Non-Interventional Study (NIS) Report Synopsis	
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A Non-interventional, multicentre study to assess prevalence of BRCA1 and BRCA2 mutation among ovarian, primary peritoneal and fallopian tube cancer patients in India

Study dates:	**First Subject In:** 22nd March 2018 **Last Subject Last Visit:** 21st December 2018

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NIS REPORT SYNOPSIS

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Background/Rationale:

Ovarian cancer is the seventh most common cancer in women worldwide (18th most common cancer overall), and the fourth most common cancer in India. Prevalence of ovarian cancer among reproductive cancers in females varies from 21.8 % to 28.4 % in India. Of the risk factors identified for ovarian cancer, one of the major etiological concerns is germline mutation in BRCA1 (BReast-CAncer susceptibility gene) and BRCA2 genes. Fallopian tube and primary peritoneal cancers are almost similar to epithelial ovarian carcinoma in terms of their histological, clinical, and etiological aspects. Understanding the pathology and risk factors become vital in guiding the management of ovarian and related cancers. The current study was designed as a non-interventional, single visit study to assess the prevalence of BRCA1 and BRCA2 mutation positive status among ovarian, primary peritoneal and fallopian tube cancer patients in India irrespective of the stage of presentation in order to facilitate screening and guiding disease management in a more logical and efficient way.

Literature review suggests that there are very few studies among ovarian cancer, primary peritoneal, and fallopian tube patients in India which can provide the prevalence of BRCA1/BRCA2 mutation in context with the real world setting. However, none of the studies contributes to the overall prevalence of mutated genes among ovarian, primary peritoneal, and fallopian tube cancer patients throughout the different geographical regions of the country. Hence, this observational study is designed to address the need to understand the prevalence of BRCA1/BRCA2 mutations among ovarian, primary peritoneal, or fallopian tube cancer patients across the geography of India.

Objectives and Hypotheses:

Primary Objective

To estimate the prevalence of BRCA1 or BRCA2 mutation positive status among previously and newly diagnosed ovarian, primary peritoneal or fallopian tube cancer patients in India.

Secondary Objectives

1. To assess the association between histopathological type and BRCA1/BRCA2 mutation-positive status.

2. To assess the association of BRCA1/BRCA2 mutation-positive status and family history of breast and/or ovarian cancer and any cancer.

3. To determine the percentage distribution of BRCA1 mutation in comparison to BRCA2 mutation in Indian population.

Methods:

Study design:

This was a non-interventional, cross-sectional, multicentre, prospective, observational study conducted at 15 sites across all geographical regions of India. The study enrolled 240 patients with approximately 16 patients from each site. Written approval of the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) and written informed consent from willing patients was obtained prior to the start of the study.

Study Population:

Inclusion Criteria

1. Patients who provide written informed consent

2. Female ≥ 18 years of age

3. Previously or newly diagnosed ovarian, primary peritoneal, or fallopian tube cancer patients.

Exclusion Criteria

1. Patient with any medical condition that, in the opinion of the Investigator would interfere with safe completion of the study

2. Patient participating in any other clinical study/ trial.

Exposure:

This was a non-interventional, observational study which targeted to capture the prevalence of patients with a BRCA1/BRCA2 mutation. The study did not aim to prescribe or provide any new or interventional drug to the patients.

Outcomes:

Primary Outcome

The proportion of previously and newly diagnosed ovarian, primary peritoneal or fallopian tube cancer patients with BRCA1 or BRCA2 mutations positive status.

Secondary Outcomes

1. Level of association between histopathological type and BRCA1/BRCA2 mutation positive status.

2. To assess the association of BRCA1/BRCA2 mutation-positive status and family history of breast and/or ovarian cancer and any cancer.

- Patients having a family history of ovarian cancer in first-degree relative
- Patients having a family history of both ovarian and breast cancer in first-degree relative,
- Patients having a family history of breast cancer in first-degree relative,
- Patients are having a family history of ovarian/other cancer before 45 years of age.
- Patients with no family history of cancer in first-degree relative

3. To determine the BRCA1/BRCA2 mutation distribution in Indian population.

Sample Size Estimations:

The main evaluation criterion of the study was to find out the prevalence rate of BRCA1/BRCA2 mutation-positive status among ovarian, primary peritoneal or fallopian tube cancer patients in India. Based on the previous reference study which demonstrated that the prevalence rate of BRCA1/BRCA2 mutation was 15.8 %, the sample size estimate was 228, assuming a precision rate of 5% and a dropout rate of 10%. A total of 240 patients were to be included in this study.

Statistical Analysis:

Descriptive statistics (mean frequency, percentage, and confidence interval) were used in the study for analysing primary outcome. Chi-square test was performed to find an association between different histopathological types and BRCA1/BRCA2 mutation-positive status and association of BRCA1/BRCA2 mutation-positive status with patients having a family history of breast and ovarian cancer.

Results:

A total of 239 females with a diagnosis of ovarian, primary peritoneal, or fallopian tube cancer were enrolled in the study. The mean (±SD) age and BMI of all enrolled subjects were 53.2 (±10.74) years and 26.1 (±5.21) kg/m^2 respectively. Majority of subjects (N= 230, 96.2%) had ovarian cancer. Fallopian tube cancer and primary peritoneal cancer were reported in 01 and 08 subjects, respectively. Thirty-six of the 239 subjects (15.1%) were categorized as the family history group and 203 subjects (84.9%) were allocated to the no family history group. Twenty

– two subjects had a family history of breast cancer and ten had a family history of ovarian cancer only. The number of subjects with a family history of ovarian cancer in the first relative and a second relative were 06 and 01, respectively.

The prevalence of germline mutations in BRCA1 and BRCA2 were investigated in 239 subjects. Of the subjects submitted to genetic testing, only 61 (25.5%) had pathogenic/ likely pathogenic or VUS mutations in either the BRCA1 or BRCA2 genes. There was no statistically significant difference observed during association between different histopathological type and BRCA 1/BRCA 2 mutation positive status (p= 0.0636). A statistically significant difference was observed in the BRCA1/BRCA2 positive ratio and family history of breast and ovarian cancer (p<0.0001). BRCA1 and BRCA2 mutations were detected in 41 (17.2%) and 20 (8.4%) subjects, respectively, and none of the subjects had mutations in both genes.

Conclusion:

In our study, the prevalence of pathogenic/likely pathogenic or VUS BRCA1 or BRCA2 was found to be one-fourth of the total study population. Nearly two-thirds of those with mutations did not have a family history of breast and/or ovarian cancers. To our knowledge, this is the first study from India to report prevalence of germline BRCA 1/2 mutations in unselected Indian patients with new or previously diagnosed ovarian cancer.