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ORIGINAL ARTICLE

Positivity of BRCA 1 & 2 Mutations in Ovarian Cancer

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ABSTRACT

Aim: Ovarian cancer is a significant gynecological malignancy, with mutations in BRCA1 and BRCA2 genes contributing to its development and progression.

Methods: This descriptive cross-sectional study was conducted at JPMC Hospital, Karachi, over six months. It involved 159 women aged 18 to 75 years with histopathologically confirmed ovarian cancer. The study employed non-probability consecutive sampling and next-generation sequencing to identify BRCA mutations.

Results: The study found a low percentage of participants with a family history of ovarian cancer, a few identified with BRCA1 mutations, none with BRCA2 alone, and a minor proportion with mutations in both genes, suggesting a higher incidence of non-mutation- associated ovarian cancer.

Conclusion: The findings indicate a relatively low rate of BRCA1 and BRCA2 variations within those suffering from ovarian cancer in Pakistan, pointing to the need for further research to understand the genetic underpinning of ovarian carcinoma in this population and to develop targeted prevention and treatment strategies.

Keywords: BRCA mutations, ovarian cancer, genetic testing, Pakistan, prevalence, cross-sectional study.

INTRODUCTION

The seventh most frequent cancer diagnosis and the fifth most common reason for deaths related to cancer is ovarian cancer (OC).[1] Ovarian cancer is a gynecologic malignancy, with 313,959 new cases and 207,252 deaths reported worldwide in 2020.[2] The majority of women with ovarian cancer become aware of it at a more severe stage, and the 5-year survival rate is 30% [3] One of the major predisposing variables is a family history of breast or ovarian cancer, with first and second degree relatives having a two- and four-fold increased risk of ovarian cancer, respectively [4]. Of the known susceptibility genes for ovarian cancer, the most significant ones are BRCA1 and BRCA2. Mutations in these genes increase the likelihood of developing breast and ovarian cancer over one's lifespan.[5] BRCA1 mutation carriers have a 40% risk of developing ovarian cancer by the age of 70, compared to 10% for BRCA2 patients.[6] Mutations in these genes are responsible for 5-13% of ovarian cancer cases in Western countries.[7] and a large proportion of the familial carriage of this illness. [8]

BRCA1/2 are crucial genes that inhibit tumor suppression and participate in DNA double-strand break repair via homologous recombination (HR), affecting the growth of cells and chromosome stability. [9] It has been thoroughly investigated how the risk of acquiring Ovarian cancer is related to germline variations in BRCA1 and BRCA2.[10] Estimates indicate that throughout their lives rate of prevalence of OC in individuals with BRCA1 mutations is 28–66%, and for people with BRCA2 mutations, they are 16–27%.[11] There exists a well-established distinction in the global prevalence of BRCA1 and BRCA2 mutations.[12] Germline BRCA1 and BRCA2 mutations can occur in EOC patients at a frequency that varies between 5% to 20%, but somatic mutations are not as prevalent (2% and 8%, respectively). [13] BRCA mutations have been linked with greater odds of surviving after OC has been diagnosed and a positive response to platinum-based therapy, which additionally enhances the prognosis overall. [14] Gupta S et colleagues discovered that the incidence of genetic alterations in BRCA1 and BRCA2 amongst ovarian cancer patients was 15.5% and 5.9%, respectively.[15] According to Jasiewicz A et al., 20.8% of ovarian cancer patients had BRCA 1, while 13.3% had BRCA 2.[16] The incidence of BRCA mutation varies with ethnicity and country [17]. As a result, we must do additional research into the pathophysiology and medication resistance mechanisms of ovarian cancer in order to develop precise strategies for prevention and early detection.[18]

According to some research studies, patients suffering from ovarian cancer with BRCA1/2 germline mutations have an enhanced prognosis than wild-type patients [19], while other research tends to contradict this. Currently, there is little investigation into the clinicopathological features of BRCA1/2 gene mutations in the Pakistani population.[20] As a result, we carried out a study to gain insight into the incidence of BRCA1 and BRCA2 gene variations in those suffering from ovarian cancer.[21] However, this study determines the rate of positivity of BRCA 1 & 2 mutations in ovarian cancer. The objective of the study was to determine the frequency of positivity of BRCA 1 & 2 mutations in ovarian cancer in our population.

METHODS

A descriptive cross-sectional study was conducted at the Department of Oncology, JPMC Hospital, Karachi, spanning six months from June 2022 to April 2023, following the approval of the synopsis. The non-probability, consecutive sampling technique was employed. Women aged 18 to 75 years, diagnosed with histopathologically confirmed ovarian cancer, and willing to sign written informed consent were included. Patients who did not consent were not made part of the study.

The study was started after approval from ERB of our institution, JPMC Hospital Karachi. After explaining the study in detail, the patients provided written informed consent. Patients presenting to the department of oncology, JPMC with ovarian cancer (as defined in the operational definition) meeting inclusion were enrolled. Demographic and clinical characteristics of the patients such as family history of breast and/or ovarian cancer, medical & surgical history, age, sex, residency status, level of education, marital status, and the monthly earnings of the family were obtained from patients' available medical information. Blood samples were collected, DNA was obtained from blood using a QIAamp DNA micro kit (Qiagen, Germany), and the collected DNA was subjected to next-generation sequencing (NGS) with the TruSight cancer sequencing panel (Illumina, San Diego, CA), which encompasses 94 high-risk genes linked with cancer susceptibility. At the follow-up appointment, the investigator told patients about the findings of their BRCA mutation tests, and appropriate genetic counselling was offered which was in accordance with the local standards of care. All acquired data was documented on a predefined organized proforma. Confounding factors were reduced by closely adhering to inclusion and exclusion criteria and stratification. Only authorized individuals had access to patient data, whichwas kept confidential.

Data was entered and analysed using the IBM-SPSS version

20 programme. All continuous variables, including age, height, weight, BMI, and monthly income, were computed using the mean and standard deviation. All categorical variables were examined for frequency and percentages, including marital status, residence status, socioeconomic status, educational status, family history of ovarian cancer, BRCA 1 and BRCA 2. BRCA 1 and 2 were stratified to control the influence of modifiers such as age, body mass index, marital status, residence status, socioeconomic status, educational status, and family history of ovarian cancer. The chi-square test was also used to investigate the relationship between psychological issues in children with thalassemia major and other demographic characteristics. A P-value of <0.05 indicates statistical significance.

RESULTS

The demographic data delineate a predominance of participants over 45 years of age, residing in rural areas, with a high marital status rate. Educational status is mainly at the secondary level, and a majority are classified in the upper occupational status (Table 1). Clinically, a low percentage of participants have a family history of ovarian cancer, with a small number identified with BRCA1 mutations, none with BRCA2 alone, and a minor proportion with both BRCA1 and BRCA2 mutations, indicating a higher incidence of non-mutation-associated ovarian cancer within the study population (Table 2).

Table 1: Demographics of Participants

Variable	N (%)
Age	
<45	7 (23.3%)
>45	23 (76.7%)
Place of Residence	
Urban	6 (20%)
Rural	24 (80%)
Marital Status	
Married	27 (90%)
Unmarried	3 (10%)
Educational Status	
Primary	12 (40%)
Secondary	15 (50%)
Graduate	3 (10%)
Occupational Status	
Lower	13 (43.3%)
Upper	17 (56.7%)

Table 2: Clinical Information of the Participants

Variable	N (%)
Family History of Ovarian Cancer	
Yes	2 (6.7%)
No	28 (93.3%)
Ovarian Cancer	
BRCA1	2 (6.7%)
BRCA2	-
BRCA1 and BRCA2	3 (10%)
None	25 (83.3%)

Age-wise, all cases in <45 years had no mutations, while in >45 years, 2 (8.7%) had BRCA1 mutations, 3 (13.0%) had both mutations, and 18 (78.3%) had no mutations. The distribution across place of residence, marital status, educational status, occupational status, and family history of ovarian cancer is also outlined, providing valuable insights into potential associations between genetic mutations and demographic factors (Table-3).

Table 3: Association of Demographic Variable with Ovarian Cancer

Variables	Ovarian Cancer		
	BRCA1 (n=2)	BRCA1	None
		BRCA2 (n=3)	(n=25)
Age Group			
<45 years	0 (0.0)	0 (0.0)	7 (100.0)
>45 years	2 (8.7)	3 (13.0)	18 (78.3)
Place of Residence			
Urban	0 (0.0)	0 (0.0)	6 (100.0)
Rural	2 (8.3)	3 (12.5)	19 (79.2)
Marital Status			
Married	1 (3.7)	3 (11.1)	23 (85.2)
Unmarried	1 (33.3)	0 (0.0)	2 (66.7)
Educational Status			
Primary	0 (0.0)	0 (0.0)	12 (100.0)
Secondary	1 (6.7)	3 (20.0)	11 (73.3)
Graduate	1 (33.3)	0 (0.0)	2 (66.7)
Occupational Status			
Lower	1 (7.7)	0 (0.0)	12 (92.3)
Upper	1 (5.9)	3 (17.6)	13 (76.5)
Family History of Ovarian Cancer			
Yes	0 (0.0)	0 (0.0)	2 (100.0)
No	2 (7.1)	3 (10.7)	23 (82.1)

Values are presented as frequency (%)
C.I. (Class Interval), OR (Odd Ratio)
P-Value for Age Group (0.401), Place of residence (0.472), Marital Status (0.135), Educational Status (0.104) and Occupational Status (0.279) & Family History of Ovarian Cancer (0.807).

DISCUSSION

In this quantitative cross-sectional investigation, we sought to identify the incidence of BRCA1 and BRCA2 gene mutation in ovarian carcinoma in the Pakistani population. From a clinical standpoint, a small percentage of participants exhibit a family history of ovarian cancer. Among them, only a few have been identified with BRCA1 mutations, none solely with BRCA2 mutations, and a minor proportion with mutations in both BRCA1 and BRCA2. These findings suggest a higher occurrence of ovarian cancer is not associated with mutations within the study population.

Many investigations have reported the incidence of BRCA1 and BRCA2 variations in patients suffering from ovarian carcinoma in various countries.[6 8 9 15 16] In line with the findings of this study, a systematic review focused on evaluating the incidence of BReast CAncer gene 1 and BReast CAncer gene 2 gene alterations in females belonging to Arab countries yielded comparable results. Specifically, the review revealed that only one of 14 studies indicated the existence of BRCA1 in ovarian cancer cases, and none of the studies revealed the presence of BRCA2 mutations in those diagnosed with ovarian cancer, indicating that this mutation is rare among Arab women. [22]

In contrast to these findings, there are a number of researches that highlight the strong association of BRCA1/2 gene mutation among women, making them more susceptible to developing breast and ovarian cancer(s). [1 6 8 9 10 11 15 16] Another study by Kulkarni et al, conducted in a tertiary care center in Pune concluded that out of a total 94 suspected patients, 35.1% were diagnosed with ovarian cancer out of which 24.2% had positive mutation.[23] Fifty percent of the individuals with ovarian cancer had a BRCA2 variation, indicating a higher occurrence in this specific subset of individuals.

The study's strength lies in its contribution to the limited existing research, providing valuable insights with a focus on the local context. Additionally, the inclusion criteria encompassed patients of all age groups within the adult category, regardless of the presence or lack of a relevant family history, which is a key part of preventive, risk mitigation, and future treatment planning.

Several limitations are associated with our study. To begin, the results may not be generalizable due to the limited number of samples and hospital-based cross-sectional character, which may induce selection bias. Additionally, our research does not encompass the full spectrum of variations, lacking representation of the genetic diversity observed across Pakistan. Therefore, conducting multicenter studies involving various regions of the incidence of germline mutations in cancers of the breast and ovary in patients.

CONCLUSION

This study reveals a relatively low rate of BReast CAncer gene 1 and BReast CAncer gene 2 gene alterations within ovarian cancer sufferers in Pakistan, suggesting that the majority of ovarian cancer cases in this population may not be linked to these genetic mutations. Despite the global recognition of BRCA mutations significantly contributing to the risk and prognosis of ovarian cancer, our findings highlight the necessity of further genetic research within the Pakistani context. It underscores the importance of exploring other genetic or environmental factors that might contribute to the high incidence of ovarian cancer in this region. Future research should focus on comprehensive genetic screening beyond BRCA mutations to include other potential genetic markers associated with ovarian cancer. Moreover, developing tailored prevention and treatment strategies that cater to the genetic makeup of the Pakistani population could significantly improve patient outcomes. This study contributes to the growing body of evidence calling for a more localized approach to understanding and managing ovarian cancer, emphasizing the need for regional genetic studies and the development of targeted therapies.

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