







Comprehensive Germline Genomic Profiling of Patients with Ovarian Cancer: A Cross-Sectional Study

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Ind J Med Paediatr Oncol 2022;43:361–368.

Abstract

Introduction Ovarian cancer is the third most common cancer among Indian women. The data on the hereditary predisposition of these cancers and the clinical outcomes of those with pathogenic mutations is meager in India.

Objective The aim of the current study was to analyze the germline-genetic profile, clinicopathological characteristics, and outcomes of patients with ovarian cancer who were referred for genetic counseling at our Institute.

Materials and Methods It was a cross-sectional observational study. Patients with histological diagnosis of carcinoma ovary at our institute who were referred for genetic counseling from July 2017 to June 2020 were included in the study. All patients underwent pretest counseling. Most patients underwent multigene panel testing with reflex multiplication ligation-dependent probe amplification for large genomic rearrangements, while some received testing for *BRCA1* and *BRCA2* only. The variants were classified as pathogenic or benign based on American College of Medical Genetics (ACMG) guidelines. Data regarding the demographic profile, clinical characteristics, histopathological findings, family history, treatment received, and outcomes were extracted from the medical record system files.

Results One hundred and one patients were referred to the genetic clinic and underwent genetic counseling. All patients were advised for genetic testing; however, only 72 (71%) underwent testing. A multigene panel testing was done in 51 (70%)

Keywords

- germline
- ovarian cancer
- BRCA

DOI <https://doi.org/10.1055/s-0042-1746197>.
ISSN 0971-5851.

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patients, and only *BRCA1* and *BRCA2* genes were tested in 21 (30%). Among the 72 patients who underwent a genetic test, the median age was 47 years (range, 28–82). The most common histopathology was serous (90%), while 85% were diagnosed having stage 3 and 4 ovarian cancer. A pathogenic/likely pathogenic (P/LP) BRCA or non-BRCA mutation was detected in 32 (44%) patients. Six patients (8%) had a variant of unknown significance (VUS). Among P/LP mutations, 85% were in the *BRCA* gene (75% in *BRCA1* and 10% in *BRCA2*), while 15% were in non-BRCA gene mutations (*RAD51*, *PALB2*, *MER11*, *HMMR*). Disease-free survival and overall survival were not different in mutation-positive and mutation-negative cohorts.

Conclusions We report 44% P/LP mutations in this selected cohort of patients with carcinoma ovaries. BRCA mutations constituted 85% of all the mutations, while 15% of mutations were in non-BRCA genes.

Introduction

Ovarian cancer (OC) is the eighth most common cancer in females (3.4% of all cancers) and leads to 4.4% of all cancer-related mortality.¹ Globally, there were 313,959 cases diagnosed with OC in 2020 and 207,252 deaths.¹ In India, the estimated incidence of OC in 2020 is 43,886 (6.7%) cases, and mortality is 32,077 (7.8%).² Though the prevalence is low, the survival of advanced OCs is dismal (20–40%).³ The most important risk factor for OC is a genetic predisposition, that is, family history of breast or OC.⁴ More than 20% of OCs are associated with a mutation in the tumor suppressor genes, most important being *BRCA1/2*.⁵ The average cumulative frequency of OC at 70 years is estimated to be 35 to 46% for individuals with *BRCA1* mutations and 13 to 23% for *BRCA2* mutation.⁶ Other genes implicated are *ATM*, *CHEK2*, *BRIP*, *RAD51C*, *RAD51D*, and *MUTYH* genes.⁵

Families with these mutations have a higher prevalence of multiple malignancies. Preventive strategies like salpingo-oophorectomy reduce the risk of OC by 96%.⁷ Detecting mutation in the *BRCA* gene has therapeutic implications and is immediately applicable to patients in the first line as maintenance and in the recurrent setting where it has shown improvements in progression-free survival.^{8,9} Identification of these pathogenic mutations is essential as this may help us plan screening and preventive strategies in families with identifiable mutations. The current literature regarding mutation-positive OC in India is meager and is often lumped with breast cancer data. The current study aimed to analyze the genetic and clinicopathological profile and outcomes of patients with OC from a tertiary care center in India.

Methodology

Materials and Methods

Patients

In this cross-sectional observational study, patients with histological diagnosis of carcinoma of the ovary, registered in our cancer center, who were referred for genetic counsel-

ing between Jan 2017 and Dec 2020 were included. A medical oncologist did pretest counseling. Patients who did not give informed consent were excluded. Most patients underwent multigene panel testing with reflex multiplication ligation-dependent probe amplification (MLPA) that detects gene specific single or multiple exon deletions and duplications, which may be missed by next-generation sequencing, while some received testing for *BRCA1* and *BRCA2* only. Those with a pathogenic/likely pathogenic (P/LP) mutation in any of the predisposing genes were discussed in a multidisciplinary tumor board for management and were offered post-test counseling. The variants were classified as pathogenic or benign based on American College of Medical Genetics (ACMG) guidelines.¹⁰ Data regarding the demographic profile, clinical characteristics, histopathological findings, family history, treatment received, and outcomes were extracted from the medical record system files. The primary outcome was the frequency of PLA mutations identified in the sample. The secondary outcomes included the comparison of response rates, overall survival (OS), and disease-free survival between the groups with and without a P/LP mutation.

Sample Preparation and Multigene Panel Design

Blood samples were collected from each patient (10 mL), and germline DNA extraction was done by kits following the manufacturer's instructions. Genomic DNA was enzymatically fragmented. Regions of interest were selectively enriched using customized capture probes targeted against coding regions of the 104 genes (listed in supplementary material), including ten bp of flanking intronic sequences for the genes *BRCA1* and *BRCA2*. In 21 patients, only two genes (*BRCA1* and *BRCA2*) were studied. The libraries underwent next-generation sequencing to mean >80–100X coverage on the Illumina sequencing platform. The sequences were aligned to the human reference genome (GRCh37/hg19) build I.D. Gene bank NM_007300.3 and NM_000059.3 were used as reference transcript sequences for *BRCA1* and *BRCA2* genes, respectively. Gene annotation of the variants was performed using the variant effect predictor (VEP) program against Ensemble release 91 human gene model.

Mutations were annotated using databases: ClinVar, OMIM, GWAS, HGMD, and SwissVar. Variants were filtered based on allele frequency in 1000 Genome phase3, gnomAD, EVS, dbSNP, 1000 Japanese Genome, and Indian database.

MLPA Testing

Reflex MLPA testing was done for patients who tested negative on the multigene panel. Copy number change in 24 exons of *BRCA1* and 27 exons of *BRCA2* was identified by hybridizing with MLPA-based assay. Each MLPA probe consisted of two hemiprobes that were bound to an adjacent site of the target sequence. Upon ligation and subsequent PCR amplification, each probe generated an amplicon with a unique length. Copy number differences of various exons between test and control DNA samples were detected by analyzing the MLPA peak patterns. The classification of variants was done as deleterious (class 5—pathogenic or class 4—likely pathogenic), a variant of unknown clinical significance (VUS, class 3), likely benign (class 2), and benign (class 1) according to the ACMG guidelines.

Data regarding the demographic profile, clinical characteristics, histopathological findings, family history, treatment received, and outcomes were extracted from the medical record system files.

Statistical Analysis

Categorical data were summarized using percentages. Numerical data were summarized as the means and standard deviations or medians and ranges. Chi-squared tests and Fisher's exact tests were used to examine the relationships between qualitative variables. The survival analysis was performed using the Kaplan–Meier method. A log-rank test was used to compare the survival curves. All tests of hypotheses were conducted at an α level of 0.05, with a 95% confidence interval. The median duration of follow-up was estimated using the reverse Kaplan–Meier method. Disease-free survival) was defined as “the interval from histological diagnosis to the date of first progression or last follow-up.” OS was defined as “the interval from histological diagnosis to the date of death or last follow-up.” All analysis was done using STATA software (ver13, Texas, United States)

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. Ethics Committee Approval was obtained from the Institutional Ethics Committee vide letter no. IEC-511/05.06.2020, RP-50/2020 dated 30.9.2020 (see supplementary material).

Results

One hundred and one patients were referred to the genetic clinic and underwent genetic counseling. All patients were advised for genetic testing; however, only 72 of them (71%) underwent testing. The various reasons for not undergoing genetic testing were financial issues in 20 patients (20%), deferral of testing due to COVID pandemic in 5 of them (5%),

Table 1 Baseline characteristics of the patients included in the study

Baseline characteristics (n = 72)	Median/mean \pm SD/percentage
Age	45.5 years (IQR: 41.5–55) (Range, 28–82)
Ethnicity	
Hindu	65 (90%)
Muslim	04 (5%)
Christian	02 (3%)
Buddhism	01 (2%)
Histology	
Serous	68 (95%)
Mucinous	1 (1%)
Endometrioid	2 (3%)
Clear cell	1 (1%)
Baseline stage	
I	7 (10%)
II	4 (6%)
III	48 (68%)
IV	13 (16%)
Newly diagnosed cases	5 (5%)
Relapsed cases	95 (95%)
Family history	
Yes	34 (34%)
No	38 (66%)
Family history of breast cancer	
Ovarian cancer	14 (41%)
Both breast and ovarian cancer	10 (29%)
Prostate cancer	01 (4%)

Abbreviations: IQR, interquartile range; SD, standard deviation.

and patient preference in 4 (5%). A multigene panel testing was done in 51 (70%) patients, and only *BRCA1* and *BRCA2* genes were tested in 21 (30%).

Among the 72 patients who underwent a genetic test, the median age was 47 years (range 28–82) (**Table 1**). Hinduism was the most common religion (89%), while four (5%) patients were Muslims and two (3%) were Christians. Seventy-three percent of these patients were literate. Seventy-four percent of these patients were from Delhi, Chandigarh, and Uttar Pradesh, while 18% were from eastern states (Bihar, Orissa, West Bengal). Six patients were from western and southern states (four from Rajasthan and two from Kerala).

Of all patients, 4 (5%) had recently been diagnosed with malignancy, whereas 68 (95%) were referred after progression on the first line of therapy. Sixty-four (89%) patients had OC, while 8 (11%) patients had both ovarian and breast cancer. The most common histopathology was serous (90%), while 85% were detected as stage 3 and 4 OCs.

A family history of breast/ovarian cancer syndrome was present in 34 (34%) cases (85% in first-degree relatives and 15% in second-degree relatives). Of these 34 patients, 9 of them (26%) had a family history of breast cancer, 14 (41%) patients had a history of OC, and 10 (29%) patients had a family history of both breast and OC.

A mutation was identified among the patients who underwent a genetic test in 38 (52%) patients. A P/LP BRCA or non-BRCA mutation was detected in 32 (44%) patients. Six patients (8%) had a VUS (► **Table 2**).

Mutations were more common in patients younger than 50 years (68%; $n=22$). However, it was not significantly different from those older than 50 years ($p=0.65$). Notably, among patients younger than 50 years and who had a positive family history, the detection rate of a mutation was 87%.

Among P/LP mutations, 85% were in the *BRCA* gene (75% in *BRCA1* and 10% in *BRCA2*), while 15% were non-BRCA gene mutations (*RAD51*, *PALB2*, *MER11*, *HMMR*). The mutations in *BRCA1* gene spanned over exon 2 to exon 24 region with maximum mutations present in exon 10 (► **Table 3**). The Ashkenazi Jewish founder mutation (c.68_69delAG) was present in two patients. The most common types of mutations in patients were nonsense mutation in 10 (42%), followed by frameshift mutations in 8 of them (33%), missense mutation in 3 (13%), splice-site mutation in 2 (8%), and a large genomic rearrangement in 1 patient (4%). In the *BRCA2* gene, all were frameshift mutations, while in non-BRCA genes, 80% were nonsense, and 20% were frameshift mutations.

VUS was present in 10 patients, among which four patients had both P/LP and VUS. Two patients had VUS in

Table 2 Frequency distribution of mutations ($n=72$)

Pathogenic/likely pathogenic (P/LP)	32 (44%)
Variant of unknown significance (VUS)	10 (14%)
Both P/LP and VUS	04 (6%)
Locus of P/LP mutations ($n=32$)	n (percentage)
BRCA 1	24 (75%)
BRCA 2	03 (10%)
MER11	01 (3%)
PALB2	01 (3%)
RAD51	02 (6%)
HMMR	01 (3%)

Abbreviations: BRCA, breast cancer gene; HMMR, hyaluronan-mediated motility receptor; MER11, meiotic recombination 11 homolog; P/LP, pathogenic/likely pathogenic; PALB2, partner and localizer of BRCA2; RAD51, DNA repair protein RAD51; VUS, variant of uncertain significance.

BRCA2, and three patients had in *ATM* gene. One patient each had VUS in *FANCI*, *MLH1*, *ERCC2*, *CHECK2*, and *FANCM* genes.

Neoadjuvant chemotherapy was given in 50% of both mutation-positive and mutation-negative cohorts. Eighteen percent of mutation-positive patients achieved complete remission (CR), while 76% had a partial response (PR) Among mutation-negative, there were no CR, and 84% achieved PR (► **Table 4**). None of the included patients received maintenance PARP inhibitors during this period.

Table 3 Comparison of the clinical characteristics of patients with and without a P/LP mutation

Patients characteristics	Positive for P/LP mutation ($n=32$)	Negative for P/LP mutation ($n=40$)	p -Value
Age	47.5 ± 9	49.5 ± 12	0.77
Age group			
< 50 years	22 (68%)	24 (60%)	0.65
> 50 years	10 (32%)	16 (40%)	
Family history present (first or second-degree having breast/ovarian cancer)	25 (78%)	09 (22.5%)	0.001
First-degree relatives	24 (70%)	5 (15%)	
Second-degree relatives	5 (15%)	02 (6%)	
Personal history of breast cancer	05 (15%)	03 (8%)	0.31
NACT received	17 (48%)	19 (53%)	0.20
Response to NACT			
CR	03 (18%)	0	
PR	13 (76%)	16 (84%)	
SD	01 (06%)	02 (10%)	
PD	0	01 (05%)	
DFS (median)	20.2 months	21.4 months	0.26
OS (median)	91.4 months	71.5 months	0.38

Abbreviations: CR, complete response; DFS, disease-free survival; NACT, neoadjuvant Chemotherapy; OS, overall survival; P/LP, pathogenic/likely pathogenic; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4 The pathogenic/likely pathogenic mutations, their description, location, and corresponding protein changes

Gene	Site	Variant	Protein change	Type of mutation
BRCA 1	EXON 10	c.3607C > T	p.Arg1203 Ter	Nonsense
BRCA 1	EXON 10	c.1450G > T	p.Gly484 Ter	Nonsense
BRCA 1	EXON 10	c.1008delA	p.Glu337LysfsTer4	Frameshift
BRCA 1	EXON 10	c.3147delC	p.Ser1050ValfsTer12	Frameshift
BRCA 1	EXON 10	c.2769del	p.Asn924IlefsTer76	Frameshift
BRCA 1	EXON 10	c.2338C > T	p.Gln780Ter	Nonsense
BRCA 1	EXON 10	c.2076_2080delTGACA	p.His692GlnfsTer18	Frameshift
BRCA 1	EXON 10	c.3607C > T	p.Arg1203 Ter	Nonsense
BRCA 1	EXON 10	c.1953_1956delGAAA	p.Lys653SerfsTer47	Frameshift
BRCA 1	EXON 11	c.4183 C > T	p.Gln1395Ter	Nonsense
BRCA 1	EXON 15	c.4738G > G/C	p.Glu1580 Gln	Missense
BRCA 1	EXON 15	c.4571 C > A	p.Ser1524Ter*	Nonsense
BRCA 1	EXON 15	c.4571 C > A	p.Ser1524Ter*	Nonsense
BRCA 1	EXON 15	c.4571 C > A	p.Ser1524Ter*	Nonsense
BRCA 1	EXON 15	c.4571 C > A	p.Ser1524Ter*	Nonsense
BRCA 1	EXON 16	c.4900_4901delinsGCC	p.Ser1634AlafsTer9	Frameshift
BRCA 1	EXON 2	c.68_69 delAG	p.Glu23ValfsTer17	Frameshift
BRCA 1	EXON 2	c.68_69 delAG	p.Glu23ValfsTer17	Frameshift
BRCA 1	EXON 7	c.470_471 delCT	p.Ser157Ter	Nonsense
BRCA 1	EXON 24	c.5572 T > C	p.Trp1858Arg	Missense
BRCA 1	EXON 24	c.5572 T > C	p.Trp1858Arg	Missense
BRCA 1	INTRON 17	c.5137 +1 G > A		Splice site
BRCA 1	INTRON 14	c.4547 + 1G > A		Splice site
BRCA 1	LGR, EXON 1-20			
BRCA 2	EXON 11	c.3182del	p.Lys1061SerfsTer16	Frameshift
		c.4570_4573delTTTC	p.Phe1524IlefsTer18	Frameshift

(Continued)

Table 4 (Continued)

Gene	Site	Variant	Protein change	Type of mutation
BRCA 2	EXON 11			
BRCA 2	EXON 11	c.5967_5968 del	p.Asp1990cysfsTer12	Frameshift
RAD51 D	EXON 5	c.423delA	p.Ala142GlnfsTer14	Frameshift
RAD51 D	EXON 5	c.423delA	p.Ala142GlnfsTer14	Frameshift
HMMR	EXON 12	c.1327C>T	p.Gln443Ter	Nonsense
MER 11	EXON 10	c.1086del	p.Val363TyrfsTer27	Frameshift
PALB2	Exon 5	c.2488delG	p.Glu830SerfsTer21	Frameshift

This mutation was found in a single family with 4 members affected with ovarian cancer.

Disease-free survival was not different in mutation-positive and mutation-negative arms. Although OS was numerically higher in the mutation-positive arm (91 vs. 71 months), it was not statistically significant (► Fig. 1).

Cascade testing was advised for the family members of patients who were positive for the mutation. However, only 13 members from 8 different families underwent testing. Four were *BRCA1* positive. Though risk reducing salpingo-oophorectomy was advised to the previvors, none of them had undergone the preventive surgery. All are under radiological surveillance.

Discussion

The current study is a cross-sectional analysis of selectively referred OC patients. We report 44% PLP mutations in this

selected cohort of patients with carcinoma ovaries. BRCA mutations constituted 85% of all the mutations, while 15% of mutations were in non-BRCA genes. The prevalence of Ashkenazi Jewish founder mutation was very scarce (2.1%) in our cohort. The presence of BRCA mutation had no impact on survival outcomes. There was poor uptake of cascade testing.

In one retrospective analysis of OC ($n=238$), where patients across India were selectively referred to the laboratory for multigene panel testing, 36% had pathogenic mutations (84.9% in *BRCA1/2* gene and 15.1% in non-BRCA gene).¹¹ In another study of selectively referred patients with OC by Mehta et al from north India ($n=74$), where only BRCA mutation testing was done, 41.5% of patients carried a mutation.¹² Both the above-mentioned studies with selective populations showed comparable mutation rates to our study. However, Gupta et al, in a prospective study ($n=239$)

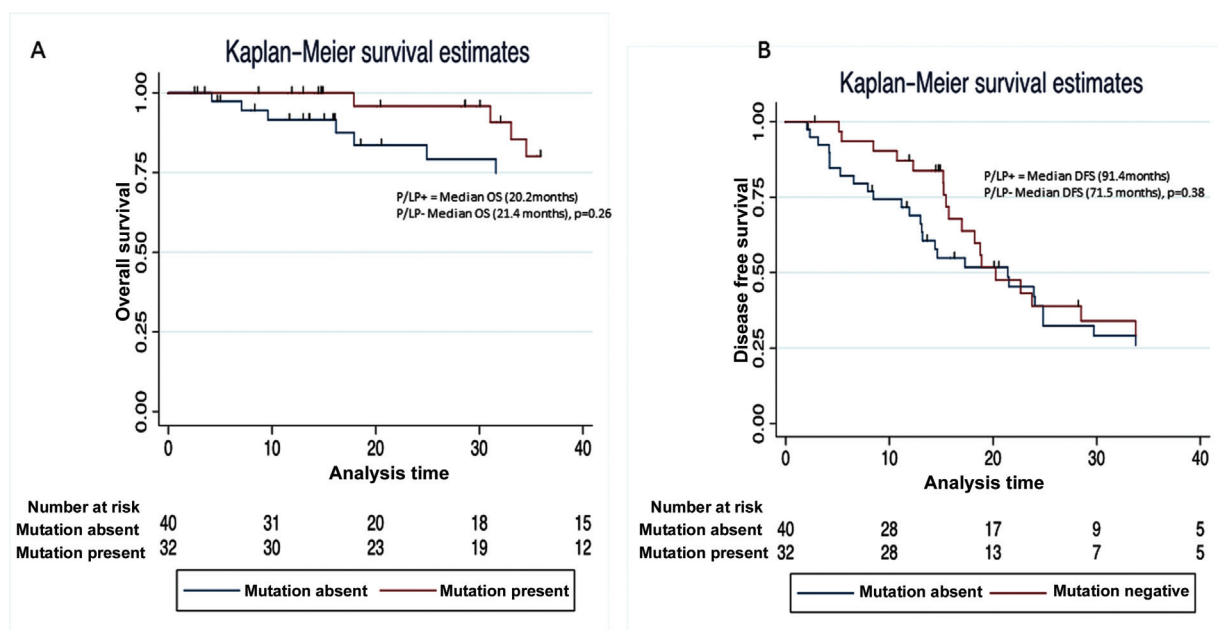


Fig. 1 Comparison of the (A) overall survival and (B) disease-free survival (DFS) of patients with and without a pathogenic/likely pathogenic (P/LP) mutation in any of the predisposing genes.

of unselected patients of carcinoma ovary from all across India, reported BRCA mutations in 25.5% of patients, which may be closer to true prevalence in the population.¹³

Reported literature from various ethnicity worldwide has shown a slightly lower prevalence of BRCA and non-BRCA mutations. In a prospective study of consecutive patients of carcinoma ovary done by Eoh et al in Korea ($n = 117$), 32.5% of patients with epithelial ovarian cancer had a pathogenic mutation in BRCA and non-BRCA genes (79.5% mutation in BRCA gene).¹⁴ In the Japanese nationwide multicentric study ($n = 634$), where OC patients were recruited prospectively, 28.5% of high-grade serous ovarian cancers had germline BRCA mutations.¹⁵ Similarly, a retrospective study by Atas-even et al in the German population ($n = 545$) showed 29.5% P/LP mutations in hereditary cancer-predisposing genes. Eighty-one percent of mutations were in the BRCA gene alone.¹⁶ Walsh et al showed that in the American population of prospectively selected OC ($n = 360$), 24% had germline mutation, 18% in BRCA1/2, and 6% in non-BRCA genes.⁵ In the study done at Royal Marsden Hospital, London, where only BRCA1 and BRCA2 were tested, the yield was 16%.¹⁷

The Ashkenazi Jewish founder mutation was present in two patients in our study. In another study done in North India, this mutation was found in only one patient.¹² However, in the study by Singh et al, which had patients from across India, this mutation was repeated 34 times.¹¹ In another study done exclusively in the South Indian population, which included both breast and OC, the Ashkenazi Jewish founder mutation was present in 10 out of 44 patients.¹⁸ The profile of BRCA1/2 mutation in South India appears to be different from North India.

Patients with pathogenic mutations had a better response to platinum-based therapy. Eighteen percent of patients with mutations achieved CR postneoadjuvant chemotherapy compared with none in patients with no detectable mutations. This may be explained due to increased platinum sensitivity in BRCA deficient tumors. In BRCA deficient tumors xenograft studies have shown differential gene expression and pathway modulation, which includes upregulation of RAD 52 and ERCC1/RRM1 downregulation that might be responsible for increased platinum sensitivity.¹⁹ However, we did not find any difference in the PFS or OS. Some studies have reported longer PFS in BRCA mutated patients,²⁰ while others have shown no difference.²¹ The heterogeneity in the outcome can be explained by other prognostic factors such as stage, optimal cytoreduction, and age.

Our study included multigene panel testing with reflex MLPA, and results were correlated with clinical details. This study reports the details exclusively from the North Indian population, chiefly Delhi and adjoining states, and the real-world challenges of access to testing, cascade testing, and counseling. Our study is the first study that uses mainstreaming of the genetic testing of OC by clinicians in India. Although no founder mutations were seen, there appears to be a significant difference in North-South Indian populations concerning the prevalence of Ashkenazi Jewish mutations.

Limitations

The patients in the study represent a highly selected population. It included those who were referred by the clinicians and who could avail of the testing. This selection may have its own biases. All patients could not undergo multigene panel testing, and some underwent BRCA only testing.

Future Directions

This study and other contemporary studies point to the significant burden of a germline mutation in carcinoma of the ovary in the Indian population. The oncology community in India has accepted universal genetic testing for BRCA1/2 genes, and given the scarcity of counselors, this is imperative that all oncologists take part in mainstreaming the test. Locus-specific database specific to the Indian population is the need of the hour.

Conclusion

OC is an aggressive disease, and it has got high genetic predisposition. Knowing the deleterious mutations in various genes can help the patients and their biological relatives. This study reports various pathogenic and VUS mutations in BRCA and non-BRCA genes in the North Indian population. Forty-four percent of P/LP mutations were found with a very low frequency of founder mutations (2%). This study would help in building up the database for the Indian population.

Ethical Approval

The study protocol was approved by the Institute Ethics Committee vide letter number-IEC-511/5.6.20 RP/50/2020

Consent to Participate

Informed consent was obtained from all patients.

Availability of Data and Material

Data regarding this study will be available from the corresponding author (RP) at reasonable request.

Authors' Contributions

R.P; A.U; S.K; L.K; P.M; M.R; S.D; and S.K contributed to the concept design, patient referrals, and conduct of the study. R.G; D.T; and V.L.R were involved in laboratory testing. A. U; R.P did the statistical analysis.

Funding

None.

Conflict of Interest

None declared.

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