Study report

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PREDICT: Prevalence of BRCA1 and BRCA2 Mutations in Ovarian Cancer Patients in the Gulf Region

A prospective, multi-centre, epidemiological observational study designed to evaluate the prevalence of BRCA1 and BRCA2 mutations in current and newly diagnosed ovarian cancer patients across different countries in the Gulf region. This study also describe the epidemiological features of the disease of the enrolled patients.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
ASIR	Age Standardized Incidence Rate
BRCA	Breast Cancer Susceptibility Gene
BRCA 1	Breast Cancer Susceptibility Gene 1
BRCA 2	Breast Cancer Susceptibility Gene 2
CA-125	Cancer Antigen 125
CCOC	Clear Cell Ovarian Cancer
CIR	Crude Incidence Rate
CRF	Case Report Form
CT	Computed Tomography
eCRF	electronic Case Report Form
EOC	Epithelial Ovarian Cancer
EOS	End of Study
FIGO	Federation of Gynecology and Obstetrics
gBRCAm	germline BRCA mutation
gBRCAwt	germline BRCA wild-type allele
GCP	Good Clinical Practices
HBOC	Hereditary Breast and Ovarian Cancer
IARC	International Agency for Research on Cancer
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
Pm	micrometer(s)
MENA	Middle East and North Africa
MRI	Magnetic Resonance Imaging
OC	Ovarian Cancer
sBRCAm	somatic BRCA mutation
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SOC	Standard of Care
UAE	United Arab Emirates

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STUDY REPORT SYNOPSIS

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A prospective, multi-centre, epidemiological observational study designed to evaluate the prevalence of BRCA1 and BRCA2 mutations in current and newly diagnosed ovarian cancer patients across different countries in the Gulf region. This study describe the epidemiological features for the disease for the enrolled patients

Milestones:	Date of first patient in (FPI): 16 Jul 2017 Date of last patient in (LPI): 24 Jul 2019 Date of last patient last visit (LPLV): 24 Jul 2019 Date of database lock: 20 Nov 2019
Phase of development:	Epidemiological, Observational
Sponsor:	AstraZeneca Gulf - GCC

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

Ovarian cancer is one of the leading causes of cancer-related deaths worldwide. A greater number of women will be affected by this disease over time as the global population grows unless targeted interventions are put into place through both public health and clinical practice. Early diagnosis of ovarian cancer plays a key role in survival. Genes are known to play a role in the development of ovarian cancer; therefore, knowledge of genetic susceptibility can be useful in prevention efforts. Yet, little is known about the prevalence of ovarian cancer genes in some parts of the world, and genetic testing is often not part of routine care, despite its potential for personalized medical treatment. The purpose of this study is to characterize the prevalence of genetic mutations among patients diagnosed in several countries in the Gulf region, with the aim of informing clinical practice and improving clinical treatments in the future.

Objectives:

Primary Objectives

The primary objective of this study is to determine the prevalence of Breast Cancer Susceptibility Gene *BRCA1* and *BRCA2* mutations in patients who have been diagnosed with ovarian cancer, peritoneal cancer, and fallopian tube cancer, as assessed by tissue genetic testing.

Secondary Objectives

1. To examine associations (or correspondence) between genetic alterations in hereditary (germline) and tissue (somatic) BRCA mutations.
2. To describe epidemiological characteristics (e.g., age, ethnicities) and clinical characteristics (e.g., comorbidities, stage) of patients being treated for ovarian cancer.
3. To assess treatment patterns among the treatment-experienced subgroup of patients who were previously diagnosed with ovarian cancer.

Study design:

An observational, prospective, multi-centre epidemiologic study proposed to evaluate the prevalence of BRCA1 and BRCA2 among a sample of adult women who have been diagnosed with ovarian cancer. Patients enrolled in this study have had genetic testing done to determine the presence of BRCA mutations in somatic (tumor) tissue cells. Individuals having somatic mutations (sBRCAm) were also tested for germline mutations (gBRCAm). Patients' medical records were reviewed for information regarding clinical and demographic characteristics, as well as treatment-related variables for the treatment-experienced group of patients, as per the CRF.

Data source:

The primary data sources are patient hospital records from the host institutions (which may include electronic medical records, paper medical records, pathology reports, imaging reports, etc.), lab test results for blood samples collected from patients who are enrolled in the study (for germline genetic testing of BRCA mutations) and tissue samples from existing repositories (for somatic genetic testing of BRCA mutations).

Prospective patients were identified by the study doctor (or 'site investigator', or 'treating physician') as this staff have knowledge of both existing ovarian cancer patients and consult with new patients who were recently diagnosed with ovarian cancer. The study doctors were responsible for appropriately identifying, screening, and recruiting patients, and may have need to work with other staff at the study site in order to facilitate the process of enrollment. Figure 1 outlines the general procedures that were undertaken during this study for each patient.

Study population:

Approximately 120 eligible patients were enrolled in this study from five sites across four contributing centres in the Gulf countries of United Arab Emirates (UAE), Kuwait, Qatar, and Oman.

Inclusion Criteria

Patients who met the following criteria were considered for enrollment:

1. Subjects willing to sign the informed consent form (ICF)
2. Female subjects 18 years of age or older
3. Have a histologically confirmed diagnosis of Federation of Gynecology and Obstetrics (FIGO) for ovarian, primary peritoneal, or fallopian tube cancer.
4. Have availability of paraffin-embedded archived tumor tissue block (preferred) or, if a block is not possible, a minimum of twenty 10-Pm sections.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

1. The diagnosis is not of a primary ovarian cancer; thus, patients were excluded if previous cancer has metastasized to the ovary, or if there is a secondary malignancy that is associated with the ovarian cancer.
2. Is not able or willing to provide written informed consent.
3. Have a diagnosis of other severe acute or chronic medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of the study.

4. Be a patient who, in the judgment of the Investigator, would be inappropriate for enrollment in this study.

Statistical Methods:

A descriptive analysis was used to analyse the sample of ovarian cancer patients, including BRCA test results, clinical characteristics of the disease, and disease management (treatment) patterns. Continuous variables such as age were presented with mean, standard deviation, median, quartiles, minimum, and maximum values. Categorical variables such as sBRCAm status were presented with the number (or frequency) and percentage relative to the whole sample.

Prevalence of somatic BRCA mutations and associated 95% confidence interval was estimated from the results of genetic tests. The prevalence of germline mutation could not be estimated due to the small number of tests done among those with somatic mutation. It was determined that the sample size of 120 would be sufficient to achieve a width of 15%, provided the prevalence of somatic mutation are within the expected range. It was expected that for the group with sBRCAm, assuming the prevalence to be 20%, the 95% CI was estimated to be 16% to 32% with a width less than 15%.

Results:

A total of 105 consenting and eligible patients were included in this analysis. Patients had an average age of 55.2±12.0 years, with most of them being Arab (68.36%), and almost all were never smokers (97.1%). Regarding the diagnosis, the vast majority of the laterality was bilateral (74.3%), and of the allele was wild type (63.8%). Most patients were diagnosed at Stage III or higher (70.3%), with a majority having a tumor size of T3 (59.4%). About two-thirds of the patients were able to continue their normal life (ECOG score of 0) with no restrictions. Less than half of the patients had metastatic tumors. The most-reported comorbidities were found to be type 1 or type 2 diabetes. The Overall somatic mutations of BRCA was found in 15 out of 88 which represents prevalence rate of 17 % across the study population who had mutation in either BRCA1, BRCA2 or both genes. And, specifically the prevalence of BRCA1 and BRCA 2 somatic mutations were 11.2% and 9.1%, respectively. Only 5 of those patients with somatic mutations had germline mutation test results. In particular, 3 out of the 5 patients described above had positive germline test result. Two patients (1.9%) were treatment naïve. About 87 (82.9%) patients had surgeries (the vast majority of which were debulking, and the rest had either no surgery (11.4%) or unknown intent for surgery (3.8%). A total of 99 (94.3%) patients received first-line chemotherapy, 4 (3.8%) patients did not and 2 (1.9%) patients were reported for unknown status. The most common first-line chemotherapy was Paclitaxel/Carboplatin (79.8%). Moreover, a total of 40 (38.1%) patients received 12 different chemotherapy regimens as second-line treatment.