Journal of Research in Pharmacy

Research Article

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The association of polymorphisms in base excision repair gene PARP1 with breast cancer in female population in Baghdad

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Received: 28 January 2024 / Revised: 21 February 2024 / Accepted: 23 February 2024

ABSTRACT

Approximately 5%-10% of breast cancer cases are believed to be hereditary, caused by inherited gene mutations. In healthy cells, these genes play a role in producing proteins responsible for repairing damaged DNA. When these genes undergo mutations, it can result in irregular cell growth, ultimately contributing to the development of cancer.The aim of this study is to investigate the association between PRAP1 rs2666428 and rs8679 gene polymorphisms with breast cancer risk in female population in Baghdad. A case-control study was involved 40 female breast cancer patients who were recruited from the Medical City, Oncology teaching hospital, Baghdad, Iraq, between June and October 2023. DNA extracted from whole blood and the gene fragments corresponding to the PARP1 rs2666428, rs8679 were amplified using conventional PCR. The genotyping was performed through Sanger sequencing. Patients' results were then compared with 40 age and gender- matched control subjects. There were significant differences in the genotypic distribution in the rs8679 polymorphism between patients and controls, in that the TG and TT genotypes showed apparent differences in the genotypic distribution that confirmed by Chi-square (Chi^2) test results. The risk of malignancy showed to be higher by about 3.18 times in patients with G allele than those with T allele. Genotypic distribution of the rs2666428 polymorphism showed a nearly similar distribution of CC, CT and TT genotypes in controls comparing to patients that also confirmed by Chi^2 results with no associated between the malignancy risk and the allelic frequency in that C and T alleles frequencies showed to be nearly similar in patients to those of controls. Genetic polymorphism of PARP1 rs8679 may be considered as a potential risk factor for the development of breast cancer and may be used as a diagnostic and prognostic marker while PARP1 rs2666428 polymorphism was not associated with breast cancer.

KEYWORDS: Genetic polymorphism; PARP1; rs2666428; rs8679; breast cancer; BER gene; Diagnostic marker; prognostic marker.

1. INTRODUCTION

Worldwide, breast cancer has emerged as the most prominently diagnosed form of cancer. In 2020, the latest worldwide cancer burden figures revealed that there were around 2.3 million newly reported cases of breast cancer. The age-standardized incidence and mortality rates of cancer among the Iraqi population in 2018 as displayed in the Global Cancer Observatory are the latest ICR and have illustrated that the total number of new cancer cases during 2018 was 31,502, with an incidence rate of 82.6/100,000 population; 43% occurred in males and 57% in females. The top registered cancers were breast cancer (19.7%), bronchus and lung (8.2%), colorectal (6.1%), leukemia (6.0%), and urinary bladder (4.9%) (1)[1]. Furthermore, this disease stands as the primary cause of cancer-related mortality among women across the world [2]. As there is evidence demonstrating a connection between inherited variations in DNA sequence and the likelihood of developing diseases in the future, genomic tests serve as objective "biomarkers" indicating an individual's susceptibility to cancer [3]. A family history of breast cancer is recognized as one of the most influential risk

How to cite this article: Algburi DYR,Abdul-Rasheed OF, Abdulhassan BA, Alsammarraie AZ. The association of polymorphisms in base excision repair gene parp1 with breast cancer in female population in Baghdad. J Res Pharm. 2024; 28(6): 1974-1981.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.871

factors for the development of this disease. Risk ratios are particularly elevated when cases occur at younger ages, and within a specific individual, the risk is greater if their relative was diagnosed at a younger age. The observed familial pattern strongly underscores the significant role played by genetic variation in influencing the risk of breast cancer (2). Within a cancer cell, the DNA repair mechanism encompasses over 150 genes and is organized into five primary pathways: "base excision repair" (BER), "nucleotide excision repair" (NER), "mismatch repair" (MMR), "double-strand break repair" (DSBR), and "homologous recombination repair" (HRR) [5].

Each DNA repair pathway is tasked with addressing distinct types of DNA damage. The repair of single-strand breaks primarily occurs through the Base Excision Repair (BER) pathway, involving key genes like PARP-1, OGG1, APE1, and XRCC1 [6]. The BER pathway specializes in repairing DNA base damages induced by oxidative reagents and alkylating agents, playing a crucial role in maintaining genomic stability and influencing the processes of carcinogenesis and tumor biology. The effectiveness of DNA repair deficiency extends to its influence on the response to DNA-damaging treatments like radiotherapy and chemotherapeutics [7]. Poly (ADP-ribose) polymerase 1 (PARP-1) is a crucial DNA repair gene intricately associated with the Base Excision Repair (BER) pathway. It plays a pivotal role in repairing single-strand breaks caused by factors such as ionizing radiation and oxidative damage [8]. Various PARP-1 inhibitors have undergone examination in clinical trials, revealing that the inhibition of PARP-1 activity has the potential to impede DNA repair. Consequently, this inhibition could enhance the damaging impact of radiotherapy and chemotherapy [9]. PARP1 stands out as the principal member within the PARP family. Its role is to promote cell survival by facilitating DNA repair. However, in the context of apoptosis, caspases cleave PARP1 into two fragments, leading to its inactivation [10]. The inactivation induced by caspases of PARP1 underscores the importance of blocking its activity to ensure the effective functioning of apoptotic processes and subsequent DNA fragmentation. It's worth noting that an increased expression of PARP1 is observed in various primary human tumors when compared to corresponding normal tissues [11]. Sanger sequencing is a DNA sequencing technique where the target DNA is denatured and paired with an oligonucleotide primer. This primer is then extended by DNA polymerase using a combination of normal deoxynucleotide triphosphates (dNTPs) and chain-terminating dideoxynucleotide triphosphates (ddNTPs). The key feature of ddNTPs is the absence of the 3' OH group, which is crucial for adding the next dNTP to the growing DNA chain. Without this 3' OH group, further nucleotides cannot be added, leading to the detachment of DNA polymerase. Consequently, the synthesized DNA chains vary in length, determined by the point at which a ddNTP was randomly incorporated [12]. The aim of the current study is to investigate the association between PRAP1 rs2666428 and rs8679 gene polymorphisms and breast cancer risk in the female population in Baghdad.

2. RESULTS

Results presented in Table 1 and Figure 1 showed that the genotypic distribution of the rs2666428 polymorphism showed a nearly similar distribution between controls and patients in that the CC, CT, and TT genotypes represent 62.5, 27.5, and 10%, respectively, of controls and 65, 15 and 20%, respectively, in the patients' group. These apparent non-significant differences in the genotypic distribution were confirmed by the Chi² results, which showed non-significant differences in the genotypic distribution between controls and the patients' group (p = 0.356, Phi = 0.217).

Table 1. Genotypic distribution of PARP1 rs2666428 polymorphism in the studied groups

			rs2666428 polymorphism			Total
			CC	CT	TT	
GROUP	CONTROL	Count	25	11	4	40
		% within GROUP	62.5%	27.5%	10%	100.0%
		Frequency	0.58	0.363	0.057	1
	CANCER	Count	26	6	8	40
		% within GROUP	65.0%	15.0%	20.0%	100.0%
		Frequency	0.526	0.399	0.076	1
Chi²		p-value		0.356		
		Phi		0.217		

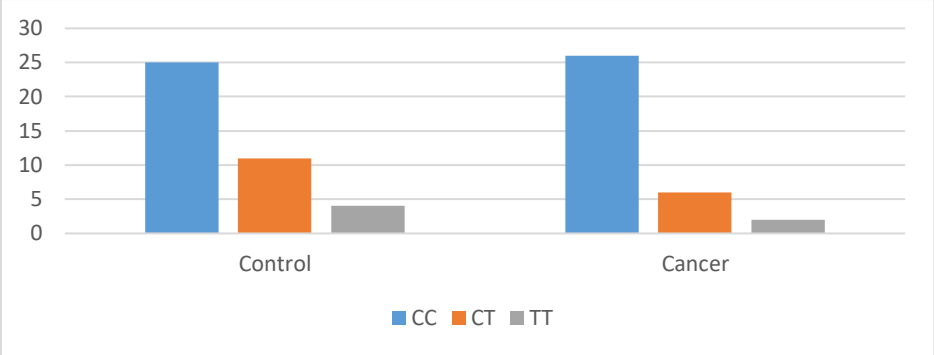

Figure 1. Genotypic distribution of PARP1 rs2666428 polymorphism in the studied groups

Results tabulated in Table 2 and illustrated in Figure 2 revealed a significant difference between patients and controls in the genotypic distribution of rs8679 polymorphism, as obtained by Chi2 results, in that patients with breast cancer showed a different pattern of genotypic distribution in comparison with controls, in which the TG and TT genotypes represent 75 and 25%, respectively, in cancerous patients in comparison with 37.5 and 62.5%, respectively, in controls. These apparent differences in the genotypic distribution were confirmed by the Chi2 results, which showed that the genotypic distribution in patients significantly differed from that in controls (p = 0.013, Phi = 0.375).

Table 2. Genotypic distribution of PARP1 rs8679 polymorphism in the studied groups

			rs8679 polymorphism		Total
			TG	TT	
GROUP	CONTROL	Count	15	25	40
		% within GROUP	37.5%	62.5%	100.0%
		Frequency	0.473	0.527	1
	CANCER	Count	30	10	40
		% within GROUP	75.0%	25.0%	100.0%
		Frequency	0.766	0.0.234	1
	Chi^2	p-value		0.013*	
		Phi		0.375	

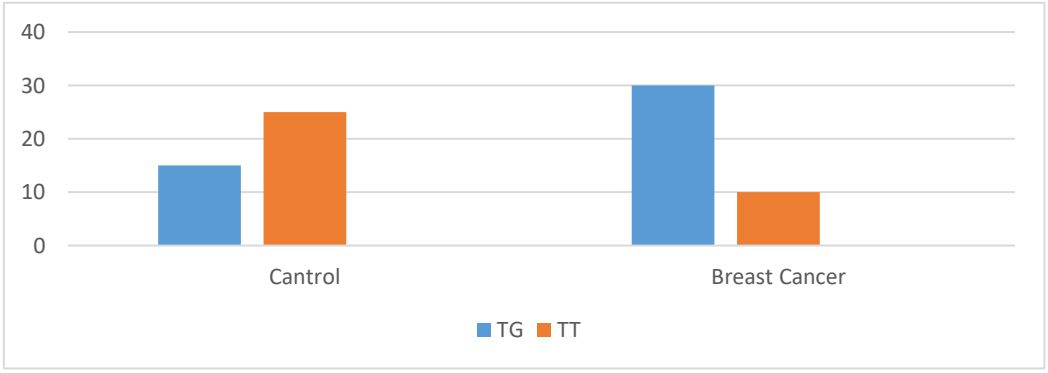

Figure 2. Genotypic distribution of PARP1 rs8679 polymorphism in the studied groups

Results postulated in Table 3 revealed that the incidence of malignant tumors was not associated with the allelic frequency of PARP1 rs2666428 in that the frequency of C and T alleles showed to be nearly similar in patients with breast cancer to that in controls, as indicated by the Odds ratio results, which showed a non-significant association between T or C allele frequency and the prevalence of cancer (p = 0.42, OR = 1.123, and 95% CI = 0.75-2.01).

Table 3. Allelic distribution of rs2666428 polymorphism in the studied groups

			rs2666428 polymorphism		Total
			C Allele	T Allele	
GROUP	CONTROL	Count	61	19	80
		% within GROUP	76.25%	23.75%	100.0%
		Frequency	0.76	0.24	1
	CANCER	Count	58	22	80
		% within GROUP	72.5 %	27.5 %	100.0%
		Frequency	0.73	0.275	1
Odds ratio		P-value		0.59	
		OR (95% CI)		1.22 (0.6 - 2.48)	

Contrary to the results of the first SNP that was subjected to the current work, the PARP1 rs8679 polymorphism showed a significant effect on the incidence of breast cancer in that the G allele showed a strong correlation with the malignant tumor in comparison with controls, as indicated by the Odds ratio results, which showed a significant association between G allele frequency and the prevalence of cancer (p= 0.005) and the results also showed that the risk of malignancy was higher by about 3.18 times in patients with the G allele than those with the T allele, as illustrated in Table 4.

Table 4. Allelic distribution of PARP1 rs8679 polymorphism in the studied groups

			rs8679 polymorphism		Total
			G Allele	T Allele	
GROUP	CONTROL	Count	15	65	80
		% within GROUP	68.75%	31.25%	100.0%
		Frequency	0.69	0.31	1
	CANCER	Count	70	10	80
		% within GROUP	87.5%	12.5%	100.0%
		Frequency	0.875	0.125	1
Odds ratio		P-value		0.005*	
		OR (95% CI)		3.18 (1.41-7.18)	

3. DISCUSSION

Many cancer research studies have confirmed the validity of biomarkers based on genetic variations associated with tumors. These biomarkers play a crucial role in predicting risks, facilitating early diagnosis, and forecasting therapeutic outcomes [13]. It is crucial to note that relying solely on biopsy blood tests may not be sufficient to distinguish an aggressive tumor [14]. The crucial function of PARP-1 in DNA repair, PARP-1 inhibitors are employed in two ways. The initial application involves using PARP-1 inhibitors as sensitizing agents for radiotherapy or chemotherapy [15]. The second approach involves exploiting the specific genetic traits of certain tumors through chemical synthetic lethality to induce DNA damage [16]. PARP1 is the predominant member of the PARP family, initially identified in 1963 by Chambon and his colleagues for its enzymatic activity that enables the generation of ADP-ribose polymers [17]. DNA double-strand breaks (DSBs) have the potential to result in the loss, fragmentation, or reorganization or rearrangement of chromosomes. Two pathways were shown to participate in the repair of DSBs, which include either error-prone non-homologous end joining (NHEJ) or homologous recombination (HR). Handling DSBs occurs either during the S-phase or outside the S-phase of the cell cycle, respectively. PARP1 plays a role in both HR and NHEJ pathways [18]. In another study, analysis of PARP-1 localization in breast cancer (BC) patients revealed its distribution in circulating tumor cells (CTCs), existing either in the nucleus or cytoplasm. The N-terminal DNA-binding domain of PARP-1 contains a nuclear localization signal [19]. The nucleus is crucial for PARP-1 to maintain genomic integrity and promote cell survival. While the significance of nuclear localization in PARP functions is well established, attention to cytoplasmic localization has also increased [20]. Another study suggests that PARP1 is a quantitative biomarker for oral, oropharyngeal, and esophageal cancer for early detection and intraoperative tumor delineation [21].

In our study, we systematically investigated the connection between PARP1 polymorphisms and breast cancer prognosis. The allelic frequencies of PARP1 rs2666428 and rs8679 did not show an association with malignant tumors, as the C and T allele frequencies were nearly identical in breast cancer patients compared to controls. The PARP1 gene is located on the long arm of chromosome 1 and comprises 23 exons

and 22 introns. Presently, there is no available literature on the polymorphisms examined in our research and their relationship with breast cancer prognosis. However, some reports suggest a correlation between the expression level of PARP1 and the survival of breast cancer patients. It's important to note that the results from these studies exhibit inconsistency [22]. In other studies their findings indicated that there is no significant association between the single nucleotide polymorphisms (SNPs) in the PARP1 gene and the risk of neuroblastoma. To the best of our knowledge, this study represents the initial assessment of PARP1 SNPs in connection with the risk of neuroblastoma [23]. Another research findings underscore the importance of PARP1 alterations as comprehensive predictive biomarkers for immune checkpoint inhibitor (ICI) treatment across various cancers. The expression levels of PARP1 appear to show correlation with the status of immunotherapy-associated signatures. Consequently, PARP1 may serve as a promising biomarker for predicting the response to immune checkpoint inhibitors in several tumor types [24]. In the high-incidence region of Cixian in northern China, the rs1136410 and rs8679 single nucleotide polymorphisms (SNPs) may not be reliable indicators for predicting the survival of esophageal squamous cell carcinoma (ESCC) patients. Further exploration is necessary to determine whether other SNPs within the PARP1 gene could have an impact on the prognosis of individuals with ESCC and suggest that these two single nucleotide polymorphisms (SNPs) may not serve as reliable predictive markers for the survival of esophageal squamous cell carcinoma (ESCC) patients [25]. Their study successfully demonstrated statistically significant increases in PARP1 expression at the epithelium as the disease progressed. Of particular clinical importance, our key finding revealed a significant upregulation of PARP1 expression in severe dysplasia/carcinoma in situ and invasive carcinomas compared to all other degrees of dysplasia and normal epithelium [26]. Genotyping analysis of SNP rs8679 revealed a decreased susceptibility to colorectal cancer, particularly in individuals with the heterozygous TC allele and at the minor allele C, PARP-1 expression levels exhibited significant differences in colorectal cancer compared to matched normal tissue. The findings further demonstrated that the upregulation of PARP-1 is associated with tumor progression and poor prognosis in Saudi patients with colorectal cancer, suggesting that PARP-1 could serve as a novel and valuable marker for predicting the clinical outcome of individuals with colorectal cancer [27].

4. CONCLUSION

Results demonstrated that the genetic polymorphism of PARP1 rs8679 was closely associated with the incidence of breast cancer and assumed to be a potential risk factor for the development of breast cancer and may be used as a diagnostic and prognostic marker. On the other hand, the PARP1 rs2666428 polymorphism was not associated with breast cancer, as demonstrated in the results of the current work.

5. MATERIALS AND METHODS

This case-control study was conducted at the College of Medicine, Al-Nahrain University, which houses departments of chemistry and biochemistry. The research proposal received approval from the Ethical Committee of the Al-Nahrain University College of Medicine. Forty Iraqi patients with breast cancer were documented by histopathology and collected from Al-Oncology Teaching Hospital in Medical City, Baghdad, Iraq. All participants in the study provided their consent, and blood samples were collected after their agreement, following hospitalization, and prior to the administration of any medications. The study was carried out from May 2022 to December 2022. All participants included in the study are between the ages of 18 and 60.

1. Control group: The sample comprises 40 individuals who are apparently healthy, with age and sex matching.

2. Case group: Includes 40(18 early, 22 advance stage) samples with confirmed breast cancer, diagnosed by true cut histopathology.

5.1. Exclusion criteria:

Female with tumor other than breast cancer, Pregnant and lactating women, Viral infected women, Women who exposure to radiotherapy and chemotherapy taken.

5.2. Blood sample collection and storage:

A blood sample of approximately 5 mL was obtained from each participant. EDTA tubes were used to collect peripheral blood samples from both the patient and control groups for the purpose of DNA

extraction. for subsequent screening of PARP1 rs2666428 and rs8679 gene polymorphisms and stored in a -4°C freezer until use. DNA was extracted from whole-blood samples using the EasyPure® Blood Genomic DNA Kit (with RNase A). After that, using NanoDrop Microvolume Spectrophotometers to measure purity and concentration for DNA extraction and give results with ng/µL units, PCR samples were prepared. 4µL DNA extracted product added to (2µL forward primer+2µL reveres primer+25µL mastrmix+17D.W) The PCR cycling was conducted using the PCR Express (Thermal Cycler, BioRad, USA), with the temperature program including 95°C as an initial denaturation temperature for five minutes, followed by 30 cycles of denaturation at 95°C for one second each, followed by the annealing step conducted at 60°C for another thirty seconds, and the temperature then increased to 72°C for an extension step for 30 seconds. After that, an extension step of 7 minutes at 72 °C was incorporated, followed by a 10-minute period of incubation at 4 °C to halt the reactions. Optimization of the PCR reaction involved multiple trials for the annealing step, and the optimal temperature yielding the best results for the PARP1 gene SNPs (rs2666428 and rs8679) was determined to be 58°C and 62°C, respectively. Gel electrophoresis was then employed to test the PCR product samples, allowing for the detection of DNA fragment sizes.

Table 5. The primers used in the study

Primer Name	Sequences	**SNPs**
PARP1-F	CTCGGTTTGGTTT GGTGTCT	rs2666428
PARP1-R	GAAGCTGGAGGA GTGACAGG	
PARP1-F	GTGTGGGAAGAC CAAAGGAA	rs8679
PARP1-R	CACTTGTCCCCTT CCGTAAA	

The size of the DNA fragments could be observed through direct examination of the gel under ultraviolet light. The PCR products were forwarded for Sanger sequencing utilizing the ABI3730XL, an automated DNA sequences, through Macrogen Corporation in Korea. Subsequently, the results were received via email and analyzed using the Geneious Prime software.

5.3. Statistical analysis

The study data were analyzed utilizing the SPSS software, specifically version 20. Categorical variables were represented using numerical expressions, which were then analyzed by cross-tabulation to assess the frequency and proportion of each variable among the groups under study. Correlations among all parameters were assessed using the Pearson correlation test, and the relationships between categorical variables were examined through the Chi-square test. The measurement of Phi, which serves as a chi-square-based measure of association, was employed to indicate the strength of the association. Values ranging from 0 to 0.5 were deemed indicative of a weak association, while values above 0.5 were considered representative of a strong association [28]. The significance level was set at ≤0.05 for p values [29]. Logistic regression was used to calculate odds ratio (ORs) and 95% confidence interval (CI) for breast cancer risk associated with the genetic polymorphisms of PARP1 gene [30].

Odds ratios are employed to compare the relative odds of the occurrence of a specific outcome (such as a disease or disorder) occurring based on exposure to a particular variable of interest (such as a health characteristic or aspect of medical history). They serve as a tool to determine whether a specific exposure acts as a risk factor for a particular outcome, and to compare the strength of various risk factors associated with that outcome.

OR=1: Exposure does not have a significant effect on the odds of the outcome.

OR>1: Exposure is associated with higher odds of the outcome.

OR<1: Exposure is associated with lower odds of the outcome [31].

Acknowledgements: The author is grateful to staff of the Department of Chemistry and Biochemistry, Medical Research Unit\ Division of Molecular Biology-College of Medicine Al-Nahrain University, Baghdad, Iraq for their facilities in performing this study and also to the head and staff members of oncology teaching hospital, Medical City, Baghdad, Iraq

Author contributions: Concept – O.A., B.A.; Design D.A., O.A.;Supervision – O.A., B.A.; Resources – D.A., B.A., F.A.; Materials – D.A.; Data Collection and/or Processing – D.A., F.A.;Analysis and/or Interpretation – D.A.; Literature Search – D.A.; Writing – D.A., O.A., B.A.;Critical Reviews – O.A., B.A.

Conflict of interest statement: The authors declared no conflict of interest in the manuscript.

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