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Recurrent *BRCA1* and *BRCA2* mutations in Mexican women with breast cancer

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Abstract

Background—Germline mutations in the *BRCA1* and *BRCA2* genes confer an estimated 58–80% lifetime risk of breast cancer. In general, screening is done for cancer patients if a relative has been diagnosed with breast or ovarian cancer. There are few data on the prevalence of mutations in these genes in Mexican women with breast cancer and this hampers efforts to develop screening policies in Mexico.

Methods—We screened 810 unselected women with breast cancer from three cities in Mexico (Mexico City, Veracruz and Monterrey) for mutations in *BRCA1* and *BRCA2*, including a panel of 26 previously reported mutations.

Results—Thirty-five mutations were identified in 34 women (4.3% of total) including 20 *BRCA1* mutations and 15 *BRCA2* mutations. Twenty-two of the 35 mutations were recurrent mutations (62.8%). Only five of the 34 mutation carriers had a first-degree relative with breast cancer (three with *BRCA1* and two with *BRCA2* mutations).

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The authors have no conflicts of interest.

Conclusion—These results support the rationale for a strategy of screening for recurrent mutations in all women with breast cancer in Mexico, as opposed to restricting screening to those with a sister or mother with breast or ovarian cancer.

Impact—These results will impact cancer genetic testing in Mexico and the identification of at-risk individuals who will benefit from increased surveillance.

Introduction

In Mexico, breast cancer has overtaken cervical cancer as the leading cause of cancer-related death in women (1–4) and mortality rates are increasing (5–7). Typically, breast cancer is diagnosed at a relatively advanced stage (III and above) (8–9) when the chance of cure is reduced. The median age of breast cancer diagnosis is 51 years (approximately one decade younger than that of women in Europe or North America) and almost one-half of Mexican women are premenopausal at breast cancer diagnosis (6–8).

The *BRCA1* (10) and *BRCA2* (11) genes account for between 5% and 10% of all breast cancer cases, and particularly in those women with a family history of breast and ovarian cancer (12–15) but the prevalence of mutations in these genes in Latin American women and their contribution to breast cancer is largely unknown. The lifetime risk of breast cancer in women who carry a *BRCA1* or *BRCA2* mutation is about 80% (12–14) but the absolute risk varies by country and by ethnic group (16). Characteristics of hereditary breast cancer include a young at age at onset and multiple cases of early-onset breast cancer or ovarian cancer in the family (12–14). However, as many as 50% of breast cancer patients with an inherited mutation in *BRCA1* and *BRCA2* do not have a close relative with breast or ovarian cancer, either because their mutation is paternally-inherited, their family is small, random segregation and incomplete penetrance (17).

The prevalence of *BRCA1* and *BRCA2* mutations combined is approximately 0.3% in North America (12–17), but may be higher than this in countries or populations where there are founder mutations, such as Israeli Jews (18–20), Dutch (21), French-Canadians (22), Icelandic (23), Greenlandic (24), Polish (25), Russia and Eastern European (26–30) and Greek populations (31–32). Recurrent mutations have also been described in women of Hispanic origin in the United States (33–38). The presence of recurrent *BRCA1* and *BRCA2* mutations has been noted in a few studies from Latin America and the Caribbean (39–42) including four small studies from Mexico (43–46). The identification of recurrent mutations greatly facilitates genetic testing of *BRCA1* and *BRCA2* (47). In this study, we screened for 26 mutations that have been observed previously in Mexican women and we have screened for other mutations in exon 11 in *BRCA1* and exons 10 and 11 in *BRCA2* in 810 Mexican women with breast cancer.

Materials and Methods

Materials

A multi-center breast cancer case-control study was established in twelve hospitals in three cities in Mexico (Mexico City, Monterrey and Veracruz). DNA and epidemiological data has been collected from January 2007 through June 2010 (48–51). Table 1 provides some of

the descriptive statistics of 810 cases. A full summary of features of the cases and controls has been published elsewhere (48–51). The controls are not the focus of this current study. This study was designed to examine predictors of breast cancer risk among women age 35 to 69 years. Cases were histologically-confirmed new diagnosis of breast cancer, including invasive and *in situ* tumors. Data collection included the administration of a structured questionnaire by means of a face to face interview and anthropometric measurements and collection of a blood sample at the hospital by a trained nurse. All participants provided a written informed consent. The study was approved by the Institutional Review Board at each participating institution. The health questionnaire collected information on socio-demographic characteristics; reproductive factors; use of oral contraceptives and hormone replacement therapy; family and personal history of chronic diseases; personal history of transmitted sexual diseases; histories of body size, smoking, and alcohol consumption; and history of medical X-rays and mammograms. Subjects were informed of the goals of the study and the implications of the possible identification of a mutation in either *BRCA1* or *BRCA2*. Subjects were permitted to decline participation for genetic testing.

Laboratory Methods

Biospecimen Processing

Once a subject agreed to participate in the study, the research nurse collected blood samples in two five ml EDTA tubes. Blood samples were stored at each hospital at −20°C to −70°C and within three weeks they were sent to the Instituto Nacional de Salud Pública, Cuernavaca, Mexico and stored at −70°C until shipment. The frozen blood was shipped on dry ice to the Narod laboratory in Toronto. Genomic DNAs were extracted from blood using the ArchivePure DNA Blood Kit (5Prime, Gaithersburg, MD) according to protocol. Stock DNA samples were bar-coded with a unique subject identification number to ensure reliable sample processing.

BRCA1 and *BRCA2* mutation screening

All samples were screened for 26 mutations found in the Mexican population; 21 in *BRCA1* (MIM113705) and 5 in *BRCA2* (MIM600185). Exon 11 of *BRCA1* and exons 10 and 11 of *BRCA2* were screened by the protein truncation test, PTT (TNT™ T7 Coupled Reticulocyte Lysate System, Promega, Madison, WI; and [^{35}S] Methionine/Cysteine, New England Nuclear, Boston, MA). Overlapping primer sequences were obtained from the Breast Cancer Information Core (BIC). PTT screening covered the three exons encompassing 17 known Mexican mutations in *BRCA1* (K654X, 943ins10, S955X, Q1200X, R1203X, 1205del56, c. 3124_3133delAGCAATATTA, c.2805_2808delAGAT, C1787S & G1788D, 2415delAG, 2525del4, 2552delC, 2925del4, 5382insC, 3148delCT, 3787delTA and 4184del4) and 5 known Mexican mutations in *BRCA2* (Q742X, W2586X, c.5114_5117delTAAA, c. 2639_2640delTG and 3492insT), as well as other Hispanic mutations and any other novel deleterious mutations in these exons.

The four remaining *BRCA1* mutations were tested by differing methods. A tetra-primer Amplification Refractory Mutation System (ARMS) assay was designed for the exon 13 R1443X mutation, a restriction fragment length polymorphism (RFLP) was designed for the

exon 18 A1708E mutation, and a TaqMan Copy Number Variation (CNV) assay (Applied Biosystems Inc., Assay ID: Hs05509065_cn) was employed to detect the *BRCA1* ex9–12del large rearrangement. The binding site of the probe for TaqMan CNV assay was on exon 10 of *BRCA1* gene. To confirm the mutations identified by the TaqMan CNV assay and also determining the extent of the deleted region, a Multiple Ligation-dependent Probe Amplification (MLPA) assay (MRC Holland Inc., Assay ID: P002) on 3500XL genetic Analyzer (Applied Biosystems Inc.) was used. The 185delAG mutation, commonly seen in the Hispanic women in the US of apparent Mexican and Jewish ancestry was coupled in a previously designed multiplex assay (52). In addition, we tested for the *BRCA1* 5382insC and *BRCA2* 6174delT mutations commonly seen in Jews and others of eastern European ancestry using the same rapid multiplex method (52). Mutation-positive controls were included in the assay. All primer designs and PCR conditions are available upon request. All deleterious mutations detected by all methods were confirmed by direct sequencing [BigDye® Terminator v.3.1 Cycle Sequencing Kit; 3130xL Genetic Analyzer (Applied BioSystems, Foster City, CA)] according to the manufacturer's protocol.

Statistical Analysis

To compare characteristics by menopausal or mutation status, Kruskal Wallis for continuous variables and Chi Square and Fisher´s exact tests for categorical variables were used. The differences were considered statistically significant when $p<0.05$. All analyses were conducted using Stata v. 12.

Results

Eight hundred and ten women with breast cancer were included in the study. Of the 810 women, 66% were from Mexico City, 22% from Monterrey and 12% from Veracruz. The median age of diagnosis was 51.5 years and 334 (41% of total) were premenopausal. A family history of any cancer was reported in 34% of the postmenopausal women and in 23% of the premenopausal women ($p = 0.001$). However, the frequency of first degree relatives with breast cancer was similar in both groups (Table 1).

Thirty-five mutations were identified in 34 of the 810 women (4.3%), (Table 2). In *BRCA1*, four recurrent mutations and four private mutations were detected in 20 women. The exon 9–12 mutation was detected in eight women. The exon 18 C5242A mutation was detected in four women and two mutations were seen twice (exon 11 2552delC and exon 13 C4446T). In *BRCA2*, two recurrent mutations and nine private mutations were detected in 14 women. Two *BRCA2* mutations were seen three times each (exon 10 2024del5 and exon 11 C4339T). One woman harbored two *BRCA2* mutations (exon 10 2024del5 and 4321insAA). No Jewish founder mutations (*BRCA1* exon 2 185delAG and exon 11 5382insC and *BRCA2* exon 11 6174delT) were detected. Eighteen of the women (53%) with a *BRCA* mutation were from Mexico City; eight mutation-carriers (23%) were from Monterrey and eight mutation-carriers (23%) with nine mutations were from Veracruz (including the woman with two *BRCA2* mutations). The *BRCA2* exon 11 2024del5 mutation was only found in three women from Veracruz (Table 2).

The mean age of breast cancer onset was 43 years in *BRCA1* carriers; 50.9 years in BRCA2 carriers and was 52 years in non-carriers ($p<0.001$) (Table 3). The prevalence of mutations was 11.8% for women diagnosed aged 30–39; 4.8% for women diagnosed aged 40–49; 3.4% for women diagnosed aged 50–59 and 1.6% for women diagnosed at 60 years or older.

A history of any cancer in a first degree relative was reported in 55% of *BRCA1* carriers, 46.7% of *BRCA2* carriers and 28.5% of non-carriers. However, breast cancer in a first-degree relative was seen in only three of 20 (15%) women with *BRCA1* mutations and two of 15 (13.3%) women with a *BRCA2* mutation and 53 of 775 (6.8%) of non-carriers. The prevalence of mutations by cancer family history is provided in Table 3.

European ancestry was not associated with either *BRCA1* or *BRCA2* carrier status (Table 3). (51)

Discussion

We conducted a breast cancer case-control collection in 12 hospitals in three cities in Mexico. Eight hundred and ten blood samples from women with breast cancer were collected of whom 334 (41%) were premenopausal and 476 (59%) were postmenopausal. Thirty-five mutations were identified in 34 of the 810 (4.3%) women tested including 8 unique *BRCA1* mutations in 20 women and 11 unique *BRCA2* mutations in 14 women (Table 2).

Genetic testing for mutations in *BRCA1* and *BRCA2* has potentially important public health implications for the detection of high risk individuals for whom targeted prevention and tailored management strategies can be implemented (53). The ability to offer genetic testing in Mexico on a widespread level would be enhanced with the identification of common mutations in the two genes so the cost of genetic sequencing is reduced. In the present study, we detected recurrent mutations in 2.7% of 810 unselected cases of breast cancer. Twenty-two of the 34 mutation carriers had a mutation that was seen more than once, therefore the strategy of looking solely for recurrent mutations would have a sensitivity of approximately 60%. Ideally, to maximize sensitivity, one would screen all breast cancer patients for both *BRCA1* and *BRCA2* in their entirety. However, given the current high costs of sequencing, this strategy is prohibitively expensive in Mexico. Alternate strategies include the testing of all high-risk patients for all mutations through full gene sequencing or testing all cancer patients (high and low-risk) for a smaller number of mutations (recurrent and founder mutations). Of interest, in the present study, only three of 20 (15%) women with *BRCA1* mutations (all with the exon 9–12 deletion) and two of 14 (14.3%) women with a *BRCA2* mutation (one harboring a 3036delACAA and another with 5770delA mutation) had a first degree relative with breast cancer (Table 3) and therefore the strategy of testing only familial cases of breast cancer would result in the identification of only a minority of mutation carriers, even if complete sequencing were done for both genes. The three women with the *BRCA1* exon 9–12 deletion developed breast cancer at 44, 44 and 56 years respectively. The two women with *BRCA2* mutations were <50 years at diagnosis (one was 42 years and the other woman was 48 years).

There are small reports of *BRCA1/2* mutation screening studies in Mexico. Ruiz-Flores et al, (43), identified one *BRCA1* 3857delT and one *BRCA2* 2663–2664insA mutation among in 51 Mexican breast cancer patients, (6% of 32 early-onset breast cancer patients). Vidal-Millan et al, (44), found three mutations in *BRCA1* and *BRCA2* genes in 40 Mexican breast cancer patients (5%). Calderón-Garcidueñas et al, 2005 (45) found one *BRCA1* mutation (exon 11, 3587delT) and one *BRCA2* mutation (exon 11, 2664insA) in 22 early-onset Mexican breast cancer patients. Vaca-Paniagua et al, 2012, (46) found four mutations in 39 Mexican breast-ovarian cancer families, three of which were novel including *BRCA1* c. 3124_3133delAGCAATATTA and c.2805_2808delAGAT and *BRCA2* c. 5114_5117delTAAA and c.2639_2640delTG. Using our mutation screening strategy including PTT for exon 11 in *BRCA1* and exons 10 and 11 in *BRCA2*, we would have detected each of the above mutations, were they present among the 810 Mexican women. However, we did not detect any of the above mutations.

Of note, no Jewish founder mutations were reported in any of these four studies, nor did we detect women harboring these mutations in this study. However, mutation screening studies performed in Latina women, mainly of Mexican origin in the United States revealed the presence of the Jewish *BRCA1* exon 2, 185delAG founder mutation. Vogel et al reported that four of 78 Hispanic women with familial breast cancer carried this mutation and ten carried other mutations including *BRCA1* 2552delC (37). John et al, found a *BRCA1* mutation in 21 of 393 (5.3%) of Hispanic women with breast cancer in California (38). They found the prevalence of *BRCA1* mutation carriers of 3.5% (95% CI, 2.1%–5.8%) in Hispanic patients (n = 393), compared with 8.3% (95% CI, 3.1%–20.1%) in Ashkenazi Jewish patients (n = 41) and 2.2% (95% CI, 0.7%–6.9%) in other non-Hispanic white patients (n = 508). The *BRCA1* 185delAG was the most common mutation in Hispanics and was found in five of 21 carriers (24%). Weitzel and colleagues (33) studied 110 unrelated Latina women at high risk of breast/ovarian cancer in Los Angeles. Thirty-four of the 110 women had a mutation (31%); of these 18 were of Mexican descent. Four mutations were seen more than once in women with Mexican origins: *BRCA1* exon 2 185delAG (four times); exon 13 C4446T (R1443X) (three times); exon 11 2552delC (2 times) and *BRCA2* exon 11 3492insT (2 times). In a more recent follow-up study (34), the *BRCA1* exon 13 C4446T (R1443X) was reported six times, four of which were in families of Mexican descent. The 2552delC was reported in four families and the A1708E was observed in three families of Mexican origin. The latter was also reported by Myriad Genetics in seven Latin American subjects in the BIC database (54). The *BRCA2* exon 11 3492insT was identified in 10 families of Mexican descent only. In this study, we also identified the *BRCA1* exon 13 C4446T (R1443X) twice; the exon 11 2552delC twice, the A1708E four times and *BRCA2* exon 11 3492insT once. Weitzel et al (33) also reported single *BRCA1* mutations which we also detected in the current study, each in a single individual: 1135insA, 2415delAG and C3717T (Q1200X). We found recurrent *BRCA2* mutations; exon 10 2024del5, (which was reported 11 times in BIC (54) but not in individuals of Latin American descent) and exon 11 C4339T (reported once in BIC (54) in an individual of Spanish descent) in three cases each. We identified a *BRCA2* 3036del4 mutation in a single case which was also identified by Osario et al, (55) in a Spanish breast cancer family, while the 2024del5 mutations appears to be of Greek origin (31–32). In summary, the *BRCA1* 1135insA, 2415delAG, 2552delC, C3717T, C4446T,

C5242A and 9–12del and *BRCA2* 2024del5, 3492insT and C4339T mutations are recurrent mutations in the Mexican population. One novel *BRCA1* mutation (2190delA) and five novel *BRCA2* mutations (2971del5, 4321insAA, 4534delAT, 5859delC and 6686delC) were also identified in our study, which were not previously reported.

However, we did not find any *BRCA1* exon 2 185delAG mutations in agreement with the four previous reports in Mexican breast cancer patients (43–46) but in contrast to the observations in Hispanic American patients of Mexican descent (33–37). We included Jewish mutation-positive controls in each multiplex assay, in which the appropriate mutations were detected so we do not consider this result to represent a false-negative. Possible explanations for the high frequency of the *BRCA1* 185delAG mutations in previous reports may be Spanish admixture of the population of Hispanic Americans in the US from which the study subjects are drawn (56). Velez et al, 2012, investigated the ancestral origin of 33 unrelated individuals of Spanish descent with *BRCA1* c.185delAG in Colorado (57). The presumed European component showed enrichment for Sephardic Jewish ancestry, consistent with historical accounts of Jewish migration from the realms that comprise modern Spain and Portugal during the Age of Discovery (58).

Weitzel and colleagues (34) also reported a founder deletion (*BRCA1* exons 9–12) in 3.8% unrelated breast cancer families of Mexican origin. A recent follow-up study has shown that the *BRCA1* ex9–12del deletion represents 10% of all *BRCA1* mutations in 746 Hispanics with a personal or family history of breast and/or ovarian cancer and 492 population-based Hispanic breast cancer cases (35). We detected this mutation in eight women (1% of the 810 women tested) or 22% of all observed *BRCA1/2* mutations.

Overall, the age of breast cancer onset was around 8 years younger in *BRCA1* carriers (43 years) compared to *BRCA2* carriers (50.9 years) and nine years younger than non-carriers (52 years) ($p<0.001$) (Table 3).

One woman with breast cancer at age 53 years harbored two *BRCA2* mutations (exon 10 2024del5 and exon 11 4321insAA). The exon 10 2024del5 mutation is a common mutation in Greek breast cancer families (31) and was found only in three women from Veracruz in this study. Biallelic *BRCA2* mutations have been reported in Fanconi anaemia (FA), specifically subtype D1 (59). FA is a recessive condition associated with progressive bone marrow aplasia, congenital abnormalities and predisposition to leukaemia and solid tumours of the head and neck, oesophagus and vulva (60). The biallelic *BRCA2* mutations form of FA is severe with high risks of childhood cancer, particularly Wilms tumour, brain tumours and acute myelogenous leukaemia (59–61). Recently, a woman with ovarian cancer was found to harbor biallelic *BRCA1* mutations (62). To our knowledge, this is the first report of breast cancer in a biallelic *BRCA2* mutation carrier. The combinations of *BRCA2* mutations that are viable are limited. The exon 11 4321insAA has not been reported previously in BIC (54) or the literature and the functional impact of this mutation is unknown. Of note the Mexican woman with bialleleic *BRCA2* mutations in this study did not show signs of FA so the 4321insAA mutation may be non-deleterious.

Medullary breast cancer has been highly associated with *BRCA1* mutations (63). In this study we found that 2/7 (28.5%) of the medullary breast cancers were from women with BRCA1 mutations. Although medullary breast cancer histologic subtypes represent a small number of the total number of breast cancers, the presence of this subtype is potentially an indicator for the presence of a *BRCA1* mutation in Mexican women.

There are several strengths to this study. This is the largest study of *BRCA1/2* mutations in Mexican women with breast cancer. The study population is not defined under the broad generational classification of 'Hispanic', rather a narrower definition of Mexican ancestry only. The lack of the Jewish founder mutations in this, and other published studies on Mexican breast cancer cases shows the importance of studies in women in Latin American countries and that more attention should be paid to more clearly define the ancestral origin of 'Hispanic' women in the US.

This study also has limitations. The samples were not fully screened for mutations in the *BRCA1* and *BRCA2* genes via sequencing or dosage analysis such as MLPA. It is entirely plausible that with full screening of the genes, additional recurrent and common mutations may have been detected. Testing of a panel of recurrent mutations would be pragmatic but larger studies would be required to more definitively delineate a better set of true Mexican founder mutations. Furthermore, there is the possibility that some of the women in the study are related which may inflate the frequency of particular mutations.

Another limitation is the inability to consider second-degree family relatives and that the presence of ovarian cancer was not adequately recorded. However, family history in second-degree relatives is considered less predictive of *BRCA*-carrier status. Indeed, our results suggest that family history of breast cancer in first-degree relatives is not particularly predictive of *BRCA*-carrier status in Mexican women either.

In conclusion, studies of this kind are essential to determine the genetic etiology of breast cancer in Mexican women. These results highlight the variability in the mutation spectrum, penetrance and phenotype of *BRCA1* and *BRCA2* mutations in Mexican women and reveal the presence of particular recurrent mutations in this population. Further comprehensive evaluation of the prevalence of *BRCA1* and *BRCA2* mutations is necessary. Through judicious testing of women believed to be at high risk for early-onset breast cancer, it is possible to identify highly-predisposed women prior to the development of cancer. Current preventive options such as preventive mastectomy or tamoxifen may be tailored to the *BRCA1/2* mutation carrier so as to improve morbidity and mortality associated with this disease.

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Table 1

Characteristics of women with breast cancer by menopausal status in Mexico City, Monterrey and Veracruz, 2007–2010

	Total		Menopausal status				*P*-value[b]
Characteristics			**Premenopausal[a]**		**Postmenopausal**		
n	n=810		n=334		n=476		
Age (years)							
Median	51.5		43.9		57.9		
Interquartile range	(44.7, 59.4)		(40.4, 47.3)		(53.1, 63.7)		<0.001
European Ancestry, n (%)[c]							
<25%	227	(28.0)	101	(30.2)	126	(26.5)	
25–50%	353	(43.6)	153	(45.8)	200	(42.0)	
51–75%	146	(18.0)	50	(15.0)	96	(20.2)	
76–100%	19	(2.3)	6	(1.8)	13	(2.7)	0.154
Breast cancer histology, n (%)[c]							
Ductal	499	(61.6)	211	(63.2)	288	(60.5)	
Lobular	99	(12.2)	38	(11.4)	61	(12.8)	
Ductal in situ	54	(6.7)	30	(9.0)	24	(5.0)	
Mixed	32	(4.0)	7	(2.1)	25	(5.3)	
Not classified	23	(2.8)	6	(1.8)	17	(3.6)	
Medullary	7	(0.9)	3	(0.9)	4	(0.8)	
Mucinous	4	(0.5)	3	(0.9)	1	(0.2)	
Lobular in situ	3	(0.4)	2	(0.6)	1	(0.2)	
Tubular/cribriform	3	(0.4)	0	(0.0)	3	(0.6)	
Papillary	3	(0.4)	1	(0.3)	2	(0.4)	
Apocrine	2	(0.2)	0	(0.0)	2	(0.4)	
Non-specified non-invasive	2	(0.2)	1	(0.3)	1	(0.2)	
Metaplastic	2	(0.2)	1	(0.3)	1	(0.2)	0.053
Stage, n (%)[c]							
0	17	(2.1)	7	(2.1)	10	(2.1)	

	Total		Menopausal status				*P*-value[b]
Characteristics			**Premenopausal[a]**		**Postmenopausal**		
I	87	(10.7)	36	(10.8)	51	(10.7)	
II	363	(44.8)	135	(40.4)	228	(47.9)	
III	178	(22.0)	83	(24.9)	95	(20.0)	
IV	15	(1.9)	8	(2.4)	7	(1.5)	
Non-classifiable	21	(2.6)	5	(1.5)	16	(3.4)	0.158
History of breast cancer in first degree, n (%)[d]							
No	752	(92.8)	310	(92.8)	442	(92.9)	
Yes	58	(7.2)	24	(7.2)	34	(7.1)	0.981
History of cancer in first degree, n (%)[c,d]							
No	552	(68.2)	253	(75.8)	299	(62.8)	
Yes	239	(29.5)	78	(23.4)	161	(33.8)	0.001

[a] Premenopause includes premenopause and perimenopause (<12 months since last period); postmenopause includes natural menopause (≥ 12 months since last period), surgical (with oophorectomy) or unknown menopausal status (considered for those women ≥48 years).

[b] Kruskal Wallis test for continuous variables, Chi square test or Fisher´s exact test for categorical variables.

[c] Percentages may not add up to 100% due to missing data.

[d] We considered parents and siblings as first degree relatives. Participants who did not know their number of siblings were excluded from the analysis.

Table 2

BRCA1 and *BRCA2* mutations in women with breast cancer in Mexico City, Monterrey and Veracruz, 2007–2010

Case	Gene	Exon	Mutation	Codon Change	HGVS nomenclature	AGE	STAGE	HISTOLOGY	FAM HX BR CA
D2062	BRCA1	9–12	del	14.7kb deletion	c.548?_4185 ?del	44	Missing	Ductal	Yes
D2073	BRCA1	9–12	del	14.7kb deletion	c.548?_4185 ?del	35	Missing	Ductal	No
M1209	BRCA1	9–12	del	14.7kb deletion	c.548?_4185 ?del	43	II	Ductal	No
M1761	BRCA1	9–12	del	14.7kb deletion	c.548?_4185 ?del	46	III	Ductal	No
M1916	BRCA1	9–12	del	14.7kb deletion	c.548?_4185 ?del	43	III	Ductal	No
M1954	BRCA1	9–12	del	14.7kb deletion	c.548?_4185 ?del	44	I	Ductal	Yes
V3044	BRCA1	9–12	del	14.7kb deletion	c.548?_4185 ?del	56	I	Ductal	Yes
V3236	BRCA1	9–12	del	14.7kb deletion	c.548?_4185 ?del	37	Missing	Missing	No
D2309	BRCA1	11	1135insA	Stop 345	c.1016–1017insA	41	Missing	Medullary	No
M1956	BRCA1	11	2190delA	Stop 700	c.2071-2071delA	51	II	Ductal	No
M2255	BRCA1	11	2415delAG	Stop 766	c.2296–2297delAG	34	II	Ductal	No
D2058	BRCA1	11	2552delC	Stop 814	c.2433delC	50	Missing	Not classified	No
D2142	BRCA1	11	2552delC	Stop 814	c.2433delC	38	I	Ductal	No
M2273	BRCA1	11	C3717T	Q1200X	c.3598C>T	39	Missing	Ductal	No
M1607	BRCA1	13	C4446T	R1443X	c.4327C>T	50	II	Ductal	No
V3053	BRCA1	13	C4446T	R1443X	c.4327C>T	38	I	Ductal	No
D2090	BRCA1	18	C5242A	A1708E	c.5123C>A	42	Missing	Ductal	No
D2377	BRCA1	18	C5242A	A1708E	c.5123C>A	39	I	Medullary	No
M1738	BRCA1	18	C5242A	A1708E	c.5123C>A	70	II	Not classified	No
M1895	BRCA1	18	C5242A	A1708E	c.5123C>A	49	III	Ductal	No
V3267	BRCA2	10	2024del5	Stop 599	c.1796–1800delTTTAT	53	III	Ductal	No
V3319	BRCA2	10	2024del5	Stop 599	c.1796–1800delTTTAT	39	II	Ductal	No
V3054	BRCA2	10	2024del5	Stop 599	c.1796–1800delTTTAT	**54**	**II**	Lobular	**No**
V3054	BRCA2	11	4321insAA	N/A	N/A	**54**	**II**	Lobular	**No**
M1768	BRCA2	11	2971del5	N/A	N/A	45	III	Ductal	No
M2251	BRCA2	11	3036del4	Stop 959	c.2808–2811delACAA	48	Missing	Ductal	Yes

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Case	Gene	Exon	Mutation	Codon Change	HGVS nomenclature	AGE	STAGE	HISTOLOGY	FAM HX BR CA
M1193	BRCA2	11	3492insT	Stop 1098	c.3264–3265insT	63	II	Not classified	No
D2379	BRCA2	11	4534delAT	N/A	N/A	51	III	Lobular	No
M1911	BRCA2	11	5770delA	Stop 1862	c.5542delA	42	III	Ductal	Yes
M1831	BRCA2	11	5859delC	N/A	N/A	56	II	Ductal	No
V3269	BRCA2	11	6686delC	P2153L	N/A	43	III	Ductal	No
M1894	BRCA2	11	6714delACAA	Stop 2166	c.6486–6489delACAA	56	III	Ductal	No
M1349	BRCA2	11	C4339T	Q1371X	c.4111C>T	39	III	Ductal	No
M1751	BRCA2	11	C4339T	Q1371X	c.4111C>T	75	II	Lobular	No
V3220	BRCA2	11	C4339T	Q1371X	c.4111C>T	52	Missing	Ductal	No

Abbreviations: HGVS= Human Genome Variation Society; FAM HX BR CA= family history of breast cancer

Table 3

Characteristics of breast cancer cases by *BRCA1/2* mutation status in Mexico City, Monterrey and Veracruz, 2007–2010

Characteristics	Total		Non carrier		BRCA 1		BRCA 2		P value[a]
n	**n = 810**		**n = 775**		**n = 20**		**n = 15**		
Age (years)									
Median	51.5		52		43		50.9		
Interquartile range	(44.7, 59.4)		(44.9, 59.7)		(38.3, 49.4)		(42.5, 56.2)		<0.001
European Ancestry, n (%)[b]									
<25%	227	(28.0)	217	(28.0)	6	(30.0)	4	(26.7)	
25–50%	353	(43.6)	336	(43.4)	11	(55.0)	6	(40.0)	
51–75%	146	(18.0)	140	(18.1)	2	(10.0)	4	(26.7)	
76–100%	19	(2.3)	19	(2.5)	0	(0.0)	0	(0.0)	0.898
Breast cancer histology, n (%)[b]									
Ductal	499	(61.6)	473	(61.0)	15	(75.0)	11	(73.3)	
Lobular	99	(12.2)	96	(12.4)	0	(0.0)	3	(20.0)	
Ductal in situ	54	(6.7)	54	(7.0)	0	(0.0)	0	(0.0)	
Mixed	32	(4.0)	32	(4.1)	0	(0.0)	0	(0.0)	
Not classified	23	(2.8)	20	(2.6)	2	(10.0)	1	(6.7)	
Medullary	7	(0.9)	5	(0.6)	2	(10.0)	0	(0.0)	
Mucinous	4	(0.5)	4	(0.5)	0	(0.0)	0	(0.0)	
Lobular in situ	3	(0.4)	3	(0.4)	0	(0.0)	0	(0.0)	
Tubular/cribriform	3	(0.4)	3	(0.4)	0	(0.0)	0	(0.0)	
Papillary	3	(0.4)	3	(0.4)	0	(0.0)	0	(0.0)	
Apocrine	2	(0.2)	2	(0.3)	0	(0.0)	0	(0.0)	
Non-specified non-invasive	2	(0.2)	2	(0.3)	0	(0.0)	0	(0.0)	
Metaplastic	2	(0.2)	2	(0.3)	0	(0.0)	0	(0.0)	0.183
Stage, n (%)									
0	17	(2.1)	17	(2.2)	0	(0.0)	0	(0.0)	
I	87	(10.7)	82	(10.6)	5	(25.0)	0	(0.0)	

Characteristics	Total		Non carrier		BRCA 1		BRCA 2		P value[a]
n	**n = 810**		**n = 775**		**n = 20**		**n = 15**		
II	363	(44.8)	353	(45.5)	5	(25.0)	5	(33.3)	
III	178	(22.0)	168	(21.7)	3	(15.0)	7	(46.7)	
IV	15	(1.9)	15	(1.9)	0	(0.0)	0	(0.0)	
Non-classifiable	21	(2.6)	21	(2.7)	0	(0.0)	0	(0.0)	0.235
History of breast cancer in first degree, n (%)[c]									
No	752	(92.8)	722	(93.2)	17	(85.0)	13	(86.7)	
Yes	58	(7.2)	53	(6.8)	3	(15.0)	2	(13.3)	0.130
History of cancer in first degree, n (%)[b,c]									
No	552	(68.1)	535	(69.0)	9	(45.0)	8	(53.3)	
Yes	239	(29.5)	221	(28.5)	11	(55.0)	7	(46.7)	0.017

[a] Kruskal Wallis test for continuous variables, Fisher´s exact test for categorical variables.

[b] Percentages may not add up to 100% due to missing data.

[c] We considered parents and siblings as first degree relatives.

[d] Participants who did not know their number of siblings were excluded from the analysis.