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Clinical Evaluation of *BRCA1/2* Mutation in Mexican Ovarian Cancer Patients

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Abstract

Ovarian cancer (OC) is an important cause of gynecologic cancer-related deaths. In Mexico, around 4700 new cases of OC are diagnosed per year and it represents the second cause of gynecological cancer mortality with more than 2700 deaths. Germline mutations in *BRCA1/2* genes are present in 13–18% of OC cases. Few studies have evaluated the presence of mutations in BRCA genes in a population of OC Mexican patients and their relationship with clinical response and survival rates.

A total of 179 OC patients were studied by molecular testing for *BRCA1/2* through next-generation sequencing and multiplex ligation-dependent probe amplification. Recurrence-free survival (RFS) was estimated by the Kaplan–Meier method. *BRCA* mutation was detected in 33% of patients. A percentage of 66.1% were *BRCA1* mutated and 33.9% were *BRCA2* mutated. *BRCA1* mutation carriers had a worst RFS compared with *BRCA2* mutation carriers (37.6 [29–46.2] vs 72.7 [38.4–107.2]; $P = 0.030$). The most common mutation for *BRCA1* was ex9-12del (28.2%) (Mexican founder mutation). The Mexican founder mutation had a better RFS than other *BRCA1* mutations (86.1 [37.2–135.1] vs 34.5 [20.7–48.2]; $P = 0.033$). The presence of *BRCA2* mutations in the ovarian cancer cluster region (OCCR) had a significantly better RFS than mutations in breast cancer cluster regions (BCCR) and not-related risk region (NRR) (NR vs 72.8 [39–106.6] vs 25.8 [8.3–43.2]; $P = 0.013$). These results demonstrate that the prevalence of *BRCA1/2* positive patients in OC Mexican patients are the highest reported. Patients with mutations in *BRCA2* have a better prognosis than those mutated in *BRCA1*. The Mexican founder mutation has an important role in clinical outcomes. These results highlight the importance to test all the HGSP (high-grade serous papillary) OC patients with or without cancer family history (CFH) in Mexican population.

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Introduction

In the world, there are 295,414 new cases and 184,799 ovarian cancer (OC) deaths per year. In Mexico, around 4759 OC new cases are diagnosed and it represents the second cause of gynecological cancer mortality with 2765 deaths (GLOBOCAN 2018).

A family history of breast and ovarian cancer has been associated with an increased probability of a genetic predisposition to these cancers [1]. This risk is increased twice when the history of an affected second-degree relative is present and increased up to four times

greater when dealing with a relative in the first degree [2]. A Mexican population study found that less than 10% of OC patients had cancer family history (CFH) [3]. The exploration of familial associations of OC with other cancers suggests that OC shares susceptibility with colorectal, breast, endometrium, liver cancer, and cancer of unknown primary [4]. This evidence suggests that these associations should have implications in genetic counseling. According to previous studies, 13−18% of OC is associated with germline mutations in *BRCA1/2* genes [5−7].

BRCA1/2, also known as breast cancer susceptibility genes 1 and 2, are tumor suppressor genes. More than one thousand mutations have been described and may be inherited in an autosomal dominant manner [8]. BRCA1 is a DNA damage response protein and works in both checkpoint activation and DNA repair. BRCA2 is a mediator of homologous recombination [9,10]. These are essential activities to prevent tumor development.

A study in Mexican OC patients found a prevalence of 28% of mutations in *BRCA1/2* genes [3].

In some specific populations such as Ashkenazi Jews, there is a higher prevalence of mutations in the BRCA1/2 genes, which in turn increases the risk by 65% for breast cancer and 40% for ovarian cancer. This risk is because of the presence of three founder mutations (*BRCA1 185delAG*, *BRCA1 538insC*, and *BRCA2 6174delT*). Around 2.5% of that population carries at least one of those mutations [11,12].

There are five OC histological subtypes: high-grade serous papillary (HGSP), endometrioid, mucinous, clear cells, and low-grade serous papillary (LGSP); *BRCA1/2* mutation is more commonly associated with the HGSP subtype. Patients carrying mutations in *BRCA* have a better response to treatment and are less likely to have a progression of the disease within six months after the end of primary therapy compared with those who do not have the mutation (14.9% vs 31.7%; $P < 0.0001$) [5].

There are currently few studies that assessed the presence of *BRCA* mutations in the Mexican population. The purpose of this study was to corroborate, in a population of Mexican OC patients, the presence of germline mutations in the *BRCA1/2* genes and their correlation with clinicopathological characteristics, clinical response, and survival rates.

Material and Methods

Study Design

A total of 179 patients with OC in clinical stages (CS) IA to IVB were enrolled from October 2015 to August 2017 at the National Institute of Cancer in Mexico. All patients provided written informed consent before entering the study. Inclusion criteria were adult patients (>18 years), diagnosed with OC with a histopathological confirmation. Clinicopathological characteristics (age, sex, born city, CFH), medical treatment, and clinical outcomes of patients were recorded. Patients received pre- and posttest genetic counseling, according to international recommendations, as well as follow-up by geneticists. Cascade screening for relatives was also provided.

Genetic Testing for BRCA Mutations

Samples of 16 mL of blood from each patient were obtained and drawn into two 8 mL EDTA tubes (BD Biosciences). The next-generation sequencing (NGS) that interrogates all coding regions and up to 50 bases in each intronic region to detect small mutations in the *BRCA1/2* genes was carried out at the clinical laboratory (Quest Diagnostics, US). To identify exon deletions and duplications, named large rearrangements of *BRCA1/2,* a multiplex ligation-dependent probe amplification (MLPA) was used. The mutation status was correlated with the standard clinicopathological characteristics of the patients. The analytical sensitivity was >99% of relevant mutations occurring in the described regions.

The clinical significance of the variants was determined according to the guidelines established by the international consortium ENIGMA (evidence-based network for the interpretation of germline mutant alleles) and ClinVar database which was provided by the Quest Diagnostics laboratory.

Statistical Analyses

Continuous variables were tabulated as medians with ranges, or as means with standard deviations, depending on data's distribution. The distribution was assessed using the Shapiro−Wilk test with a *P*-value higher than 0.05 considered as normally distributed. Two groups' comparisons were tested using Student's *T*-test or Mann−Whitney *U*. Nominal data were analyzed using the chi-square (χ^2) test. RFS was calculated as the difference between the date of recurrence or the last follow-up and the beginning of surveillance of first-line treatment. RFS curves were estimated by the Kaplan−Meier method, whereas comparisons among groups were analyzed with log-rank or Breslow tests. Statistically significant and borderline variables ($P \leq 0.05$) were included in the multivariate analyses. All data were analyzed using the SPSS software package version 23 (SPSS, Inc., Chicago, IL, US).

Results

Total Population Characteristics

A total of 179 OC patients were studied. Median patients' age was 48 years, with the majority between 35 and 54 years old. We tested patients from 19 out of 32 states in our country. Positive CFH was reported in 63.7% of patients, and the most common familial cancer type reported was breast cancer (51.8%). The most common histological subtype and CS were HGSP and IIIC, respectively (69.3% and 45.8%). Twenty-four patients (13.4%) had a double primary malignancy, the most frequent being breast/ovarian (79.2%). The most common chemotherapy schedule administrated as a primary treatment was carboplatin and paclitaxel every three weeks (87.7%). Rates of complete response, partial response, stable disease, and progression of the disease with primary treatment were 57%, 27.4%; 5.6%, and 10.1%, respectively (Table 1).

Presence of Germinal BRCA Mutations

BRCA mutations were detected in 33% of the patients (59/179); 66.1% (39/59) were *BRCA1*, and 33.9% (20/59) were *BRCA2* mutations. The most common mutation for *BRCA1* carrier patients was *BRCA1 ex9-12del* (Mexican founder mutation), which was found in 28% (11/39) of cases. Among *BRCA2* mutations, *c.8168 A > G* was the most prevalent in 25% (5/20) of cases (Table 2).

Location of BRCA1 and BRCA2 Mutations

A total of 34 variants or mutations were detected in the *BRCA* genes, 22 mutations in *BRCA1*, and 12 in *BRCA2*. The majority of the mutations (74%) were located in the areas known as the ovarian cancer cluster regions (OCCR) and breast cancer cluster regions (BCCR) in both genes (*BRCA1/2*). Among *BRCA1* gene mutations,

Table 1. Baseline and Clinical Characteristics of Ovarian Cancer Patients

Characteristics	Total
Age (years) at diagnosis	
Median (range)	48 (18–76)
Mean ± SD	49.4 ± 10.6
Group of age at diagnosis	
≤34	4.5 (8/179)
35–44	32.4 (58/179)
45–54	32.4 (58/179)
55–64	21.2 (38/179)
≥65	9.5 (17/179)
Born city	
Aguascalientes	0.6 (1/179)
CDMX	38 (68/179)
Chihuahua	0.6 (1/179)
Coahuila	0.6 (1/179)
Guanajuato	1.1 (2/179)
Guerrero	1.7 (3/179)
Hidalgo	8.9 (16/179)
Jalisco	1.1 (2/179)
México	24.6 (44/179)
Michoacán	4 (7/179)
Morelos	2.8 (5/179)
Oaxaca	1.7 (3/179)
Puebla	4.5 (8/179)
Querétaro	2.2 (4/179)
San Luis Potosí	1.1 (2/179)
Tabasco	0.6 (1/179)
Tlaxcala	3.4 (6/179)
Veracruz	2.2 (4/179)
Zacatecas	0.6 (1/179)
CFH	
Negative	36.3 (65/179)
Positive	63.7 (114/179)
Type of CFH	
Breast	51.8 (59/114)
Prostate	19.3 (22/114)
Ovarian	13.2 (15/114)
Melanoma	9.6 (11/114)
Pancreas	6.1 (7/114)
Endometrium	3.5 (4/114)
Number of related cancer associated to BRCA	
Not associated	26.3 (30/114)
Associated	73.7 (84/114)
1	64.3 (54/84)
2	29.8 (25/84)
3	6 (5/84)
Clinical stage at diagnosis	
IA	3.9 (7/179)
IC	7.8 (14/179)
IIA/B	7.7 (3/179)
IIIA	3.4 (6/179)
IIIB	8.4 (15/179)
IIIC	45.8 (82/179)
IVA	11.7 (21/179)
IVB	17.3 (31/179)
Histological subtypes	
Clear cells	4.5 (8/179)
HGSP	69.3 (124/179)
LGSP	5.6 (10/179)
Mucinous	0.6 (1/179)
Endometroid	12.8 (23/179)
G1	17.4 (4/23)
G2	69.6 (16/23)
G3	13 (3/23)
Adenocarcinoma	2.8 (5/179)
Mixed	4.5 (8/179)
HGSP/endometroid	62.5 (5/8)
HGSP/clear cells	12.5 (1/8)
Endometroid/clear cells	12.5 (1/8)
Endometroid/HGSP	12.5 (1/8)
Double primary malignancy	
Negative	86.6 (155/179)
Positive	13.4 (24/179)
Breast/ovarian	79.2 (19/24)
Endometrium/ovarian	20.8 (5/24)
1° Line treatment	
CBP/TXL per week	7.8 (14/179)
CBP/TXL 3 weeks	87.7 (157/179)
Other	7.8 (14/179)
Line of treatment	
1° Line	38 (68/179)
2° Line	27.9 (50/179)
≥3	34.1 (61/179)
Treatment response at 1° line of treatment	
CR	57 (102/179)
PR	27.4 (49/179)
SD	5.6 (10/179)
PD	10.1 (18/179)
Platinum-based therapy	
Platinum sensitive	91.6 (164/179)
Platinum resistant	8.4 (15/179)

CFH = cancer family history.

22 (56.5%) were in the OCCR region, 9 (23%) in the BCCR region, and 8 (20.5%) in the not-related risk region (NRR) (Table 2, Figure 1A). For *BRCA2* gene mutations, locations in the OCCR, BCCR, and NRR regions were 8 (40%), 7 (35%), and 5 (25%) (Table 2, Figure 1B).

Clinical Significance of Mutations

Genetic variants of *BRCA1/2* are classified according to the possibility of increasing the risk of developing cancer. Among 22

Table 2. BRCA Status of Ovarian Cancer Patients

BRCA status	% (*N*)	
Wild-type	67 (120/179)	
Mutated	33 (59/179)	
BRCA1	66.1 (39/59)	
BRCA2	33.9 (20/59)	
Mutation	**% (*N*)**	**Location**
BRCA1		
1) ex9-12del (Mexican Founder Mutation)	28.2 (11/39)	OCCR
2) c.2806–2809 del GATA	5.1 (2/39)	
3) c.1860 del T	5.1 (2/39)	
4) c.1723 dup G	2.6 (1/39)	
5) c.1961 del A	2.6 (1/39)	
6) c.2101 A > T	2.6 (1/39)	
7) c.2551 G > T	2.6 (1/39)	
8) c.3598 C > T	2.6 (1/39)	
9) c.3648 dup A	2.6 (1/39)	
10) c.3858–3861 del TGAG	2.6 (1/39)	
11) c.4868 C > G	5.1 (2/39)	BCCR
12) c.211 A > G	2.6 (1/39)	
13) c.5353 C > T	2.6 (1/39)	
14) exon 18–19 del	5.1 (2/39)	
15) c.4327 C > T	7.7 (3/39)	NRR
16) c.798–799 del TT	5.1 (2/39)	
17) c.4976 del C	2.6 (1/39)	
18) c.68–69 del AG	2.6 (1/39)	
BRCA2		
19) c.4325 C > A	10 (2/20)	OCCR
20) c.5116–5119 del AATA	10 (2/20)	
21) c.4749–4750 del AG	5 (1/20)	
22) c.5542 del A	5 (1/20)	
23) c.5616–5620 del AGTAA	5 (1/20)	
24) c.5631 del C	5 (1/20)	
25) c.8168 A > G	**25 (5/20)**	BCCR
26) c.1796–1800 del CTTAT	10 (2/20)	

OCCR = ovarian cancer cluster region; BCCR = breast cancer cluster region; NRR = not-related risk region.

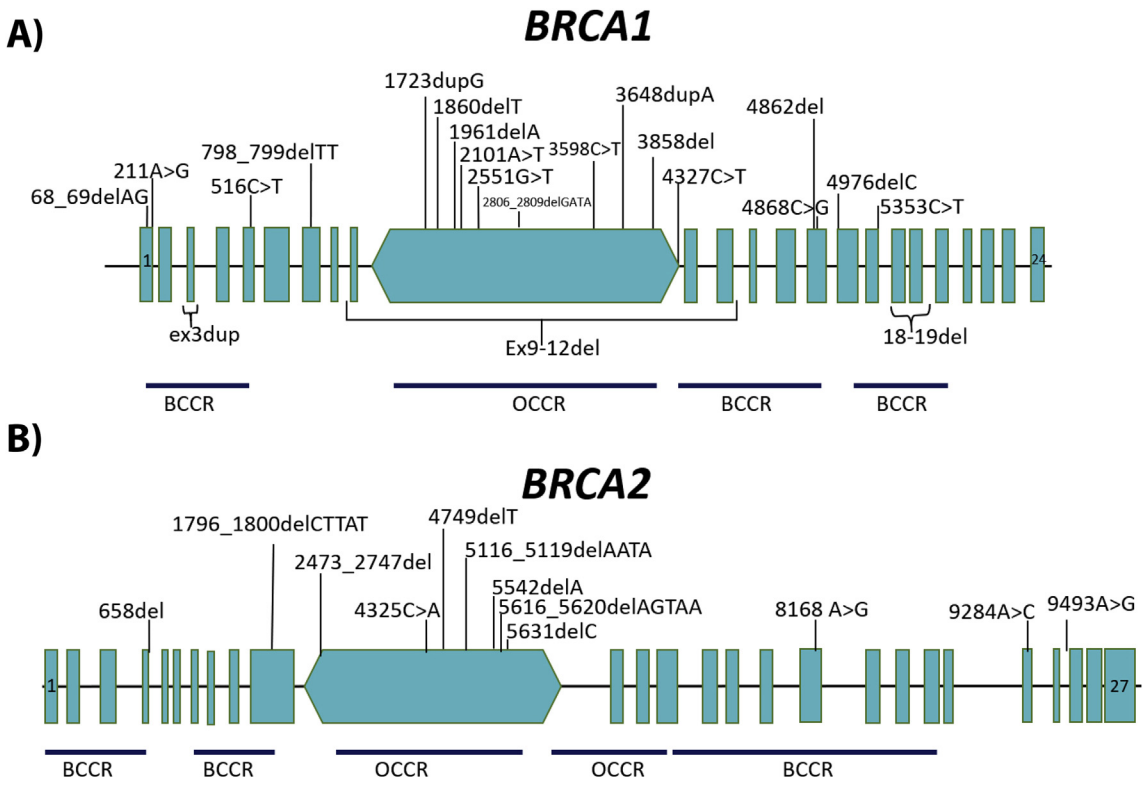

Figure 1. Location of 34 mutations detected in *BRCA1/2* genes (BRCA exchange database and verified in the ClinVar database). (A) Location of 22 reported mutations in *BRCA1* gene. (B) Location of the 12 mutations in *BRCA2* gene. OCCR, ovarian cancer cluster region; BCCR, breast cancer cluster region; NRR, not-related risk region.

BRCA1 mutation types detected, 81.8% (18/22) were pathogenic and affected 32 of 39 patients (Table 2), and 18.1% (4/22) were not yet reviewed variants and affected 7 out of 39 patients (Supplementary Table 1).

With respect to *BRCA2*, 12 different mutations types were detected, 66.7% (8/12) were pathogenic mutations and affected 15 of 20 patients (Table 2), and 33.3% (4/12) were not yet reviewed variants and affected 5 of 20 patients (Supplementary Table 1).

Correlation Analysis Between Clinicopathological Characteristics and BRCA Mutations

For BRCA mutations carriers, median age was 50 years (range = 27−73). The most common state of birth of BRCA mutations carriers detected was Mexico City (30.5%), followed by the Estado de Mexico (27.1%), Oaxaca and Puebla (5.1%); $P = 0.034$) (Table 3).

Almost 75% of the patients with BRCA mutations reported CFH in at least one relative ($P = 0.034$). The most frequently reported CFH type associated with BRCA mutation was breast ($P < 0.0001$) and we only found a trend for the presence of OC CFH ($P = 0.068$). Fourteen *BRCA* positive mutated patient (23.7%) had double primary malignancy ($P = 0.004$), and all of them were breast/ovarian ($P = 0.003$) (Table 3).

Clinicopathological Characteristics Associated with BRCA1/2 Mutations

According to *BRCA* mutations types, *BRCA1* mutations were more commonly detected in younger patients than in those with *BRCA2* mutations (median age, 46 vs 54 years; $P = 0.001$) (Supplementary Table 1). The clinicopathological characteristics according to the *BRCA1* mutation subtypes (Mexican founder mutation vs other *BRCA1* mutations) analysis showed that all patients with the Mexican founder mutation (11/39) had CFH ($P = 0.047$) (Supplementary Table 2).

Association of Clinical Characteristics of the Whole Study Population and Recurrence-free Survival

At the time of data cutoff, 123 patients (68.7%) had recurrence disease and 56 patients (31.3%) had no recurrence (both groups were ultimately included in the analysis). The mean follow-up was 41 months (SD 29.7 months) and the median of RFS was 47.7 months [95% CI 40.4−55] for all the patients. Patients with clinical stage I−II had better RFS compared with those with stages IIIA−B, IIIC, IV (96.9 vs 46.3 vs 43.4 vs 41.8 months; $P = 0.001$). Patients with endometroid histological subtype also had better RFS compared with those with HGSP, clear cell and LGSP (91.8 vs 37.2 vs 40.3 vs 33.8 months; $P = 0.004$) (Table 4).

RFS Analysis According to BRCA1/2 Status

In *BRCA1/2* mutated patients (59/179), there was a trend toward a better RFS in those patients without CFH compared with those with CFH (56.6 [44.1−69.1] vs 37.6 [28.4−46.9]; $P = 0.096$). There was no significant difference in RFS between *BRCA* mutated carriers and no mutation carriers (wild-type patients) ($P = 0.949$) (Table 5, Figure 2A), but *BRCA1* mutated patients group did show a worse RFS than its counterpart of patients with *BRCA2* mutation (37.6 [29−46.2] vs 72.8 [38.4−107.2]; $P = 0.030$) (Table 5, Figure 2B). Particularly, in the *BRCA1* patient subpopulation, the specific

Table 3. Bivariate Analysis of Clinical Characteristics of Ovarian Cancer Patients with BRCA Status

Characteristics	BRCA −	BRCA +	*P*
	% (*N*)	% (*N*)	
Age (years) at DX			
Median (range)	47 (18−76)	50 (27−73)	0.467
Mean ± SD	49.1 ± 11.3	49.9 ± 9.1	0.583
Group of age at DX			**0.041**
≤34	5.8 (7/120)	1.7 (1/59)	
35−44	35.8 (43/120)	25.4 (15/59)	
45−54	25 (30/120)	47.5 (28/59)	
55−64	22.5 (27/120)	18.6 (11/59)	
≥65	10.8 (13/120)	6.8 (4/59)	
Born city			**0.034**
Aguascalientes	0 (0/120)	1.7 (1/59)	
CDMX	41.7 (50/120)	30.5 (18/59)	
Chihuahua	0.8 (1/120)	0 (0/59)	
Coahuila	0 (0/120)	1.7 (1/59)	
Guanajuato	0 (0/120)	3.4 (2/59)	
Guerrero	0.8 (1/120)	3.4 (2/59)	
Hidalgo	11.7 (14/120)	3.4 (2/59)	
Jalisco	1.7 (2/120)	0 (0/59)	
México	23.3 (28/120)	27.1 (16/59)	
Michoacán	5 (6/120)	1.7 (1/59)	
Morelos	2.5 (3/120)	3.4 (2/59)	
Oaxaca	0 (0/120)	5.1 (3/59)	
Puebla	4.2 (5/120)	5.1 (3/59)	
Querétaro	1.7 (2/120)	3.4 (2/59)	
San Luis Potosí	0 (0/120)	3.4 (2/59)	
Tabasco	0 (0/120)	1.7 (1/59)	
Tlaxcala	3.3 (4/120)	3.4 (2/59)	
Veracruz	2.5 (3/120)	1.7 (1/59)	
Zacatecas	0.8 (1/120)	0 (0/59)	
Patients with CFH			**0.034**
Negative	41.7 (50/120)	25.4 (15/59)	
Positive	58.3 (70/120)	74.6 (44/59)	
Patients with CFH associated with BRCA			**0.015**
No associated	34.3 (24/70)	13.6 (6/44)	
Associated	65.7 (46/70)	86.4 (38/44)	
Type of cancer reported in CFH patients			
Breast	37.1 (26/70)	75 (33/44)	**<0.0001**
Prostate	22.9 (16/70)	13.6 (6/44)	0.225
Ovarian	8.6 (6/70)	20.5 (9/44)	0.068
Melanoma	10 (7/70)	9.1 (4/44)	0.873
Pancreas	8.6 (6/70)	2.3 (1/44)	0.173
Endometrium	4.3 (3/70)	2.3 (1/44)	0.570
1	42.9 (30/70)	54.5 (24/44)	
2	18.6 (13/70)	27.3 (12/44)	
3	4.3 (3/70)	4.5 (2/44)	
Clinical stage at Dx			
IA	5 (6/120)	1.7 (1/59)	0.123
IC	10 (12/120)	3.4 (2/59)	
IIA	0.8 (1/120)	0 (0/59)	
IIB	0 (0/120)	3.4 (2/59)	
IIIA	5 (6/120)	0 (0/59)	
IIIB	9.2 (11/120)	6.8 (4/59)	
IIIC	44.2 (53/120)	49.2 (29/59)	
IVA	10 (12/120)	15.3 (9/59)	
IVB	15.8 (19/120)	20.3 (12/59)	
Histological subtype			
Clear cells	5 (6/120)	3.4 (2/59)	0.111
HGSP	64.2 (77/120)	79.7 (47/59)	
LGSP	7.5 (9/120)	1.7 (1/59)	
Mucinous	0.8 (1/120)	0 (0/59)	
Endometroid	16.7 (20/120)	5.1 (3/59)	
G1	15 (3/20)	33.3 (1/3)	
G2	70 (14/20)	66.7 (2/3)	
G3	15 (3/20)	0 (0/3)	
Adenocarcinoma	1.7 (2/120)	5.1 (3/59)	
Mixed	4.2 (5/8)	5.1 (3/8)	
HGSP/endometroid	40 (2/5)	100 (3/3)	
HGSP/clear cells	20 (1/5)	0 (0/3)	
Endometroid/clear cells	20 (1/5)	0 (0/3)	
Endometroid/HGSP	20 (1/5)	0 (0/3)	
Double primary malignancy			
Negative	91.7 (110/120)	76.3 (45/59)	**0.004**
Positive	8.3 (10/120)	23.7 (14/59)	
Breast/ovarian	50 (5/10)	100 (14/14)	**0.003**
Endometrium/ovarian	50 (5/10)	0 (0/14)	
1° line treatment			
CBP/TXL per week	8.3 (10/120)	6.8 (4/59)	0.410
CBP/TXL 3 weeks	85.8 (103/120)	91.5 (54/59)	
Other	5.8 (7/120)	1.7 (1/59)	
Lines of treatment			
1° Line	40 (48/120)	33.9 (20/59)	0.256
2° Line	30 (36/120)	23.7 (14/59)	
≥3° Line	30 (36/120)	42.4 (25/59)	
Treatment response at 1° line of Tx			
CR	58.3 (70/120)	61 (36/59)	0.375
PR	25.8 (31/120)	30.5 (18/59)	
SD	15.8 (19/120)	8.5 (5/59)	
Platinum-based therapy			
Platinum sensitive	93.3 (112/120)	88.1 (52/59)	0.238
Platinum resistant	6.7 (8/120)	11.9 (7/59)	

CFH = cancer family history.

mutation *ex9-12del* (Mexican founder mutation) showed a better RFS than those with other types of *BRCA1* mutations (86.1 [37.2−135.1] vs 34.5 [20.7−48.2]; $P = 0.033$) (Figure 2C).

RFS Depending on the Location of BRCA1/2 Mutation

The analysis considering the location of the mutations globally in the OCCR, BCCR and NRR regions, showed a superior benefit on RFS for those mutations located in BCCR (41.6 [19.5−64.0] vs 72.8 [27.5−118.0] vs 40.1 [19.4−60.7]; $P = 0.155$; Figure 1D). RFS analysis of *BRCA1* mutated subpopulation when classified by mutation location (OCCR, BCCR, NRR) do not shown differences (27.4 [5.9−48.8] vs 79.5 [39.1−119.9] vs 40.1 [25.7−54.4]; $P = 0.611$) (Table 5, Figure 2E). In contrast, the RFS analysis of mutation locations for *BRCA2* has shown a better RFS to OCCR than those with mutations in BCCR and NRR (NR vs 72.8 [39−106.6] vs 25.8 [8.3−43.2]; $P = 0.013$) (Table 5, Figure 2F).

Multivariate analysis showed that *BRCA2*-mutated OC patients are likely to have better RFS than those with *BRCA1* mutations (HR = 0.426; $P = 0.035$) and patients with a *BRCA1* mutation other than ex9-12del (Mexican founder mutation) have a higher recurrence risk (HR = 3.07; $P = 0.042$).

Discussion

BRCA genes are important elements in the suppression of tumors [13]. In neoplasms such as breast and ovarian cancer, mutation of *BRCA1/2* genes is linked to the hereditary development of diseases [14]. Analysis of *BRCA* status has quickly become a standard clinical test in OC in developed countries. Benefit is being reflected in risk determination and appropriate treatment decisions [15]. The NCCN has concentrated a series of guidelines to be used in the assessment and evaluation of genetic risk. The Society of Gynecologic Oncology (SGO) and the American College of Obstetricians and Gynecologists have joined in a consensus statement regarding genetic counseling as well [16]. According to these guidelines, all women diagnosed with OC are advised to receive genetic counseling and testing for germline *BRCA* mutations.

Table 4. Clinical Characteristics Associated Factors with Recurrence-free Survival

Variable	Total ($N = 179$)				BRCA (−) ($N = 120$)				BRCA (+) ($N = 59$)			
	Median	95% Confidence interval		*P*	Median	95% Confidence interval		*P*	Median	95% Confidence interval		*P*
		Lower bound	Upper bound			Lower bound	Upper bound			Lower bound	Upper bound	
RFS (months)	47.7	40.4	55.0		49.2	40.6	57.8		43.7	34.8	52.6	
Age (years)				0.970				0.818				0.873
≤48	46.3	34.2	58.4		46.3	31.2	61.4		46.5	20.1	72.9	
>48	48.1	39.9	56.2		51.4	30.9	72.0		41.8	33.1	50.5	
Group of age at DX				**<0.0001**				**<0.0001**				**<0.0001**
≤34	14.7	7.4	22.1		16.3	12.3	20.2		–	–	–	
35−44	51.7	42.5	61.0		51.8	31.7	72.0		46.5	20.5	72.5	
45−54	49.0	29.1	68.9		57.7	34.6	80.8		47.7	34.7	60.7	
55−64	61.4	32.3	90.4		51.4	25.0	77.9		37.2	0.0	85.1	
≥65	43.7	20.7	66.7		30.4	22.8	69.2		56.6	36.0	77.2	
Clinical stage at Dx				**0.001**				**0.001**				0.199
I & II	96.9	86.6	107.3		96.9	86.5	107.3		NR	NR	NR	
III (A & B)	46.3	21.2	71.4		38.4	16.8	60.0		59.6	5.4	113.8	
IIIC	43.4	28.5	58.2		50.8	37.7	63.9		37.2	23.2	51.1	
IV	41.8	23.9	59.6		28.5	8.2	48.9		43.7	34.4	49.2	
Histology				**0.004**				**0.004**				**<0.0001**
Clear cells	40.3	26.7	53.8		40.3	26.5	54.1		–	–	–	
HGSP	37.2	27.0	47.3		33.4	19.4	47.5		40.1	30.7	49.5	
LGSP	33.8	28.5	84.6		62.5	16.3	132.3		–	–	–	
Endometroid	91.8	50.7	132.8		96.9	86.2	107.6		–	–	–	
Adenocarcinoma	88.1	69.7	106.5		NR	NR	NR		79.5	29.2	129.8	
Mixed	54.5	33.6	75.4		102.9	43.6	110.9		54.5	37.2	71.9	
Double primary malignancy				0.887				0.720				0.897
Negative	47.7	40.4	54.9		49.2	41.4	57.0		43.7	35.0	52.3	
Positive	80.6	11.6	149.5		NR	NR	NR		34.5	29.2	96.0	
Breast/ovarian	34.5	4.7	93.5	0.868	NR	NR	NR	–	34.5	29.2	96.0	–
Endometrium/ovarian	NR	NR	NR		NR	NR	NR		–	–	–	
1° line treatment				0.793				0.875				0.937
CBP/TXL per week	42.8	32.5	53.1		42.8	3.4	49.4		40.1	9.2	71.0	
CBP/TXL 3 weeks	46.5	37.5	55.4		49.2	6.3	61.6		43.7	32.3	55.1	
Other	61.4	9.2	113.5		61.4	26.6	113.5		–	–	–	
Line of treatment				**0.043**				**0.023**				0.659
1° Line	62.3	49.8	74.9		62.5	48.6	76.4		34.5	21.0	48.0	
2° Line	47.7	37.9	57.4		46.3	23.0	69.6		43.4	20.9	65.9	
≥3° Line	37.6	30.02	45.21		33.8	20.8	46.8		47.7	30.0	65.4	

CHF = cancer family history.

Table 5. BRCA Mutations Associated Factors with Recurrence-free Survival

Variable	*N*	Median	95% Confidence interval		*P*
			Lower bound	Upper bound	
RFS (months)	179	47.7	40.4	55.0	
BRCA status					0.949
WT	120	49.2	41.59	56.8	
Mutated	59	43.7	34.8	52.6	
Type of BRCA mut					**0.030**
BRCA1	39	37.6	29.0	46.2	
BRCA2	20	72.77	38.37	107.17	
BRCA location					0.080
OCCR	30	41.8	19.5	64.0	
BCCR	16	72.8	27.5	118.1	
NRR	13	40.1	19.4	60.7	
Type of BRCA1 mut					**0.033**
Endemic (exon 9−12 del)	11	86.1	37.2	135.1	
Other	28	34.5	20.7	48.2	
Type of BRCA2 mut					0.442
c.8168 A > G	5	72.8	51.9	93.6	
Other	15	62.3	19.2	105.3	
BRCA1 location					0.584
OCCR	22	27.4	4.4	50.5	
BCCR	9	79.5	39.1	119.9	
NRR	8	40.1	25.7	54.4	
BRCA2 location					**0.013**
OCCR	8	NR	NR	NR	
BCCR	7	72.8	39.0	106.6	
NRR	5	25.8	8.3	43.2	

OCCR = ovarian cancer cluster region; BCCR = breast cancer cluster region; NRR = not-related risk.

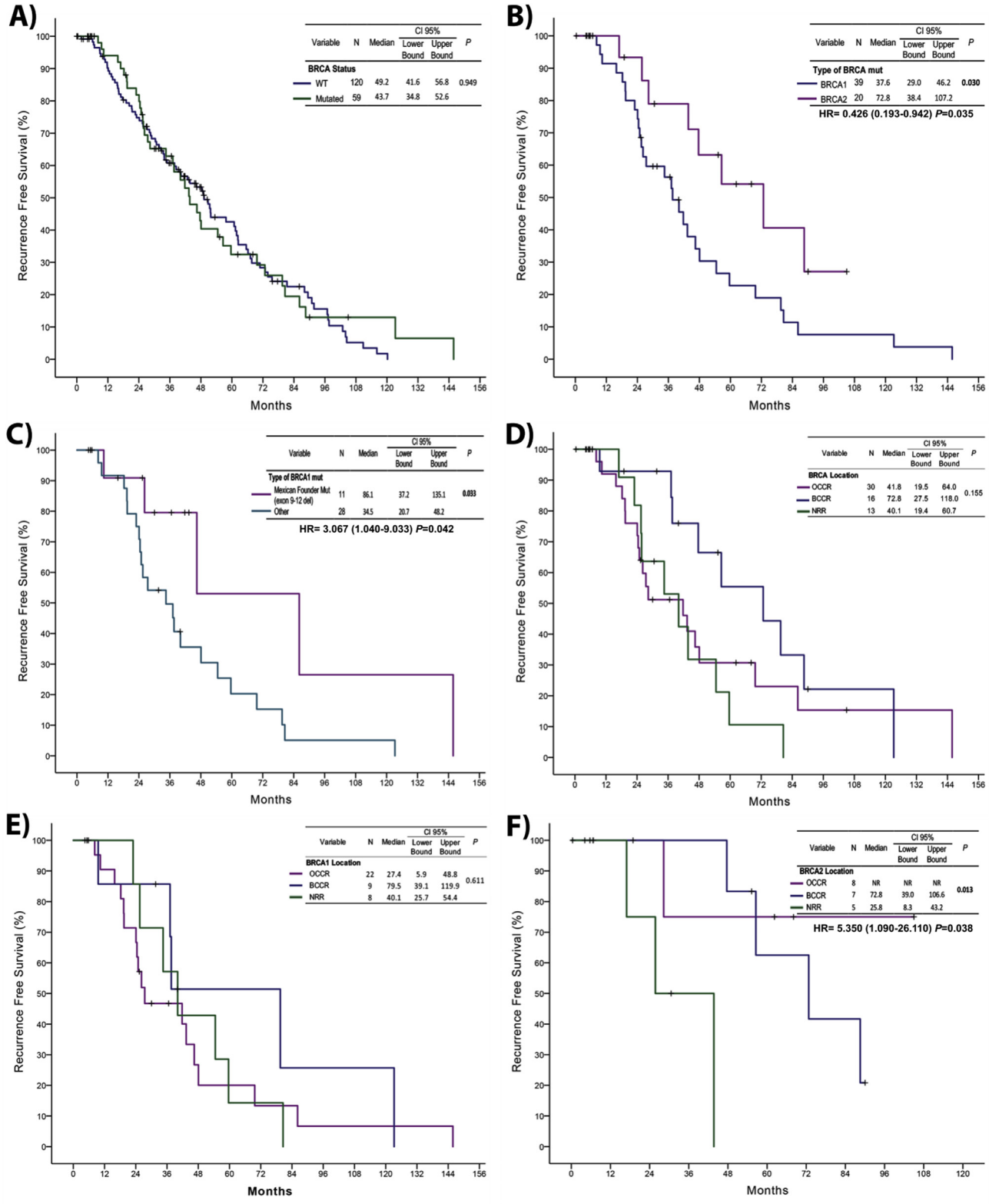

Figure 2. Impact of BRCA mutations on recurrence-free survival of Mexican ovarian cancer patients. (A) RFS of patients with BRCA wild-type (blue line) vs mutated BRCA (green line) (49.2 [41.6—56.8] vs 43.7 [34.8—52.6] $P = 0.949$). (B) RFS compared between *BRCA1* mutations carriers (blue line) vs *BRCA2* mutations carriers (green line) (37.6 [29—46.2] vs 72.8 [38.4—107.2]; $P = 0.030$). (C) *BRCA1* mutation carriers, comparing survival between carriers of the Mexican founder mutation *(ex9-12del)* (purple line) vs other mutations in *BRCA1* (blue line) (86.1 [37.2—135.1] vs 12.0, 95% C.I. [11.7—12.3]; $P = 0.033$). (D) RFS comparison in *BRCA* OCCR (violet line), BCCR (purple line), and NRR (green line) (41.6 [19.5—64.0] vs 72.8 [27.5—118.0] vs 40.1 [19.4—60.7]; $P = 0.155$). (E) RFS comparison of *BRCA1* locations: OCCR (violet line), BCCR (purple line) and NRR (green line) (27.4 [5.9—48.8] vs 79.5 [39.1—119.9] vs 40.1 [25.7—54.4]; $P = 0.611$). (F) RFS *BRCA2* locations: OCCR (violet line), BCCR (purple line) and NRR (green line); (NR vs 72.8 [39—106.6] vs 25.8 [8.3—43.2]; $P = 0.013$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Integrated models of close collaborations between geneticists and oncologists has allowed the exploration of BRCA and other OC-associated genes [17], but despite the clinical importance of germline *BRCA* mutations, widespread use of genetic testing is still low in some regions of the world.

This work is the largest analysis of *BRCA* genes status in a Mexican OC population.

Frequency of *BRCA1/2* mutations was considerably higher than previously reported by studies in other predominantly Caucasian population studies [7]. In the same way, our study reported a higher frequency of BRCA mutations carriers than a cohort of Hispanic cancer patients with breast and ovarian cancer [3].

In our study, most of the mutations were located in the central regions of both genes. The OCCR and BCCR regions were characterized as risk regions for developing ovarian and breast cancer, respectively. For the *BRCA1* gene, it was determined that the mutations that occurred between exons 1−11, and particularly in the central region of exon 11, conferred an elevated risk of OC compared with the mutations present in exons 12−24. It was also observed that mutations in the OCCR region decreased the risk of breast cancer and increased the risk of OC [18,19]. Similarly, for the *BRCA2* gene, it was observed that the mutations in exon 11 confer an increased risk of OC compared with a lower risk of breast cancer [19,20]. The advance in the study of mutations in the BRCA genes has made it possible to elucidate new regions OCCR and BCCR, which amplifies the inclusion of mutations in new regions now proven to contribute to the risk of OC and breast cancer [21].

Among BRCA1 mutations, those located in OCCR regions represented a higher percentage than mutations in BCCR and mutations in NRR regions. For BRCA2, half of the mutations were located in OCCR regions; however, mutations in BCCR occurred less frequently than mutations in NRR regions. It should be mentioned that in the present work were found OCCR and BCCR regions mutations that were not previously reported, which indicates that these mutations can be part of the characteristic mutations of carrier patients with OC.

The possible effect that a certain mutation may have on the risk of cancer is of clinical significance. Among the mutations detected in our study, we observed the predominance of pathogenic variants in both *BRCA1/2*. This finding represents more than double than the observed in a study of 333 nonselected cases of OC in a Polish population [22]. Another study that included 158 nonselected Brazilian OC patients identified a proportion of BRCA1 pathogenic variants similar to our study [23].

Almost 75% of the patients with mutations in a *BRCA* gene had a CFH and most of these cases were related to breast cancer. This data could serve to support the recommendation of providing genetic counseling to OC patients. The risk of OC in *BRCA1/2* mutation carriers considering the position of the mutation has been previously analyzed. In some studies, mutations in OCCR and BCCR were found to be associated with a higher incidence of OC compared with the incidence of breast cancer [19]; in addition, it has been found a slightly lower association between CFH and the risk of OC compared with the correlation analysis performed independently of the cluster regions for OCCR [24].

Several studies have reported that the presence of mutations in *BRCA* genes correlates with better survival in patients with OC [5,25]. This finding may correspond to a better response to chemotherapy treatment [26,27], which becomes more successful because of deficiency in the mechanisms of damage repair to DNA in which *BRCA1/2* are involved [28−30].

Our results do not show a significant difference in survival analyses between *BRCA* mutated and wild-type carriers. In this context, a study of 1421 OC patients showed an initial survival advantage among BRCA mutation carriers, but this response did not predict long-term (10 years) survival) [31]. Also, another study that analyzed the survival of OC patients carrying germline mutations in the *BRCA1/2* genes compared with survival of patients with strong family history for breast or ovarian cancer and with a negative genetic testing for *BRCA* mutation showed no survival advantage for *BRCA* mutation carrier patients [32].

In our study population, the RFS analysis between *BRCA1* mutation and *BRCA2* mutation carriers detected a better prognosis for those with the *BRCA2* mutation. This finding is consistent with previous reports [33].

Finally, we observed a *BRCA1 ex9-12del* prevalence of 28.2% (11/39) as well as an association with a better RFS compared with RFS of other mutations in *BRCA1*. The Mexican founder mutation *BRCA1 ex9-12del* was first detected in 2013, in a study that sought to analyze the prevalence and types of mutations in BRCA. In that study, 46 Hispanic patients with a personal or familial history of ovarian and breast cancer were included. A subpopulation of 492 breast cancer patients was analyzed to characterize the large rearrangements of *BRCA1 ex9-12del*. This analysis found that this mutation accounted for 10−12% of all mutations in *BRCA1* [33]. On the other hand, a study by Garza-Villarreal included 92 patients with ovarian cancer found that the prevalence of Mexican founder mutation was 35% (considering all BRCA mutated OC patients) [3]. The difference in the prevalence of the *BRCA1 ex9-12del* mutation compared with the reported in our study (39.1% vs 28.2%) may be because of the methodological characteristics of both studies. The association of *BRCA1 ex9-12del* mutation with a better RFS may be because of the biological effect of the deletion, which causes the loss of a vast extension of thousands of base pairs of nucleotides in the *BRCA1* gene [34], generating a truncated and less functional form of the protein compared with those generated by other mutations that give rise to not so radical changes [34]. The association of Mexican founder mutation and better RFS rate could result in a very useful tool in genetic counseling to predict the prognosis of OC in patients with this specific mutation.

In conclusion, this study reports the highest prevalence of BRCA1/2 mutations in an OC patient population. Patients with mutations in *BRCA2* have a better prognosis than those mutated in *BRCA1*. The Mexican founder mutation, *BRCA1* ex9-12del, has an important role in the clinical outcomes. These results highlight the importance to test all the OC patients with CFH and HGSP histology in to integrate into the national health system as a diagnostic test.

Conflict of Interest

DGR, RMAG, and GAG have participated in Speakers' Bureau to AstraZeneca. DGR also has participated as speaker with Roche and Lilly. The other authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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