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Identify BRCA1 Gene Mutations in exon 11 in Ovarian Cancer Patients in Sudan

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Abstract*: Ovarian cancer (OC) is a leading cause of death from gynecological malignancies worldwide. In Sudan, limited studies have examined the genetic factors contributing to OC, particularly BRCA1 mutations. Aim of study to identify BRCA mutations in exon 11 using direct sequencing in Sudanese women with OC diagnosis who have a family history of the disease. To detect potential pathogenic mutations in high-risk patients. Targeted Sanger sequencing of BRCA1 exon 11 was performed on 11 OC samples from women with a family history of OC or early-onset disease. pathogenic BRCA1 mutations were detected in the sequenced samples for a BRCA1 rs799917 SNP in one patient. The study highlights the need for broader genomic studies to clarify genetic and non-genetic risk factors in this population. This is the first study to examine BRCA1 mutations in Sudanese OC patients. The findings suggest that other genes may contribute to OC susceptibility in this population. Further research integrating demographic and genetic analyses is necessary to develop effective prevention and treatment strategies.*

Keywords: ovarian cancers, BRCA1, exon 11, Sudan

Introduction

Cancer is a major global public health concern, significantly impacting life expectancy worldwide. The global burden of cancer, in terms of both incidence and mortality, is rapidly rising (1). Genetic mutations, particularly inherited ones, play a key role in cancer risk across generations. (2). Ovarian cancer (OC) is a prevalent and highly lethal gynecological malignancy. According to the Global Cancer Observatory (GLOBOCAN) report, OC accounted for 1.6% of all cancers and 2.1% of cancer deaths worldwide in 2020 (1,3). Early-stage OC often presents with no clear symptoms, leading to late diagnoses in approximately two-thirds of patients (4).

The precise incidence of OC in Sudan remains unclear. However, a previous study conducted utilizing hospital data from various institutions, including the National Cancer Institute, Gezira University, and the Radiation Isotopes Center in Khartoum, revealed that OC comprised 6.8% (949 cases) of all recorded cancers (226,652 cases) (5). Data from the Khartoum State National Cancer Registry suggests OC is the fourth most common cancer among women, with an estimated incidence rate of 188 per 100,000 population (gender-specific rate: 8.0 per 100,000, age-standardized rate: 7.0 per 100,000) (6). While the mortality rate for OC in Sudan is unknown, Abuidris et al. reported a high relapse rate among Sudanese OC patients (7).

BRCA1 and BRCA2 mutations are the most prominent genetic risk factors for OC, found in up to 17% of patients (8). BRCA1 and BRCA2 are tumor suppressor genes essential for DNA repair and genomic stability. The 11th exon is the largest, containing over 60% of the coding sequence (9). The BRCA1 protein, composed of 1,863 amino acids, contains a Ring Finger domain and interacts with RAD51, a key protein in DNA double-strand break repair (10).

Mutations in these genes disrupt the repair of DNA damage, increasing the risk of ovarian and breast cancer. Studies indicate that women with BRCA1/2 germline mutations have a better overall survival rate compared to those without mutations. For instance, the average 5-year survival rate for BRCA2 mutation carriers is 52%, compared to 36% for non-carriers. However, this protective effect appears to diminish after 10 years (11). Notably, BRCA testing plays a crucial role in tailoring treatment strategies, as Olaparib monotherapy is licensed as a first-line maintenance therapy in BRCA-mutated OC patients following platinum-based chemotherapy (12). This underscores the importance of identifying BRCA mutations in women with OC to guide personalized treatment and improve patient outcomes.

Despite the well-established role of BRCA mutations in OC, data from African and Middle Eastern populations, including Sudan, remain scarce. Given ethnic and regional differences in genetic mutations, population-specific studies are necessary to determine whether BRCA mutation prevalence and its impact on OC in Sudanese women differ from Western populations. Additionally, limited access to genetic testing in Sudan underscores the need for such research.

Material and method

This is hospital-based case-control study was conducted to evaluate the BRCA1 polymorphisms and genetic susceptibility of ovarian cancer among Sudanese women in Gezira state. The study was conducted in National Cancer Institute (NCI), Gezira University Wad Medani, Sudan. All Patients come from Gazira state. The patients were received from Gezira Hospital for Obstetrics and gynecology and Patients who recruit to NCI during the study period and have been diagnosed with Ovarian Cancer will be selected for the study after taking consent. Special questionnaire containing personal and demographic characteristics will recorded at time of admission for case women diagnosed with ovarian cancer age under 35 years or family history with cancer or both.

Laboratory Method

After written informed consent, 3 mL venous blood sample was collected into EDTA container (whole blood) for DNA extraction.

DNA extraction method

Genomic DNA was extracted by The G-spinTM Total DNA Extraction Mini Kit from iNtODEWORLD, Inc. USA was used for DNA extraction from blood samples

Polymerase Chain Reaction (PCR)

PCR reactions were performed in a total volume of 30 µl containing 200 ng genomic DNA, 15-20 picomoles of each primer, 200 µM dNTP (dATP, dTTP, dCTP and dGTP), 3µl from 10 x Taq Gold Buffer (100mM TrisHCl, pH 8.3, 500 mMKCl, 15 mM MgCl2 and 0.01 % (w/v) gelatin (Perkin Elmer Cetus), 1.5 U AmpliTaqGoldTM polymerase (Perkin Elmer Cetus) and completed to final volume with deionized water. The efficiency of the amplification was tested by electrophoresis in 1.5-2.5% agarose (SeaKemÒ GTGÒ agarose, FMC BioProducts) in 1.5x TBE at 100-140 Volts for about 30minutes and visualized under gel documentation system (GDS). Both The agarose concentration in gel electrophoresis and the current in the gel depend on the length of the Electrophoresed DNA fragment.

DNA Sequencing (Sanger Sequencing)

In this study, DNA sequencing was use to scan for mutations in exon 11 of BRCA1 gene in samples from patients with a family history and patients under 35 years of age. Using Sanger sequencing technique.

A30µl was taken from each sample and prepared for sequencing, testing prime (modified from the PE ABI BigDye Ready Reaction Termination Mix protocol)

The 10 µM stock solution of sequencing primer was diluted 1:15 with sterile dH_2O. Two microliters (2 µl) of the diluted sequencing primer were pipetted into appropriately labeled, thin-walled PCR tubes. Another 2 µl of the BigDye Ready Reaction Termination Mix was pipetted into each tube. One microliter (1 µl) of each PCR product was added to the appropriate tube, ensuring that all three reaction components were mixed together. These were 1/4 size reactions, with a total reaction volume of 5 µl, as compared with the 20 µl total reaction volume suggested in the ABI BigDye sequencing manual

The following cycling program was run: initial denaturation at 96°C for 10 seconds, followed by 50°C for 5 seconds and 60°C for 2 minutes. Steps 1, 2, and 3 were repeated for a further 29 cycles

After the cycling program, the tubes were removed from the thermal cycler. Fifteen microliters (15 µl) of sterile dH_2O were added to each tube to bring the reaction volume to 20 µl. Two microliters (2 µl) of 3M NaOAc, pH 4.6, and 50 µl of EtOH were added to labeled 1.5 ml Eppendorf tubes. Each 20 µl sequencing reaction was added to the appropriate tube containing the salt/EtOH mixture. The tubes were vortexed briefly to mix and then incubated at room temperature for 15 minutes

The tubes were spun for 15-30 minutes at maximum speed. Immediately after spinning, the supernatant was removed using a pipette. The pellets were washed by adding 500 µl of 70% EtOH to each tube and spinning again at maximum speed for another 10 minutes. As much of the EtOH as possible was carefully removed to reduce dye blobs, and the pellets were dried in a vacuum dryer at a medium rate. The dried pellets could be stored at -20°C until they were ready for loading onto a sequencing gel.

Sequencing method result

Targeted Sanger sequencing of BRCA exon 11 was performed on 11 OC samples from women with either a family history of OC, age under 35 years of age at diagnosis or both (Figure 1). One mutations were discovered in the exon 11 (rs799917). The clinical and demographic characteristics of the patients included in the sequencing analysis are presented in Table 1.

Table 1: Clinical and Demographic Characteristics of Ovarian Cancer Patients Included in Sequencing Analysis.

Sample	Age (Years)	Type of Ovarian Cancer	Stage	Family history	Marital status
1	42	Serous carcinoma	III	yes	married
2	85	Serous carcinoma	II	yes	married
3	45	Serous carcinoma	III	no	married
4	56	Serous carcinoma	III	yes	married
5	50	Serous carcinoma	II	yes	married
6	70	Serous carcinoma	III	yes	married
7	30	Serous carcinoma	II	yes	married
8	27	Serous carcinoma	II	yes	single
9	30	Serous carcinoma	III	no	married
10	32	Serous carcinoma	III	yes	single
11	26	Serous carcinoma	III	no	single

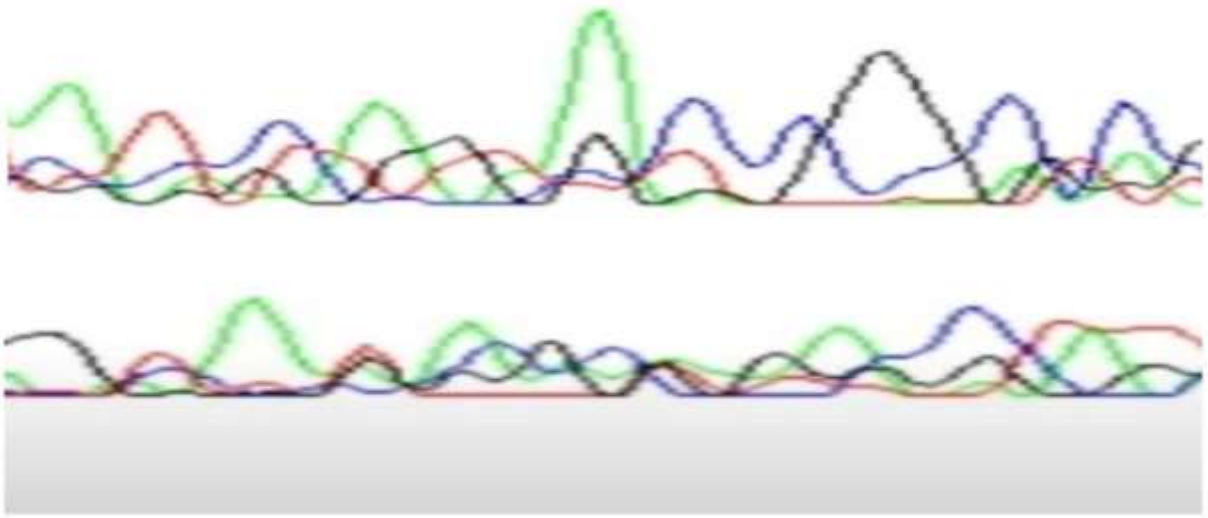

Figure 1. Showed Sequencing result. (C allele change to T allele). Among the sequenced samples, a BRCA1 rs799917 SNP was detected in a 27-year-old patient diagnosed with Stage III, Grade III serous carcinoma (sample No 8 in table 1). This patient was single and reported a positive family history of OC. The detected mutation involved a C to T substitution in the BRCA1 gene.

DISCUSSION

Ovarian cancer (OC) is the leading cause of death from gynecological malignancies and ranks among the most common cancers worldwide. While pathogenic BRCA1 mutations are well-established drivers of hereditary OC risk, their prevalence and clinical impact in African populations, including Sudan, remain largely unknown. Ethnic and regional genetic variations may influence mutation patterns, yet access to genetic testing in Sudan is extremely limited.

There is a significant knowledge gap regarding OC in Sudan. While the etiology of this disease has been explored elsewhere, scarce research has addressed it within the Sudanese context. Specifically, no prior studies in Sudan have investigated the role of family

predisposition or BRCA1 mutations in women with OC. Consequently**,** the prevalence of BRCA1 mutations in the Sudanese population and its association with OC risk is unknown.

Previous research has shown a significantly increased risk of OC in individuals with BRCA1 or BRCA2 mutations (13). Determining the presence of these mutations in women with OC diagnosis helps guide decisions regarding genetic counseling and testing for both the patients and their at-risk family members.

BRCA mutations can also influence treatment decisions. Patients with these mutations are more likely to benefit from specific targeted therapies, such as PARP inhibitors (14). Knowing the prevalence of BRCA mutations can optimize treatment strategies and improve outcomes of patients with OC diagnosis.

As BRCA mutations are inherited, detecting them in OC patients can identify family members at increased risk of developing ovarian and other related cancers (15). Early identification allows for improved surveillance programs and personalized prevention strategies.

Among the sequenced samples, a BRCA1 rs799917 SNP was detected in a 27-year-old patient diagnosed with Stage III, Grade III serous carcinoma (sample No 8 in table 1). This patient was single and reported a positive family history of OC. The detected mutation involved a C to T substitution in the BRCA1 gene. The small sample size and the limited number of mutation carriers, this result should be interpreted with caution. It remains possible that rs799917 could contribute to OC risk in this population, but larger studies are needed to clarify whether this trend reflects a true association or random variation.
Our findings are partly consistent with studies from Algeria and Tunisia (16), where the T allele was also the predominant variant. However, unlike those studies — which reported a significant association with OC — our results did not demonstrate a clear link. This discrepancy may reflect population-specific genetic differences, insufficient statistical power, or the influence of other unmeasured genetic or environmental factors.

Frequencies of mutations in exon 11 of BRCA1 in ovarian cancer

Globally

In 1996, De Benedetti *et al*., demonstrated in an Italian study that frame shift and nonsense mutations, leading to truncated proteins, are the most common mutations in the BRCAI gene associated with familial breast and OC susceptibility. Using protein truncation testing, the examined BRCAI exon 11, (contain approximately 61% of the coding region) in germline DNA from 70 Italian breast and/or OC patients. BRCAI mutations were found in nine of 29 (approximately 31%) patients with a family history of cancer and three of 41 (approximately 7%) women with early-onset breast carcinomas, and six affected relatives of two positive index cases. Sequence analysis was used to characterize these mutations.(17)

Cherbal *et al.,* (2010) screened for germline mutations in *BRCA1* and *BRCA2* in Algerian families with a history of breast and/or ovarian cancer, including the *BRCA1* rs179997polymorphism. This study provides insights into the prevalence of these mutations in a North African population with familial cancer history. (16)

Regionally (In Arab Countries of North Africa)

In the Arab countries of North Africa, specifically in Morocco, Algeria, and Tunisia, certain BRCA1 mutations exon 11, c.68_69delAG, c.181T>G, and c.798_799delTT—have been identified in families affected by breast cancer. These mutations have been recognized as the founder mutation in this regional context, indicating their prevalence and potential significance in contributing to the genetic predisposition to breast cancer within these populations (18).

Sub-Saharan Africa

Comparing regional differences, Rambau *et al.,* (2020) investigated the diagnostic accuracy and tumor type distribution of OC in East Africa in comparison to North America. This comparative approach highlights potential disparities in disease presentation and access to diagnostic resources across different geographical settings (19). Schildkraut *et al.,* (2014) focused specifically on risk factors for OC in African American women in the USA, exploring the role of age, family history of ovarian or breast cancer, obesity, lifestyle, and hormonal factors. This study underscores the importance of considering ethnicity and specific risk factor profiles within diverse populations. Notably, none of these demographic studies included an analysis of genetic mutations.(20)

Sudan

No studies have been conducted in Sudan to investigate the frequencies of mutations in exon 11 of the BRCA1 gene in OC. However, several studies have focused on characterizing the demographic profiles of patients with OC. Abuidris *et al.,* (2016) evaluated the

incidence rate and demographic data, including age and stage at diagnosis, among patients at the National Cancer Institute – University of Gezira, Sudan (7). Similarly, Wisal Adam *et al.*, (2017) examined demographic data, specifically age, grade, and stage at diagnosis, in another Sudanese population. These studies provide essential baseline information on the epidemiological (21)

Targeted Sanger sequencing

In this study, sequencing analysis was performed to confirm BRCA1 mutations in 11 selected patients, particularly those with a family history of OC or early-onset disease (age less than 30). As these subgroups would have a higher probability of harboring BRCA1 mutations (22). Whole Gene Sequencing, also known as Whole Genome Sequencing (WGS), is a comprehensive genetic testing technique that determines the complete DNA sequence of an organism's genome. It involves sequencing all the genes in an individual's genome, Overall, Whole Gene Sequencing is a powerful tool that can provide valuable insights into an individual's genetic makeup and help improve healthcare outcomes (23). In low-resource settings like Sudan, comprehensive NGS or full-gene sequencing may not be feasible due to costs, lack of infrastructure, or technical expertise. Many studies in similar contexts focus only on high-frequency known hotspots or use limited panels for pragmatic reasons. There is no information or studies about on the use of whole gene sequencing in patients with OC diagnosis in Sudan.

Sanger sequencing enhances the accuracy of mutation detection that may be missed by standard genotyping methods. While our sequencing of high-risk patients—those younger than 35 years and those with a family history of ovarian cancer (OC)—aimed to detect pathogenic *BRCA1* mutations, no such mutations were discovered in the exon, apart from the polymorphisms already included in this study. This highlights the need for more targeted screening strategies to improve early detection in diverse populations. Several other genes, such as TP53, PTEN, MLH1, MSH2, RAD51C, and PALB2, have also been associated with increased OK risk, although mutations in these genes do not invariably cause cancer in all carriers, (10). The test did not monitor the existence of any of them in the collection of samples that we conducted the test

It is important to note that our sequencing approach focused only on exon 11 of BRCA1, which, although it is the largest exon and a known hotspot for mutations, does not cover the full gene (10). Therefore, pathogenic mutations in other exons or intronic regions may have been missed. This limitation, combined with the fact that we did not investigate BRCA2 or other high-risk genes such as TP53 or mismatch repair genes (24), means that some hereditary cases may still be explained by mutations we did not assess. Additionally, familial clustering could partly reflect shared environmental or reproductive risk factors rather than purely genetic inheritance. These considerations highlight the need for comprehensive whole-gene or multi-gene panel sequencing in future studies to fully characterize hereditary OC risk among Sudanese women.

Study Limitations

This study has several important limitations that should be acknowledged. First, the small sample size substantially limits the statistical power to detect significant associations between BRCA1 polymorphism and OC risk, Second, the sequencing analysis targeted only exon 11 of the BRCA1 gene leaving other exons, intronic regions, and large genomic rearrangements unexplored; thus, pathogenic mutations elsewhere in BRCA1 or in other susceptibility genes could have been missed. Finally, the lack of comprehensive environmental exposure data — such as quantified pesticide use or detailed reproductive histories — prevents definitive conclusions about the relative contribution of genetic versus environmental factors in this population.

The Future studies should increase sample size and explore additional genetic markers to better understand OC susceptibility in Sudanese women.

Conclusion

This study provides novel insights into the genetic landscape of ovarian cancer (OC) in Sudanese women, focusing on BRCA1 mutations. Despite the limited sample size, our findings suggest that pathogenic BRCA1 mutations may not be a major contributor to OC susceptibility in this population. The detection of a BRCA1 rs799917 SNP in one patient highlights the importance of further investigation into the genetic risk factors underlying OC in Sudanese women. Given the study's limitations, including the small sample size and targeted sequencing approach, larger studies incorporating whole-genome sequencing and comprehensive environmental exposure data are necessary to elucidate the complex interplay between genetic and environmental factors in OC susceptibility. Ultimately, this research contributes to the growing body of evidence on OC genetics in diverse populations, informing the development of targeted screening strategies and personalized medicine approaches for OC prevention and treatment in Sudan and beyond.

Recommendation

- Larger, multicenter studies with expanded sample sizes are needed to achieve sufficient statistical power to detect meaningful associations between BRCA1 SNPs and OC risk, age at diagnosis, and clinical features.

- Future studies should perform whole-gene sequencing of BRCA1 (and BRCA2), rather than limiting analysis to a single exon or known SNPs. This would enable detection of pathogenic variants that may exist in other exons, intronic regions, or regulatory elements that were not covered in this study.

- Given the low prevalence of BRCA1 SNPs detected in the current study, future research should also investigate additional genetic, epigenetic, and environmental factors that may contribute to OC risk in Sudanese women. Whole-genome or whole-exome sequencing may reveal other relevant genes or pathway.

- Investments in local laboratory infrastructure and training are necessary to make comprehensive genetic testing and counseling accessible and affordable in Sudan. This will help integrate genetic risk assessment into clinical practice and enable more personalized prevention and treatment strategies.

- Efforts should be made to raise awareness among clinicians and the public about the importance of BRCA testing for women with strong family history of OC. Access to trained genetic counselors is critical to ensure appropriate interpretation of results and informed decision-making.

The high cost and limited availability of genetic testing in Sudan pose significant barriers to early detection and personalized treatment. Investment in affordable genetic screening programs, in collaboration with global cancer research networks, can improve patient outcomes.

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