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Research Article

THE ASSOCIATION BETWEEN BRCA1 GENE POLYMORPHISM AND PROSTATE CANCER IN SUDAN

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Abstract

Background: In Sudan, prostate cancer is the most prevalent form of cancer among men. The most prevalent genetic variants are single-nucleotide polymorphisms (SNPs), which may be associated with a number of cancers due to their role in DNA repair genes. Carriers of the BRCA1 mutation had 1.8 times the risk of prostate cancer compared to the general population. **Material and method: A** prospective case-control study was conducted during 2020 to 2023 at National Cancer Institute, Gezira University to evaluate the relationship between BRCA1 rs1799950 A > G polymorphism and the risk of prostate cancer. Known prostate cancer patients who had their diagnosis confirmed by histopathology were selected for the study and eighty-one healthy individuals with mean age of 67.93±8.13 and no history of any type of cancer were selected as control group. SNP stat online, a web-based application programmed, was utilized to assess the role of the mutation under various genetic models, and statistics package for social sciences version (21) was employed to analyse the sociodemographic and clinical aspects of the study patients. **Results:** No significant association of the study mutation with prostate cancer was observed among study subjects. P (0.412, 0.553, 0.536, 0.012, 0.521, 0.491, 0.694, 0.823, 0.334, and 0.241). Furthermore, no association was observed when justified with other patient's characteristics. **Conclusion:** According to the study's findings, the study suggests BRCA1 polymorphisms may be crucial in cancer a etiology, but there is no conclusive evidence linking BRCA1 rs1799950 gene polymorphisms with Sudanese prostate cancer.

Keywords: BRCA1, rs1799950 SNP, prostate cancer, Sudan.

INTRODUCTION

A tumor suppressor gene called BRCA1 is found on chromosome 17q21. It was cloned in 1994 after being mapped in 1990 [1, 2]. It was first discovered that the BRCA1 gene is a leading candidate for regulating ovarian and breast cancer susceptibility [2]. The BRCA1 gene has 22 exons and codes for a 220kDa nuclear protein with 1863 amino acids. An acidic carboxyl terminus, which is conserved across species and throughout evolution, and a zinc-binding RING domain at the amino terminus region make up BRCA1 [3, 4]. BRCA1 interacts with various proteins and has multiple functional domains. These proteins include transcriptional activators and repressors, oncogenes, DNA damage repair proteins, cell cycle regulators, and tumor suppressors. Genetic instability and the DNA damage response could occur from anomalies in the S phase, G2/M phase, and spindle checkpoints brought on by BRCA1 deletion., which raises the likelihood of tumor development [2]. BRCA1 mutations traditionally has been associated with hereditary breast and ovarian cancers, but emerging evidence suggests their potential involvement in prostate cancer as well. Previous studies has demonstrated that BRCA1 mutations are more prevalent in aggressive forms of prostate cancer, particularly in those with early-onset and hereditary prostate cancer [5, 6]. According to reports, BRCA1 is expressed in a variety of organs, including the lymph nodes, skin, bladder, cervix, liver, kidney, bone, and brain. It is linked to several malignancies, including breast, ovarian, endometrial, pancreatic, prostate, and colon cancers. [9, 10]. The results of numerous studies [11, 12].

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BRCA1 genes, in this order, were found to have 0.2% of prostate cancer cases and 0.1% of control group cases in a study of germline mutations in Japan [7, 8]. Because the frequency of BRCA1/BRCA2 germline and somatic mutations are nearly equal in prostate cancer, assessment of both germline and somatic variations is required [19]. The fact that this is distinct from ovarian or breast malignancies should be taken into consideration [4]. In both germline and somatic cell lineages, BRCA1/BRCA2 pathogenic mutations have been observed in 4–18% of patients with localized/castration-resistant prostate cancer [4]. For instance, whereas Nicoloso et al. claimed that rs799917 increased the incidence of breast cancer [13]. In exon 11, rs1799950 is found in the area where Rad50, a component of the DNA damage repair complex, interacts [14]. Many families who are at a high risk for prostate cancer have the gene rs1799950 [15]. Dunning et al. discovered that rs799917 exhibited no significant connection with breast cancer [11]. Because studies on rs1799966, rs1799950, and rs16941 are also erratic, we carried out this study to detect association between BRCA1 rs1799950 gene polymorphism and Prostate cancer-Gezira State Sudan.

MATERIALS AND METHODS

Study design and data collection

A prospective case-control study was conducted during 2020 to 2023 at National Cancer Institute, Gezira University to evaluate the relationship between BRCA1 rs1799950A > G polymorphism and prostate cancer risk. The study included eighty-one prostate cancer patients whose diagnosis was verified by histological examination. Table 1 is showing the characteristics of the study cases. The study analyzed prostate

cancer patients, with twenty-eight present less than 65 years old and seventy-two presents in the age group above 65 years. The mean age was 67.93±8.13, with a median age of 67.93±8.13. Only sixteen percent of men were not married, while Eight-four percent were married. Eighty-three percent of those present were obese, while the remaining seventeen percent were not. Eight-six percent were from Arab tribes, and fourteen percent were from African tribes. Eight-tow percent presented with negative family history of cancer, while nineteen were presented with a positive family history of cancer, twenty-one present were smokers, and Seven present was consumed alcohol. Ninety-seven percent have PSA level more than 20, also the majority of the prostate cancer patients had a Gleason Stage more than 7 which account Sixty-three percent, with fifty-one percent having metastases.

Sample collection

A peripheral vein was used to venipuncture the sample, and 3 mL of whole blood was drawn into EDTA-containing tubes (Becton Dickinson, USA) and DNA was extracted from blood samples using the G-spinTM Total DNA Extraction Mini Kit from iNtODEWORLD, Inc. USA.

Screening BRCA1 (rs799950) polymorphism among study subjects by PCR-CTPP Method

The polymerase chain reaction with confronting two-pair primers (PCR-CTPP) method's basic tenet is the full matching of the primer sequence at the 3'endFour primers are therefore required for the PCR-CTPP genotyping system: two common primers on either side of the polymorphic site's border, but with varied length from the polymorphic site. The other two primers are specific to specific alleles and were designed with a specific allele sequence in mind, especially at the 3' end. PCR-CTPP can be used to accurately genotype SNPs. It is quick and affordable to complete [30]. BRCA1 polymorphisms (rs799950, A > G) in study participants and controls were screened using this method. For the PCR-CTPP genotyping method for BRCA1 polymorphisms (rs799950, A > G), four primers were created as follows:

Asp950-G: TTCTCTGAGCATGGCAGTTACC
CP950F: ACAGATGGGCTGGAAGTAAG
Asp950-A: GAGAGAAAAGAATGGAATACGCA
CP950R: TGTCTTCAATATTACTCTCTACT

Asp950-G and 133 bp were amplified using primer CP950F to get a PCR fragment of 133 bp when the G allele was present, and Asp950-A and 133 bp were amplified with primer CP950R to yield a PCR fragment of 331 bp when the A allele was present. Both the CP950F and CP950R may result in a third 420 bp PCR product. After the PCR product was electrophoresed in a 2% agarose gel, it was visible under a UV lamp with GDS after being stained for 20 to 30 minutes with a solution of 1µg/ml ethidium bromide. The genotypes were assigned based on the profile that was obtained. Two bands, 420 and 133 bp, were homozygote GG, while three bands, 420, 331, and 133 bp, were heterozygote AG. There were two bands with homozygote AA, 420 and 133 bp. 5 µl of the master mix, 1.5 µl of DW, 3 µl of DNA sample, 0.2 µl of primer (CP950F and CP950R), and 0.4 µl of primer (Asp950-G and Asp950-A) were employed in the PCR mixture. The rs799950 SNP PCR condition was carried out using this programmed: Denaturation took place at 95 °C for 30 seconds, annealing at 52 °C for 30 seconds, and extension at 72 °C for 45 seconds. 35 heat cycles were performed under these circumstances.

Data analysis

IBM SPSS Statistics (Version 23. Armonk, NY: IBM Crop) was used to analyse the data. Demographic information about the patient clinic was condensed into the number and percentage of patients or the means and standard deviation range of data. The variations in the frequency distribution of BRCA1 and their correlation with the various factors were ascertained using the Chi-square test. Odd's ratio was utilized to ascertain the genotype and allele associations between the groups. A p-value of less than 0.05 is considered statistically significant. Using SNP Stats (https://www.snpstats.net/start.htm), codominant, dominant, over dominant, and recessive models were employed to determine the importance of various genotype frequency combinations in cases relative to controls. The presence of a certain allele in each genotype allowed for the classification of these models.

RESULTS

Table 1. Study subjects' sociodemographic and clinical characteristics

Characteristics		Cases N=81	Control N=81
		Frequency	Frequency
Age group	45 – 55 Years	6(7.4%)	8(9.9%)
	56 – 65 Years	27(33.3%)	33(40.7%)
	66 – 75 Years	38(46.9%)	30(37.0%)
	>75 Years	10(12.3%)	10(12.3%)
Education Level	Illiterate	33(40.7%)	19(23.5%)
	Basic	28(34.6%)	27(33.3%)
	Secondary	15(18.5%)	19(23.5%)
	University	5(6.2%)	16(19.8%)
Marital Status	Married	68(84.0%)	56 (69.1%)
	Un - married	13(16.0%)	25(30.9%)
Smokers	No	64(79.0%)	68(84.0%)
	Yes	17(21.0%)	13(16.0%)
Family History	Positive Family history	15(18.5%)	0(0.0%)
	Negative Family history	66(81.5%)	81(100.0%)
Obesity	Obese	67 (83%)	-
Alcohol	Alcoholism	6 (7%)	-
level of PSA	≥ 20	79 (97%)	0 (0%)
	< 20	2 (3%)	81 (100%)
Gleason score	≥7	51 (63%)	-
Metastasis	Presence of metastasis	41 (51%)	-

Allele Frequencies

There was no conclusive correlation between prostate cancer and SNP, A/G was observed in two healthy individuals but only in one patient with prostate cancer. Furthermore, neither the patient nor the control had the G/G genotype. Furthermore, BRCA1 (rs1799950) SNP the A allele frequencies were the most frequent among case and control 321(99%), in cases group it was 161(99%) while it was 160(99%) in control group Table 2.

Table 2. BRCA1 (rs1799950) association with prostate cancer among study subjects

Model	Genotype	Status=cases	Status=control	OR(95%)	p. value
Allele effect	A	161	160		
	G	1	3		
	A/A	80 (98.2%)	79 (97.5%)	2.03	0.56
Codominant	A/G	1 (1.8%)	2 (2.5%)	(0.18 - 22.79)	
	G/G	0 (0%)	0 (0%)		

There was no significant correlation between prostate cancer P (0.412, 0.553, 0.536, 0.012, 0.521, 0.491, 0.694, 0.823, 0.334

and 0.241) and the risk variables for age, marital status, BMI, race, family history, smoking, alcohol, PSA level, Gleason score, and metastasis Table 3.

Table 3. The association between BRCA1 (rs1799950) and prostate cancer risk factors

Parameter	Class	Mutation		P. value
		Absent	Present	
Age group	< 65	23	0	0.412
	≥ 65	57	1	
Marital status	Non married	13	0	0.553
	Married	67	1	
BMI	Non obese	14	0	0.536
	Obese	66	1	
Race	Arab	70	0	0.012
	African	10	1	
Family history	No	65	1	0.521
	Yes	15	0	
Smoking	No	63	1	0.491
	Yes	17	0	
Alcohol	No	74	1	0.694
	Yes	6	0	
PSA	< 20	2	0	0.823
	≥ 20	78	1	
Gleason score	< 7	30	0	0.334
	≥ 7	50	1	
Metastasis	No	40	0	0.241
	Yes	40	1	

DISCUSSION

A complicated and varied disease, prostate cancer has a diversified genomic aetiology and poses a considerable therapeutic challenge. Recent studies have demonstrated the involvement of various genetic alterations, including BRCA1 mutations, in the pathogenesis and progression of prostate cancer. The finding agrees with (Gabriela Angélica *et al.,* 2020) [28] study as A allele was a common allele frequency among cases, controls, and overall subjects. Prostate cancer and the BRCA1 (rs1799950) mutation were not linked in our study. Furthermore, only three persons had the mutation; one of them had prostate cancer, and the other two were carriers who were otherwise healthy. The evidence presented here supports the theory that African Americans are admixed with Europeans. The G/G genotypes were not detected in our study, which may have been due to the G/G genotypes' low frequency, which is consistent with a prior study carried out in Cuernavaca, Morelos, Mexico (Gabriela Angélica *et al.,* 2020) [28]. Additionally, they indicate that African-American men who carrying (Julie A. Douglas *et al.,* 2007) [29]. This conclusion conflicts with research from julie A. Douglas et al that found three BRCA1 rs1799950 Among white non-Hispanic men with and without prostate cancer (PC) to be associated with PC risk. Regarding to one prostate cancer with BRCA1 (rs1799950) mutation was diagnosis with high Gleason ≥7, more than 65 years old, with metastatic. Moreover, there was no correlation found between African tribal stock and PC risk., this finding is considered a risk factor for poor prognosis. Moreover, BRCA1 has been associated with worse clinical outcomes and aggressive characteristics in prostate cancer patients. A meta-analysis by Castro et al. (2013) demonstrated that patients with BRCA1 mutations had significantly higher Gleason scores, advanced disease stages, and poorer overall survival compared to those without mutations. These findings suggest that BRCA1 status could serve as a valuable prognostic marker in the management of prostate cancer [6]. BRCA1 mutations [16,17,18-19,20,21,22-23]. Although two studies have found RRs of 2-4 for BRCA1 carriers under the age of 65, BRCA1 mutations and PCa risk had a moderate relationship, according to a meta-analysis (pooled odds ratio 1.35, 95% confidence interval 1.03-1.76). [19]. Also observed in studies are variations in PCa risk according to mutation type and site[19,24,25,21,26,27]. This research confirms our conclusion that there is no link between BRCA1 and prostate cancer.

Conclusion

BRCA1 (rs1799950) mutation was very rare among Sudanese prostate cancer patients and there is no convincing evidence linking the BRCA1 (rs1799950) mutation to prostate cancer. As the results were not totally evident yet. The emerging role of BRCA1 mutations in prostate cancer underscores their clinical relevance as potential prognostic markers and therapeutic targets. Identifying BRCA1 mutations can provide essential insights into the pathogenesis of prostate cancer and guide personalized treatment strategies. Further research is needed to determine how BRCA1 mutations interact with other genetic and environmental factors to enhance risk assessment, therapeutic decision-making, and disease management.

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Conflicts of Interest

No conflicting financial interests are disclosed by the authors.

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Authors' Contributions

All authors worked together to complete this work. The final manuscript was read and approved by all the authors.

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