original reports abstract

Prevalence of *BRCA1* and *BRCA2* Mutations Among Patients With Ovarian, Primary Peritoneal, and Fallopian Tube Cancer in India: A Multicenter Cross-Sectional Study

Sudeep Gupta, MBBS, MD, DM[1]; Senthil Rajappa, MD, DNB, DM[2]; Suresh Advani, MBBS, MD[3]; Amit Agarwal, MBBS, MD, DM[4]; Shyam Aggarwal, MBBS, MD[5]; Chanchal Goswami, MBBS, MD[6]; Satya Dattatreya Palanki, MBBS, MD[7]; Devavrat Arya, MBBS, MD, DM[8]; Shekhar Patil, MBBS, MD, DM[9]; and Rohit Kodagali, MBBS, MD[10]

PURPOSE There are deficient data on prevalence of germline mutations in breast cancer susceptibility genes 1 and 2 (*BRCA1*/*BRCA2*) in Indian patients with ovarian cancer who are not selected by clinical features.

METHODS This prospective, cross-sectional, noninterventional study in nine Indian centers included patients with newly diagnosed or relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer. The primary objective was to assess the prevalence of *BRCA1*/*BRCA2* mutations, and the secondary objective was to correlate *BRCA1*/*BRCA2* status with clinicopathologic characteristics. Mutation testing was performed by a standard next-generation sequencing assay.

RESULTS Between March 2018 and December 2018, 239 patients with a median age of 53.0 (range, 23.0-86.0 years) years were included, of whom 203 (84.9%) had newly diagnosed disease, 36 (15.1%) had family history of ovarian or breast cancer, and 159 (66.5%) had serous subtype of epithelial ovarian cancer. Germline pathogenic or likely pathogenic mutations in *BRCA1* and *BRCA2* were detected in 37 (15.5%; 95% CI, 11.1 to 20.7) and 14 (5.9%; 95% CI, 3.2 to 9.6) patients, respectively, whereas variants of uncertain significance in these genes were seen in four (1.7%; 95% CI, 0.5 to 4.2) and six (2.5%; 95% CI, 0.9 to 5.4) patients, respectively. The prevalence of pathogenic or likely pathogenic *BRCA* mutations in patients with serous versus nonserous tumors, with versus without relevant family history, and ≤ 50 years versus > 50 years, were 40 of 159 (25.2%; 95% CI, 18.6 to 32.6) versus 11 of 80 (13.8%; 95% CI, 7.1 to 23.3; $P = .0636$), 20 of 36 (55.6%; 95% CI, 38.1 to 72.1) versus 41 of 203 (20.2%; 95% CI, 14.9 to 26.4; $P < .0001$), and 20 of 90 (22.2%; 95% CI, 14.1 to 32.2) versus 31 of 149 (20.8%; 95% CI, 14.6 to 28.2; $P = .7956$), respectively.

CONCLUSION There is a high prevalence of pathogenic or likely pathogenic germline *BRCA* mutations in Indian patients with ovarian cancer.

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INTRODUCTION

Ovarian cancer is one of the most common gynecologic cancers, with 313,959 new cases and 207,252 deaths reported worldwide in 2020.[1] It accounted for more deaths than any other cancer of the female reproductive system.[2] In the Indian context, ovarian cancer is the third leading cancer among women, after cervical and breast cancer.[3]

A majority of patients with ovarian cancer are diagnosed at an advanced stage, wherein the 5-year survival is < 30%.[4-7] Family history of ovarian or breast cancer is one of the important predisposing factors, with first- and second-degree relatives having four-fold and two-fold higher risk of developing ovarian cancer, respectively.[8-10] Inherited mutations in the key tumor suppressor genes, the breast cancer susceptibility gene 1 or 2 (*BRCA1* or *BRCA2*), are prevalent in 3%-27% of patients with ovarian cancer who are not selected on the basis of clinical features like family history.[11,12] By age 70 years, ovarian cancer risk is 40% in *BRCA1* and 18% in *BRCA2* mutation carriers.[13] Germline mutations in *BRCA* genes also confer high risk for the development of fallopian tube carcinoma and primary papillary serous carcinoma of the peritoneum.[14-16]

Some studies have suggested that ovarian cancer patients with germline *BRCA1/2* mutations (especially *BRCA2*) have improved prognosis compared with those lacking *BRCA* mutations.[17-21] Thus, as recommended

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What is the incidence of germline mutations in *BRCA1* or *BRCA2* genes in Indian patients with ovarian cancer who are not selected by clinical criteria like family history or age?

Knowledge Generated

In this multicenter Indian study involving nine tertiary centers and 239 patients, germline pathogenic or likely pathogenic mutations in *BRCA1* and *BRCA2* were detected in 15.5% and 5.9% of patients, respectively. The prevalence of these mutations in patients with nonserous tumors, without relevant family history, and with age > 50 years was 13.8%, 20.2%, and 20.8%, respectively. This suggests that selection of patients for germline testing by serous histology, suggestive family history, and young age is likely to miss *BRCA1* and *BRCA2* mutations in many patients.

Relevance

There is a high incidence of germline *BRCA1* and *BRCA2* mutations in Indian patients with epithelial ovarian cancer. Efforts should be made to make such testing widely available in India.

by numerous clinical guidelines, screening for *BRCA* mutations may help not only in developing patient management strategies but also in prognosticating patients with ovarian cancer.[22-26] For example, the recent National Comprehensive Cancer Network guidelines (version 1, 2020) recommend genetic testing for *BRCA1/2* mutations along with other panels of mutations like *CDH1*, *PALB2*, *PTEN*, and *TP53* in patients with breast cancer, ovarian cancer, and pancreatic cancer on the basis of their family history, ethnicity, age, and tumor histology.[27] Although a few regional studies have been reported,[11,28,29] these have included patients with breast and/or ovarian cancer who were chosen because of clinical features like suggestive family history or young age, with pathogenic or likely pathogenic mutation being reported in 25.5%-30.1% of them. Hence, this multicenter Indian study was undertaken in patients with ovarian cancer not selected for any predisposing clinical features, who were evaluated for prevalence of germline *BRCA* mutations and its association with clinical and pathologic characteristics.

METHODS

The study protocol (ClinicalTrials.gov identifier: NCT03471572) was approved by the regulatory authorities and the ethics committees or institutional review boards of all the participating centers. The study was conducted in accordance with the Declaration of Helsinki, the International Council on Harmonization Good Clinical Practice guidelines, Good Pharmacoepidemiological Practice, and the applicable legislation(s) on noninterventional studies and/or observational studies.[30,31] All patients provided written informed consent before their study participation.

Study Population

Women age 18 years or older with previously or newly diagnosed ovarian, primary peritoneal, or fallopian tube cancer were enrolled in the study. Patients were excluded if they failed to provide written informed consent or had any medical condition that, in the opinion of the investigator, would interfere with safe completion of the study, or were participating in any other clinical trial.

Study Design and End Points

This was a prospective, noninterventional, cross-sectional, multicenter study that enrolled patients between March 2018 and December 2018 at 9 centers across India (Appendix Table A1). Data pertaining to demographics, family history of breast and/or ovarian cancer, and medical and surgical history were collected from patients' available medical records and transcribed on to the electronic case report forms. Blood samples were collected, coded for confidentiality, stored at ambient temperature, and sent to a central laboratory at Bangalore, India, for germline mutation testing. DNA was extracted from blood using a QIAamp DNA mini kit (Qiagen, Germany), and next-generation sequencing (NGS) was performed on the extracted DNA using the TruSight cancer sequencing panel (Illumina, San Diego, CA), covering 94 high-risk genes associated with cancer predisposition. The list of genes is the same as that previously reported.[28] From 50 ng of input genomic DNA of each patient, NGS libraries were prepared and hybridized to a custom pool of oligonucleotides, targeting genomic regions as previously described, followed by paired end sequencing of up to 150 base pair read lengths.[28] The mutations were classified as pathogenic or likely pathogenic or variants of uncertain significance (VUS) as per International Agency for Research on Cancer classification.[32] At the devolution visit, the investigator informed patients about their *BRCA* mutation test results and appropriate genetic counseling was provided as per the local standard of care. The primary objective was to determine the proportion of patients with germline pathogenic or likely pathogenic *BRCA1* and *BRCA2* mutations and variants of uncertain significance. We also assessed the association of *BRCA1* and *BRCA2* mutation with family history of breast and/or ovarian cancer and histopathologic type of ovarian

cancer. The study did not aim to provide any new or interventional drug to the patients.

Statistical Analysis

On the basis of an estimated *BRCA1/2* prevalence rate of 15.8% in the study population, a sample size of 228 was calculated with a precision of 5%.[33] With an assumed dropout proportion of 10%, a total of 240 patients were planned to be included in this study. Statistical analyses were performed using Statistical Analysis Software (version 9.4). The *BRCA1/2* mutation–positive status was summarized in terms of frequency (n) and percentages along with corresponding binomial exact 95% CI using Clopper Pearson method. For analysis of secondary end points, chi-square test was used to test the differences in *BRCA 1/2* mutation status between subgroups defined by histopathologic type and family history of breast and/or ovarian cancer at a significance level of 0.05.

RESULTS

Clinical and Pathologic Characteristics

Between March and December 2018, 242 female patients with epithelial ovarian or primary peritoneal cancer were enrolled in the study, of whom three patients had to be excluded from the analysis, two because of not fulfilling the eligibility criteria and one being a duplicate enrollment. Table 1 shows the demographic characteristics of the patients, and Appendix Figure A1 shows the study flow. The median age of patients was 53.0 (range, 23.0-86.0 years) years; 203 (84.9%) patients had newly diagnosed disease.

TABLE 1. Patient and Disease Characteristics

Characteristic	Population (N = 239)
Age, years, median (range)	53.0 (23.0-86.0)
BMI, kg/m^2, median (range)	25.7 (15.5-52.0)
Patients with history of ovarian cancer, No. (%)	137 (67.8)
Histologic finding, No. (%)	
Ovarian cancer	230 (96.2)
Primary peritoneal cancer	8 (3.3)
Fallopian tube cancer	1 (0.4)
Disease grade, No. (%)	
Undifferentiated	20 (8.4)
Poorly differentiated	90 (37.7)
Moderately differentiated	28 (11.7)
Well-differentiated	37 (15.5)
Not known	64 (26.8)
Patients with family history, No. (%)	36 (15.1)
Ovarian cancer	13 (5.4)
Breast cancer	21 (8.8)
Both ovarian and breast cancer	2 (0.8)

Abbreviation: BMI, body mass index.

A majority of patients (230, 96.2%) had ovarian cancer followed by primary peritoneal cancer (8, 3.3%) and fallopian tube cancer (1, 0.4%). Most patients (203, 84.9%) did not have a family history of ovarian or breast cancer.

Prevalence of *BRCA1* and *BRCA2* Mutations

Of the analyzed 239 patients, pathogenic or likely pathogenic *BRCA1/2* mutations were detected in 51 (21.3%; 95% CI, 16.3 to 27.1) patients, 37 (15.5%; 95% CI, 11.1 to 20.7) with *BRCA1* mutations and 14 (5.9%; 95% CI, 3.2 to 9.6) with *BRCA2* mutations. None of the patients had mutations in both genes. Variants of uncertain significance (VUS) were detected in 10 (4.2%; 95% CI, 2.0 to 7.6) patients, four (1.7%; 95% CI, 0.5 to 4.2) in *BRCA1* and six (2.5%; 95% CI, 0.9 to 5.4) in *BRCA2.* Among the 61 patients with *BRCA1/2* or VUS mutations, the numbers of patients (percentage) with frameshift mutation, missense mutation, nonsense mutation, splice site mutation, and other mutations were 31 (50.8%), 13 (21.3%), eight (13.1%), four (6.6%), and five (8.2%), respectively (Fig 1).

Table 2 presents the prevalence and distribution of *BRCA* mutations according to the number of lines of systemic therapy and family history. Of the 182 (76.2%) patients who had received ≤ 1 line of treatment, 36 (19.8%; 95% CI, 14.3 to 26.3) had germline pathogenic or likely pathogenic mutation compared with 15 of 57 (26.3%; 95% CI, 15.5 to 39.7) patients who had received ≥ 2 lines of treatment. Of the 36 patients with family history of breast and/or ovarian cancer, 20 (55.6%; 95% CI, 38.1 to 72.1) had pathogenic or likely pathogenic *BRCA1/2* mutations compared with 41 of 203 (20.2%; 95% CI, 14.9 to 26.4) patients with no family history ($P < .0001$). There was a trend toward higher prevalence of pathogenic or likely pathogenic *BRCA1/2* mutations in patients with serous subtype of ovarian cancer (40 of 159, 25.2%; 95% CI, 18.6 to 32.6) compared with patients with nonserous subtypes (11 of 80, 13.8%; 95% CI, 7.1 to 23.3; Fig 2). Among patients with known endometrioid, clear cell, or mucinous histology, two of 34 (5.9%; 95% CI, 0.7 to 19.7) had germline *BRCA1/2* mutations, including, notably, none of the 15 patients with clear cell or mucinous histology. There was no statistically significant difference in the association of *BRCA* mutations with tumor histology ($P = .0636$). There was no significant association of pathogenic or likely pathogenic *BRCA1/2* mutations with patients' age, with prevalence being 20 of 90 (22.2%; 95% CI, 14.1 to 32.2) in patients ≤ 50 years compared with 31 of 149 (20.8%; 95% CI, 14.6 to 28.2) in patients > 50 years ($P = .7956$; Table 3). The variations for the detected mutations in BRCA 1/2 are reported in Appendix Table A2.

DISCUSSION

Our analysis in this multicenter cohort of Indian patients with ovarian or primary peritoneal cancer suggests a high prevalence (21.3%) of germline pathogenic or likely pathogenic mutations in *BRCA1* or *BRCA2* genes with an

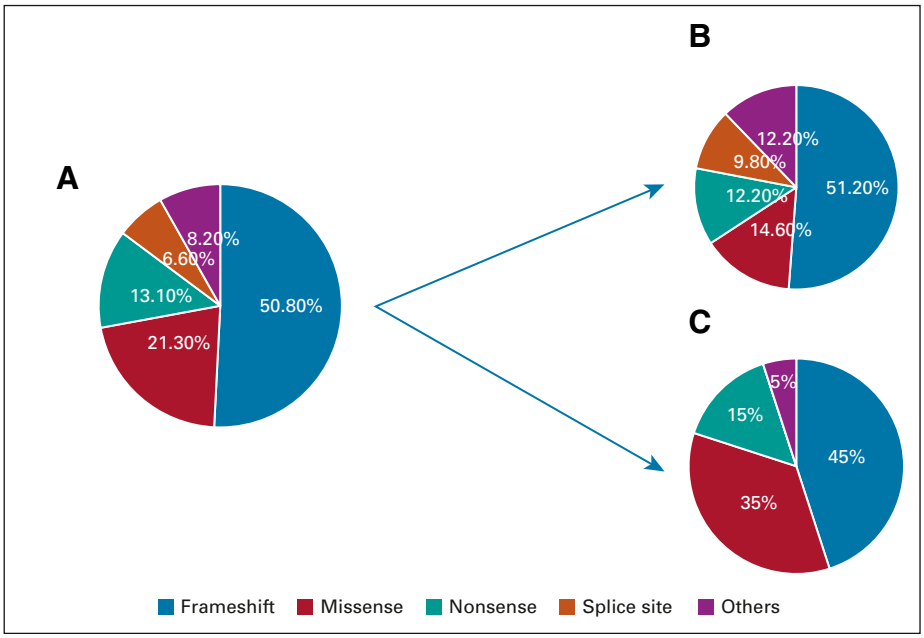

FIG 1. (A) Distribution of pathogenic or likely pathogenic and VUS *BRCA1/2* mutations per mutation type (n = 61). (B) BRCA1 (n = 41). (C) BRCA2 (n = 20). VUS, variant of uncertain significance.

additional 4.2% having variants of uncertain significance in these genes. To our knowledge, this is the first such report in a cohort from India that is not selected by clinical features like family history and provides important, clinically actionable information of relevance to patients and physicians.

Of note, our analysis suggests that, although the prevalence of *BRCA1/2* mutations was higher in patients with family history of breast and/or ovarian cancer, a considerable minority of patients without such history (20.2%) also harbored the mutations. This suggests that the absence of family history is not adequate as a screening strategy for germline testing. The prevalence of these mutations was higher in patients with serous histology, and no patient with known clear cell or mucinous tumors had a pathogenic mutation, suggesting that histologic subtype may be used to triage patients for testing. Age was not associated with the prevalence of these mutations and should not be incorporated in clinical decision making to test for germline predisposition. The commonest pathogenic mutation reported in this data set was the 187delAG in *BRCA1* (c.68_69delAG in four patients, Appendix Table A2), which is a

TABLE 2. Prevalence and Distribution of *BRCA* Mutations

Finding	No. (%) of Patients (N = 239)
Pathogenic or likely pathogenic *BRCA1/2* germline mutations, No. (%)	51 (21.3)
BRCA1 mutation[a]	37 (15.5)
BRCA2 mutation[b]	14 (5.9)
Distribution of *BRCA* mutations as per lines of therapy, No. (%)[c]	
Pathogenic or likely pathogenic *BRCA1/2* germline mutations receiving ≤ 1 line of therapy	36 of 182 (19.8)
Pathogenic or likely pathogenic *BRCA1/2* germline mutations receiving ≥ 2 lines of therapy	15 of 57 (26.3)
P	.2932
Distribution of *BRCA* mutations as per family history, No. (%)	
Patients with family history of ovarian and/or breast cancer	36 (15.1)
BRCA mutations and family history of ovarian and/or breast cancer	20 (55.6)[c]
Patients without family history of ovarian and/or breast cancer	203 (84.9)
BRCA mutations without family history of ovarian and/or breast cancer	41 (20.2)[c]
P	< .0001

Abbreviation: VUS, variants of uncertain significance.
[a]Patients with VUS having *BRCA1* mutations were not included. There were four patients with *BRCA1* VUS mutations.
[b]Patients with VUS having *BRCA2* mutations were not included. There were six patients with *BRCA2* VUS mutations.
[c]Percentage was calculated on the basis of the total number of participants available within each level.

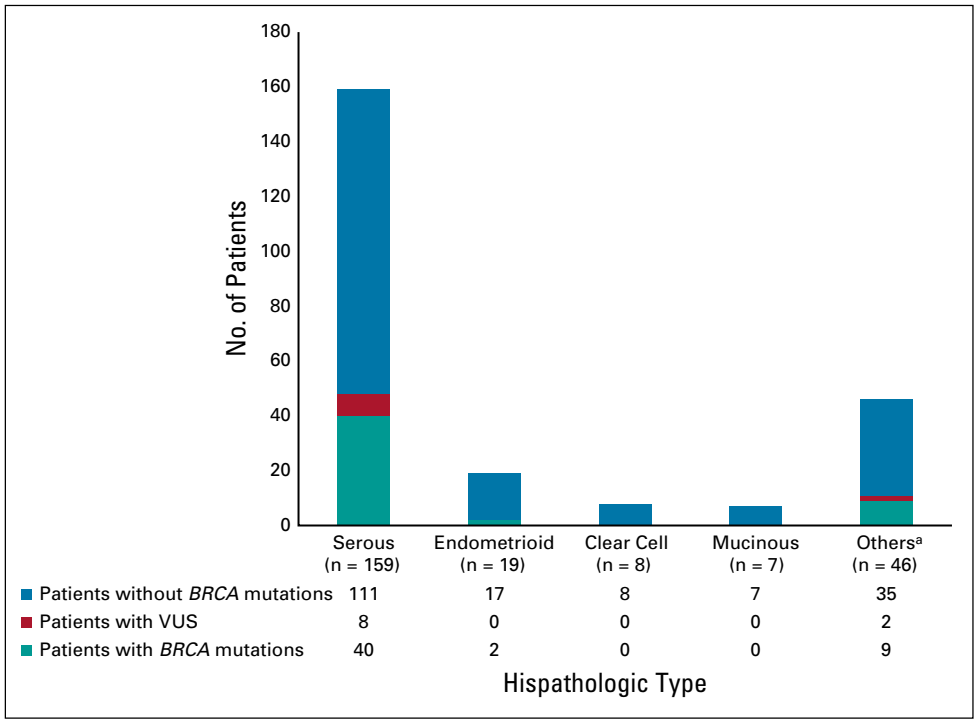

FIG 2. Association of histopathologic type and *BRCA1/2* mutation status. [a]Other histopathologic subtypes include seromucinous, undifferentiated or other epithelial subtypes, or unclassified variants. VUS, variant of uncertain significance.

frameshift, loss of function, and founder mutation in the Ashkenazi Jewish population and has also been reported in previous Indian studies with variable frequency.[28,29] These patients were not of Ashkenazi Jewish descent and did not belong to any single geographical region in India. Among patients with a *BRCA2* mutation, the commonest mutation was c.5851_5854del, which was reported in two unrelated patients and, to our knowledge, has not been reported in previous Indian studies.

Table 4 summarizes selected previous reports from India and other countries, in patients with ovarian cancer.[11,12,28,29] The prevalence of germline pathogenic or likely pathogenic *BRCA 1/2* mutations in patients not selected by family history or histology ranged from 14.1% to 30.1%, and in previous reports selecting patients with relevant family history, it ranged from 38.7% to 100%. In previous reports of patients with serous histology, the prevalence of germline pathogenic or likely pathogenic *BRCA 1/2* mutations ranged from 16.6% to 97.14%. Our results do not show any notable outliers compared with what has been reported by others. Another incidental finding in our study is that 36 of 182 (19.8%) patients who had received ≤ 1 line of treatment had germline pathogenic or likely pathogenic mutation, whereas 15 of 57 (26.3%) patients receiving ≥ 2 lines of treatment had germline pathogenic or likely pathogenic mutation. This finding needs to be evaluated further since ours is a cross-sectional study. It is possible that patients who survive long enough to receive multiple lines of treatment are enriched for BRCA mutations, which is known to confer sensitivity to repeated courses of chemotherapy, as has also been reported earlier.[12]

TABLE 3. Distribution of *BRCA* Mutations (including VUS) With Age

Age (years)	All Enrolled	*BRCA1* No. (%)[a]	*BRCA2* No. (%)[a]	*BRCA1* VUS[a] No. (%)	*BRCA2* VUS[a] No. (%)
All patients	239	37 (15.5)	14 (5.9)	4 (1.7)	6 (2.5)
≤ 50	90	15 (16.7)	5 (5.6)	2 (2.2)	0 (0.0)
> 50	149	22 (14.8)	9 (6.0)	2 (1.3)	6 (4.0)

Abbreviation: VUS, variants of uncertain significance.

[a]Percentage was calculated on the basis of the total number of participants available within each level. No significant association between pathogenic or likely pathogenic *BRCA1/2* mutations and patients' age was observed ($P = .7956$).

The strength of our analysis is inclusion of patients from multiple centers in India, of all age in the adult group, of all histologic subtypes, and those with or without relevant family history. This makes the results of this study generalizable to the patient population with ovarian cancer seen in routine practice in India. These study results can be used by physicians to counsel patients about the need for germline testing. Germline testing was performed in a single laboratory with a proven record of quality control. *BRCA* mutation testing in ovarian cancer offers prognostic ability and therapeutic decision making from the perspective of patient. *BRCA* mutation status can guide the use of poly(ADP ribose) polymerase inhibitors, which are associated with favorable outcomes in patients with *BRCA* mutations. Patients with germline mutations act as a proband for further testing of first-degree relatives (cascade screening).[34] In this context, the results of this study reinforce recently published Indian guidelines, which recommend genetic

TABLE 4. Comparison With Other Reports of *BRCA* Mutation Prevalence in Patients With Ovarian Cancer

Characteristic	This Study (N = 239), No. (%)	South India (HBOC patients with positive family history only)[29] (N = 61), No. (%)	Strand (India) (preselected patients with HBOC and their relatives)[28] (N = 1,010), No. (%)	RGCI (North India) (preselected breast and/or ovarian cancer) (N = 206), No. (%)[11]	Australian Ovarian Cancer Study Group (patients with newly diagnosed ovarian cancer excluding those with mucinous type) (N = 1,001), No. (%)[12]
BRCA1/2 pathogenic or likely pathogenic mutations	51 (21.3)	17 (28)	258 (25.54)	62 (30.1)	141 (14.1)
BRCA1	37 (15.5)	15 (24.6)	198 (19.6)	45 (21.84)	88 (8.8)
BRCA2	14 (5.9)	2 (3.28)	60 (5.93)	17 (8.25)	53 (5.3)
VUS	10 (4.2)	Not reported	74 (7.3) (*BRCA1/2* VUS)	13 (6.31)	83 (8.3)
BRCA1/2 mutation in serous subtype	40 (25.2)	Not reported	Not reported	34 (97.14)	118 (16.6)
Stratification by age, years	≤ 50: 20 (22.2) > 50: 31 (20.8)	≤ 40: 23.33% > 40: 32.25%	< 40: 120 (40) 40-50: 79 (28) > 50: 76 (23)	Not reported	≤ 40: 7 (15.6) 40-50: 37 (24.2) 51-60: 59 (17.1) ≥ 61: 38 (8.3)
Patients with mutation who have family history	36 (15.1)	61 (100)	Not reported	Not reported	75 (38.7)

Abbreviations: HBOC, hereditary breast and ovarian cancer; NA, not applicable; RGCI, Rajiv Gandhi Cancer Institute; VUS, variants of uncertain significance.

testing in all patients with ovarian cancer and discuss the potential therapeutic and familial impact and likely challenges in the Indian context.[35]

There are some limitations of our study. Although the study was designed to include patients not selected by clinical features, it is difficult to establish that the included set is representative of the entire ovarian cancer population without access to the clinical and pathologic characteristics of the latter. Moreover, because India is a diverse country with many regions having populations of distinct genetic background, it is not certain that our sample captures this diversity. One exclusion criterion in our study was participation in any other research study, which could have introduced a selection bias. However, this is unlikely to be an important consideration because there were no ongoing clinical trials for BRCA mutation–positive patients at the participating sites during the recruitment period. We are unable to correlate the prevalence of *BRCA* mutations with sensitivity to chemotherapy because this was beyond the scope of this study. From a technical standpoint, copy number variations were not evaluated in this study, either as part of the analytical pipeline of NGS data[36] or by multiplex ligation-dependent probe amplification technique, which could have resulted in some underestimation of pathogenic alterations in *BRCA1* and *BRCA2*, especially large genetic rearrangements. Despite these limitations, our results provide valuable information relevant to the scope and need for germline testing in patients with ovarian, fallopian tube, or primary peritoneal cancers in India.

In conclusion, our results, in a cohort of Indian patients with epithelial ovarian, primary peritoneal, or fallopian tube cancers, suggest a high prevalence of germline pathogenic or likely pathogenic *BRCA1/2* mutations with no association with age. Evaluation of germline mutations in *BRCA1* and *BRCA2* should be considered in most patients with this disease.

AFFILIATIONS

[1]Medical Oncology, Tata Memorial Centre, Mumbai, India
[2]Medical Oncology, Basavatkaram Indo American Cancer Hospital, Hyderabad, India
[3]Medical Oncology, Sushrut Hospital, Mumbai, India
[4]Medical Oncology, BLK Superspeciality Hospital, New Delhi, India
[5]Medical Oncology, Sir Gangaram Hospital, New Delhi, India
[6]Medical Oncology, Medica Superspeciality Hospital, Kolkata, India
[7]Medical Oncology, Omega Hospitals, Hyderabad, India
[8]Medical Oncology, Max Institute of Cancer Care, Saket, New Delhi, India
[9]Medical Oncology, HCG Cancer Hospital, Bengaluru, India
[10]Medical Affairs, AstraZeneca Pharma India Ltd, Bangalore, India

CORRESPONDING AUTHOR

Sudeep Gupta, MBBS, MD, DM, Tata Memorial Centre, Room 1109, HBB, Tata Memorial Hospital, Parel, Mumbai 400012, India; e-mail: sudeepgupta04@yahoo.com.

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AUTHOR CONTRIBUTIONS

Conception and design: Sudeep Gupta, Senthil Rajappa, Suresh Advani, Shyam Aggarwal, Satya Dattatreya Palanki, Shekhar Patil, Rohit Kodagali
Administrative support: Senthil Rajappa
Provision of study materials or patients: Sudeep Gupta, Senthil Rajappa, Amit Agarwal, Shyam Aggarwal, Chanchal Goswami, Devavrat Arya
Collection and assembly of data: Sudeep Gupta, Senthil Rajappa, Suresh Advani, Amit Agarwal, Shyam Aggarwal, Chanchal Goswami, Satya Dattatreya Palanki, Devavrat Arya, Shekhar Patil, Rohit Kodagali
Data analysis and interpretation: Sudeep Gupta, Senthil Rajappa, Suresh Advani, Amit Agarwal, Satya Dattatreya Palanki, Rohit Kodagali
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Sudeep Gupta

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Shyam Aggarwal

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Devavrat Arya

Honoraria: Eisai, Roche India, AstraZeneca, Merck Serono, Intas, Mylan, Novartis, Boehringer Ingelheim, Pfizer, Fresenius Kabi
Consulting or Advisory Role: Mylan, Intas
Speakers' Bureau: Mercke, Eisai

Rohit Kodagali

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APPENDIX

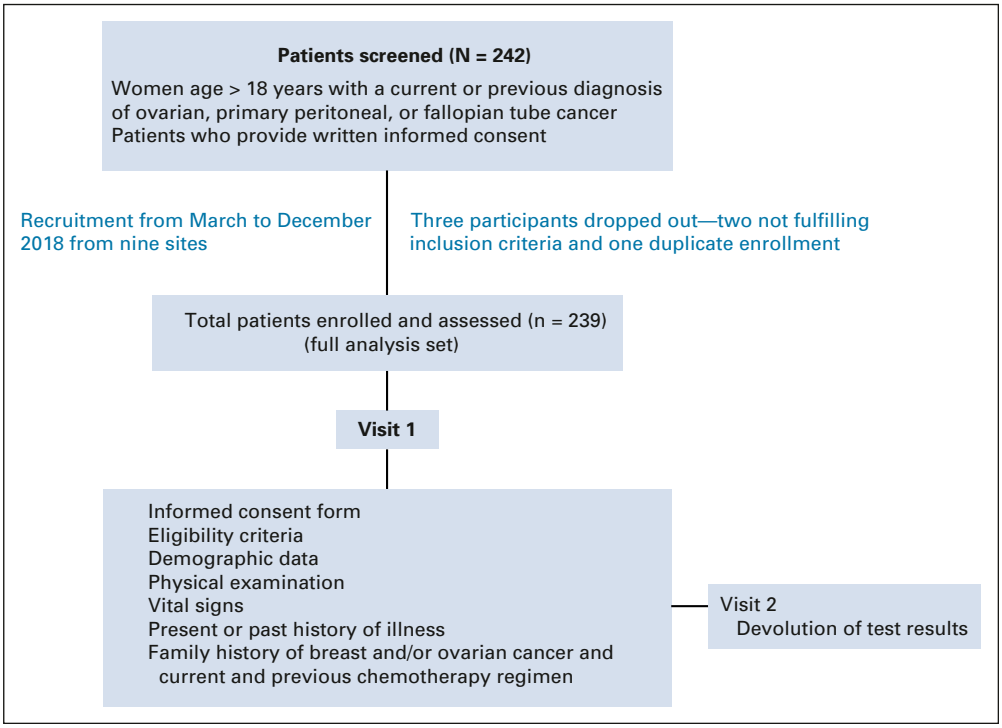

FIG A1. Study flow.

TABLE A1. List of Participating Centers

Site No.	Principal Investigator Name	Site Name and Address	City
1	Dr Sudeep Gupta	Tata Memorial Centre, Tata Memorial Hospital, Dr Ernest Borges Marg, Parel, Mumbai 400012	Mumbai
2	Dr Senthil Rajappa	Basavatarakam Indo American Cancer Hospital & Research Institute, Road No 10, Banjara Hills, Hyderabad 500034	Hyderabad
3	Dr S. H. Advani	Sushrut Hospital, 365 Swastik Park, Eastern Express Highway, Chembur East, Mumbai 400071	Mumbai
4	Dr Amit Agarwal	Dr B. L. Kapur Hospital, Department Of Medical Oncology, OPD-7, First Floor, Pusa Road, New Delhi 110005	New Delhi
5	Dr Shyam Agarwal	Sir Ganga Ram Hospital, Sir Ganga Ram Hospital Marg, Rajinder Nagar, New Delhi 110060	New Delhi
6	Dr Chanchal Goswami	Medica Superspecialty Hospital, 127, Mukundapur, EM Bypass, Kolkata 700099	Kolkata
7	Dr Satya Dattatreya Palanki	Omega Hospitals, MLA Colony, Main Road, Road No. 12, Anjata Hills, Hyderabad 500034, Telangana, India	Hyderabad
8	Dr Devavrat Arya	Max Super Speciality Hospital, 1, 2, Press Enclave Road, Mandir Marg, Saket, New Delhi 110017	Delhi
9	Dr Shekar Patil	HeathCare Global Enterprises Limited, No 8 HCG Towers, P. Kalinga Rao Road, Sampangi, Ram Nagar, Bengaluru, Karnataka 560027	Bangalore

NOTE. Tertiary care centers with a high volume (> 50 patients with ovarian cancer/year) of patients with ovarian cancer were included.

TABLE A2. Participants With *BRCA1* and *BRCA2* Gene Mutations

Age, years	Variation	Zygosity	Inheritance	Clinical Significance
Participants with *BRCA1* gene mutations detected				
45	Chr17: 41243480_41243483delttgalc.4065_4068deltcaalp.Asn1355lysfster10	Heterozygous	Dominant	Pathogenic
72	Chr17: 41242986_41242990delgaggalc.4158_4162delctctclp.Ser1387glufster2	Heterozygous	Dominant	Pathogenic
52	Chr17: 41219624c>tlc.5074+1g>a	Heterozygous	Dominant	Pathogenic
48	Chr17: 41243794_41243795delgalc.3754_3755delctlp.Leu1252valfster2	Heterozygous	Dominant	Pathogenic
56	Chr17: 41244567_41244568delca C.2981_2982delgt P.Cys994ter	Heterozygous	Dominant	Pathogenic
43	Chr17: 41226471delg C.4552delc P.Gln1518argfster30	Heterozygous	Dominant	Likely pathogenic
56	Chr17: 41234419a>g C.4357+2t>c	Heterozygous	Dominant	Pathogenic
53	Chr17: 41245253delc C.2295delg P.Ser766valfster26	Heterozygous	Dominant	Likely pathogenic
43	Chr17: 41215912t>c C.5131a>g P.Lys1711glu	Heterozygous	Dominant	VUS
56	Chr17: 41219664delg C.5035delc P.Leu1679ter	Heterozygous	Dominant	Pathogenic
39	Chr17: 41243779_41243780delctlc.3770_3771delaglp.Glu1257glyfster9	Heterozygous	Dominant	Pathogenic
35	Chr17: 41276047_41276048delctlc.68_69delaglp.Glu23valfster17	Heterozygous	Dominant	Pathogenic
43	Chr17: 41215948g>a C.5095c>t P.Arg1699trp	Heterozygous	Dominant	Likely pathogenic
47	Chr17: 41246360dela C.1188delt P.Asp396glufster14	Heterozygous	Dominant	Pathogenic
42	Chr17: 41244562delt C.2990dela P.Asn997ilefster3	Heterozygous	Dominant	Pathogenic
54	Chr17:41246615dela C.933delt P.Gly312alafster2	Heterozygous	Dominant	Pathogenic
53	Chr17: 41276034-?_41276113+?d Ellc.(?_-1)_(80+1_81-1)del (exon 2 deletion)	Heterozygous	Dominant	Pathogenic
46	Chr17: 41243941g>a C.3607c>t P.Arg1203ter	Heterozygous	Dominant	Pathogenic
54	Chr17: 41251792-?_41251897+?d El C.(441+1_442-1)_(547+1_548-1)d El (deletion of exon 7)	Heterozygous	Dominant	Pathogenic
52	Chr17: 41244321_41244322delctlc.3228_3229delaglp.Gly1077alafster8	Heterozygous	Dominant	Pathogenic
53	Chr17: 41203127c>t C.5285g>a P.Arg1762lys	Heterozygous	Dominant	VUS
39	Chr17: 41246360dela C.1188delt P.Asp396glufster14	Heterozygous	Dominant	Pathogenic
52	Chr17: 41246539dupc C.1009dupg P.Glu337glyfster9	Heterozygous	Dominant	Pathogenic
60	Chr17: 41246538dupt C.1016dupa P.Val340glyfster6	Heterozygous	Dominant	Pathogenic
37	Chr17: 41245210g>a C.2338c>t P.Gln780ter	Heterozygous	Dominant	Pathogenic
54	Chr17: 41267755deltlc.122delalp.His41profster9	Heterozygous	Dominant	Pathogenic
67	Chr17: 41249261-?_41249306+?d Uplc.(547+1_548-1)_(593+1_594-1)d Up (Duplication Of Exon 8)	Heterozygous	Dominant	Pathogenic
56	Chr17:41215970deltlc.5075-2dela	Heterozygous	Dominant	Pathogenic
58	Chr17: 41267743-?_41276113+?d El C.(?_-1)_(134+1_135-1)del (deletion of exon 2-3)	Heterozygous	Dominant	Pathogenic

(Continued on following page)

TABLE A2. Participants With *BRCA1* and *BRCA2* Gene Mutations (Continued)

Age, years	Variation	Zygosity	Inheritance	Clinical Significance
53	Chr17: 41276047_41276048delct C.68_69delag P.Glu23valfster17	Heterozygous	Dominant	Pathogenic
63	Chr17: 41276047_41276048delct C.68_69delag P.Glu23valfster17	Heterozygous	Dominant	Pathogenic
55	Chr17:41219669_41219672delgt Ta C.5030_ 5033delctaa P.Thr1677ilefster2	Heterozygous	Dominant	Pathogenic
53	Chr17: 41258533a>g C.152t>c P.Leu51pro	Heterozygous	Dominant	VUS with probable damaging effect (VUSd)[a]
59	Chr17: 41245281delc C.2269delg P.Val757phefster8	Heterozygous	Dominant	Pathogenic
50	Chr17: 41267746c>t C.131g>a P.Cys44tyr	Heterozygous	Dominant	Likely pathogenic
44	Chr17:41234420c>g C.4357+1g>c	Heterozygous	Dominant	Likely pathogenic
47	Chr17: 41245170_41245171duptt C.2377_ 2378dupaa P.Ala794argfster10	Heterozygous	Dominant	Likely pathogenic
52	Chr17: 41228619g>c C.4370c>g P.Ser1457ter	Homozygous	Dominant	Pathogenic
29	Chr17: 41243921dupt C.3627dupa P.Glu1210argfster9	Heterozygous	Dominant	Pathogenic
43	Chr17: 41215932a>g C.5111t>c P.Phe1704ser	Heterozygous	Dominant	VUS
59	Chr17: 41243680_41243681deltt C.3869_ 3870delaa P.Lys1290metfster4	Heterozygous	Dominant	Pathogenic
Participants with *BRCA2* gene mutations detected				
58	Chr13: 32914343_32914346delagttlc.5851_ 5854delagttlp.Ser1951trpfster11	Heterozygous	Dominant	Pathogenic
61	Chr13: 32968949g>a C.9380g>a P.Trp3127ter	Heterozygous	Dominant	Pathogenic
49	Chr13: 32954050g>alc.9117g>alp.Pro3039pro	Heterozygous	Dominant	Pathogenic
61	Chr13: 32929379_32929382deltc Aalc.7389_ 7392deltcaalp.Asn2463lysfster3	Heterozygous	Dominant	Pathogenic
67	Chr13: 32913123delalc.4631delal p.Asn1544thrfster24	Heterozygous	Dominant	Pathogenic
56	Chr13: 32910551_32910555delga Tta C.2059_ 2063delgatta P.Asp687ter	Heterozygous	Dominant	Pathogenic
58	Chr13: 32914723g>c C.6231g>c P.Lys2077asn	Heterozygous	Dominant	VUS
62	Chr13: 32969027delglc.9458delgl p.Gly3153alafster10	Heterozygous	Dominant	Pathogenic
52	Chr13: 32915179a>c C.6687a>c P.Glu2229asp	Heterozygous	Dominant	VUS
52	Chr13: 32913530_32913531delins Aa C.5038_ 5039delinsaa P.Ser1680105-004	Heterozygous	Dominant	VUS
55	Chr13: 32912001c>t C.3509c>t P.Ala1170val	Heterozygous	Dominant	VUS
57	Chr13:32914514a>t C.6022a>t P.Lys2008ter	Heterozygous	Dominant	Pathogenic
54	Chr17: 41276047_41276048delct C.68_69delag P.Glu23valfster17	Heterozygous	Dominant	Pathogenic
47	Chr13: 32953482c>t C.8783c>t P.Ala2928val	Heterozygous	Dominant	VUS
72	Chr13: 32914977a>g C.6485a>g P.Lys2162arg	Heterozygous	Dominant	VUS
44	Chr13: 32929398_32929399deltt C.7408_ 7409deltt P.Phe2470hisfster4	Heterozygous	Dominant	Pathogenic
48	Chr13: 32954267delg C.9241delg P.Val3081leufster2	Heterozygous	Dominant	Likely pathogenic

(Continued on following page)

TABLE A2. Participants With *BRCA1* and *BRCA2* Gene Mutations (Continued)

Age, years	Variation	Zygosity	Inheritance	Clinical Significance
45	Chr13: 32911115_32911116delgt C.2623_2624delgt P.Val875glnfster5	Heterozygous	Dominant	Pathogenic
52	Chr13: 32914343_32914346delag Tt C.5851_5854delagtt P.Ser1951trpfster11	Heterozygous	Dominant	Pathogenic
52	Chr13: 32911578dupt C.3086dupt P.Met1029ilefster7	Heterozygous	Dominant	Pathogenic
58	Chr13: 32945135g>a C.8530g>a P.Glu2844lys	Heterozygous	Dominant	VUS

Abbreviation: VUS, variant of uncertain significance.
[a]Considered as a VUS for the purpose of analysis.