Gynecologic Oncology 124 (2012) 236–243

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

BRCA1 and *BRCA2* mutations among ovarian cancer patients from Colombia

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ARTICLE INFO

Article history:
Received 26 August 2011
Accepted 25 October 2011
Available online 29 October 2011

Keywords:
Colombia
Ovarian cancer
Hereditary
BRCA1
BRCA2

ABSTRACT

Objective. The contribution of *BRCA1* and *BRCA2* mutations to ovarian cancer in Colombia has not yet been explored. Five founder mutations have been identified in two previous studies of breast cancer patients in the Bogota region [1,2]. It is important that the frequency of mutations be established among unselected cases of ovarian cancer in order to estimate the genetic burden of this cancer in Colombia and to plan genetic and preventive services.

Methods. We enrolled 100 unselected women with ovarian cancer from the Bogota region, and from northern and southern central regions of Colombia. A detailed family history was obtained from each patient and a blood sample was processed for DNA analysis. DNA quality was adequate for *BRCA* testing for 96 women. Mutations in *BRCA1* and *BRCA2* were sought using a Hispanic *BRCA* mutation testing panel. All mutations were confirmed by direct sequencing.

Results. Fifteen mutations were identified (two in *BRCA2* and thirteen in *BRCA1*) representing 15.6% of the total (95% CI: 7.8% to 21.3%). Among the 15 mutation-positive families there were nine breast-ovarian cancer families, one gastric cancer family, one prostate cancer family, three uterine cancer families, and one family with no history of cancer. A single founder mutation in *BRCA1* (3450del4) was seen in 11 patients.

Conclusion. In summary, *BRCA1* founder mutations are common in Colombian women with ovarian cancer. Approximately 11.5% of all ovarian cancer cases in the Bogota region are attributable to a single *BRCA1* founder mutation.

Introduction

Colombia is the second largest country in South America and has a population of nearly 45 million inhabitants. Approximately 1900 new cases of ovarian cancer are diagnosed each year in Colombia [3]. The age-standardized incidence for ovarian cancer in Colombia is estimated to be 10.1 cases of ovarian cancer per 100,000 per year [3], compared to 11.6 per 100,000 per year in Canada [3] and 13.2 cases per 100,000 per year (whites) in the USA (SEER Registry). Approximately 13% of all epithelial ovarian cases in Canada are found to have a mutation in *BRCA1* or *BRCA2*[4]. Both *BRCA1* and *BRCA2* confer susceptibility to ovarian cancer; the cumulative risk of ovarian cancer in women to 70 years of age was estimated to be 39% in *BRCA1* carriers and 11% in *BRCA2* carriers [5], but the risk may vary according to the specific mutation, the country of residence, and the family history [6–9].

At the present, genetic testing is offered in many centers in North America, Europe, Australia and Israel, but is not generally available in South America. Genetic testing is gaining acceptance worldwide because of the increasing numbers of preventive options available to women with a mutation, and because of the development of novel, individualized, cancer therapies [10]. However, genetic testing is expensive and is unavailable to most women from developing countries. When a large proportion of genetically associated cancers are attributable to founder mutations in a given population there can be an opportunity for relatively low cost testing compared to the cost of complete sequencing of both *BRCA1* and *BRCA2* genes [11]. The presence of founder effects within specific ethnic groups such as the Ashkenazi Jewish [12,13], Polish [13], and French-Canadians [14], has allowed for rapid screening and enhanced mutation detection in these groups.

The prevalence of *BRCA1* and *BRCA2* mutations in ovarian cancer cases in the Colombian population has not yet been evaluated. To determine the prevalence of *BRCA* founder germline mutations in Colombian ovarian cancer patients, we performed mutation analysis of *BRCA1* and *BRCA2* on unselected patients with ovarian cancer from Colombia.

Material and methods

Patient population

Study subjects were unselected ovarian cancer patients, diagnosed at any age, in Colombia from April 2007 to February 2008. Patients were treated for ovarian cancer in both public and private settings

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doi:10.1016/j.ygyno.2011.10.027

in the Bogota region as well from northern and southern central regions of Colombia. To ensure that we included patients from a range of ethnic and social backgrounds, patients were recruited from three public hospitals (Unidad de Cáncer Hospital Departamental de Villavicencio, Oncomédica Montería, Seguro Social Clínica San Pedro Claver); and from two private clinics (Hospital Universitario Hernando Moncaleano Perdomo and Instituto de Cancerología de Sucre). Patients were approached by the research coordinator to participate in the study during an out-patient visit to the medical oncology clinic, or during hospital admission. At the time of the clinic appointment, a risk factor questionnaire was completed and a family history was recorded. The institutional review boards at the participating centers approved the protocol and all of the women in the study gave written informed consent.

All participants were interviewed in person for their family history of cancer, with specific reference to a history of breast or ovarian cancer. Tumor histology, tumor size, lymph node involvement and grade were abstracted from the medical records. A blood sample was obtained on all the women.

Laboratory methods

In order to perform genetic testing, DNA was extracted from blood samples using Puregene DNA extraction kits at the Grupo de Genética y Oncología Molecular in Bogota. An adequate amount of DNA was obtained for 96 of the 100 patients (96%) and a sample of this DNA was sent to the laboratory of Dr. Narod. Mutation analysis took place in the laboratory of Dr. Weitzel at City of Hope National Medical Center in California.

DNA samples from study subjects were tested for a panel of mutations that is estimated to account for up to 90% of Hispanic *BRCA* mutations [15]. The panel consists of fifty *BRCA1* and forty-six *BRCA2* mutations, including the five recurrent Colombian *BRCA* mutations reported in the literature, *BRCA1* (A1708E; 3450delCAAG) and *BRCA2* 3034delACAA; 6076delGTTA; 6503delTT [1,2,16], distributed across four multiplex PCR reactions and analyzed with Sequenom MassArray technology. All deleterious mutations were confirmed by direct DNA sequencing.

Samples were also genotyped using four multiplex PCR reactions containing Ancestry Informative Markers (AIMs) derived from Kosoy et al. and Saetrom et al. [17,18] with the Sequenom MassArray technology. Population structure analysis was also performed in combination with reference populations which included those of Latin descent to determine ancestry of the study population. Admixture analyses using AIMS indicated that both the *BRCA* carriers and non-carriers were of mixed ancestries with similar proportions of European (54% vs. 47%), Amerindian (38% vs. 38%), African (3% vs. 6%) and South Asian (5% vs. 9%) ancestors.

Results

In total, 100 women were approached and agreed to participate in the study. On average, two years had elapsed between the date of diagnosis and the date of interview. The 100 women were diagnosed with ovarian cancer between the ages of 16 and 75. Sixty-eight percent of the patients were recruited from public hospitals and 32% were recruited from private clinics. Five of the patients had a diagnosis of breast cancer; four of these had breast cancer prior to the ovarian cancer. A total of 96 patients were tested for 96 mutations in *BRCA1* and *BRCA2* which have been reported in Hispanic women. The mean age of the patients at diagnosis was 50 years (range 16–75) and the mean age at interview was 51.8 years (range 16–76). 18.75% of the patients were diagnosed before the age of 40 and 55.2% were diagnosed before the age of 50. Only five of the patients (5.2%) had a first-or second degree relative diagnosed with breast cancer or ovarian cancer at any age.

Overall, a mutation was found in 15/96 (15.6%; 95 CI%: 7.8%–21.3%) patients; thirteen with a mutation in *BRCA1* (13.5%) and two with a mutation in *BRCA2* (2.1%) (See Table 1). The *BRCA1* 3450del4 Colombian founder mutation accounted for 11 of 15 detected mutations. A mutation was detected in two of 18 patients diagnosed with ovarian cancer at age 40 or below (11.1%), in six of 35 patients diagnosed between ages of 41 and 50 (17.1%), and in seven of 43 cases diagnosed above age 50 (16.3%).

A mutation was seen in seven of eight patients (87.5%) with a history of ovarian cancer in a first-degree relative, in five of five patients (100%) with a family history of breast and ovarian cancer in a first-or second degree relative, in four of twenty patients (20%) with a first-or second-degree relative with gastric cancer, in two of seven patients (28.6%) with a first-or second-degree relative affected with prostate cancer, and in four of twelve patients (33.3%) with a first-or second-degree relative affected with uterine cancer. Overall, 14 of 15 women with a mutation had either at least one first- or second-degree relative affected with breast or ovarian cancer or had at least one first- or second-degree relative affected with gastric, prostate, or uterine cancer. Mutation positive pedigrees are shown in Fig. 1. Only one of 33 patients (3%) without a family history of any cancer was found to carry a mutation.

Discussion

A previous study of familial breast cancer cases in Colombia identified three founder mutations among 53 families from the Bogota region: two in *BRCA1* (3450del4 and A1708E) and one in *BRCA2* (3034

Table 1
BRCA1 and *BRCA2* Mutations Identified in Colombian Ovarian Cancer Patients.

Patient	Gene	Exon	Mutation	Age of diagnosis	Family history in first-second degree relatives
BOG001	*BRCA1*	11	3450del4	56	Ovarian cancer, gastric cancer
BOG016	*BRCA2*	11	6252insG	57	Gastric cancer (4 cases)
BOG019	*BRCA1*	11	3450del4	57	None
BOG020	*BRCA1*	11	3450del4	37	Uterine cancer
BOG021	*BRCA1*	11	3450del4	47	Breast cancer, ovarian cancer (2 cases), uterine cancer
BOG024	*BRCA1*	11	3450del4	48	Gastric cancer, uterine cancer
BOG026	*BRCA1*	11	3450del4	54	Breast cancer, ovarian cancer (3 cases), uterine cancer
BOG028	*BRCA1*	11	3450del4	57	Breast cancer (2 cases), ovarian cancer, prostate cancer
BOG068	*BRCA1*	11	1793delA	37	Breast cancer, gastric cancer
BOG077	*BRCA1*	11	3450del4	48	Breast cancer, ovarian cancer, throat cancer
BOG078	*BRCA1*	11	3450del4	47	Ovarian cancer, lung cancer, mouth cancer
BOG081	*BRCA1*	11	3450del4	63	Uterine cancer
BOG083	*BRCA1*	11	3450del4	44	Ovarian cancer, uterine cancer (2 cases)
BOG086	*BRCA2*	11	S1630X	66	Prostate cancer (2 cases), bladder cancer, leukemia
BOG101	*BRCA1*	18	A1708E	49	Ovarian cancer (3 cases), breast cancer (2 cases)