599857 seems to serve as a protective factor against the onset of BC, in affected individuals.

This study revealed a notable disparity in the distribution of XRCC1 G/C rs139599857 genes and alleles within the examined cohort, with the GC gene exhibiting the highest prevalence among breast cancer patients, while the G allele was more prevalent in the (BC) group relative to the control group. A notable correlation existed between XRCC1 C/T rs2293035 and breast cancer incidence, particularly among BC patients with CT genotypes, with the allelic distribution indicating that the T allele was more prevalent in the breast cancer cohort than in the control group. The loci exhibited linkage disequilibrium, suggesting that both may functionally affect the development of BC in patients.

The constraints of our study include a limited sample size, a case-control design, and the representation of only one ethnic group (Iraqis).

CONCLUSION

According to our research, the CT and T genotype and XRCC1 C/T allele (rs2293035) may be linked to an increased risk, of breast cancer, while the GC genotype, and G allele, of XRCC1 G/C rs(139599857) may be linked to an increased risk of BC. The relevance of these SNPs in (BC) should be investigated further.

Conflict of interest

The author reports no conflicts of interest in this work.

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