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Significant clinical impact of recurrent *BRCA1* and *BRCA2* mutations in Mexico

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Abstract

Background—Frequent recurrent *BRCA1* and *BRCA2* gene (*BRCA*) mutations among Hispanics, including a large rearrangement Mexican founder mutation (*BRCA1* ex9-12del), suggest that an ancestry-informed *BRCA*-testing strategy could reduce disparities and promote cancer prevention by enabling economical screening for hereditary breast and ovarian cancer in Mexico.

Methods—In a multistage approach, 188 cancer cases unselected for family cancer history (92 ovarian cancer and 96 breast cancer) were screened for *BRCA* mutations using a Hispanic

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mutation panel (HISPANEL®) of 115 recurrent mutations in a multiplex assay (114 on a mass spectroscopy platform, and a PCR assay for the *BRCA1* ex9-12del mutation), followed by sequencing of all *BRCA* exons and adjacent intronic regions, and *BRCA1* multiplex ligation-dependent probe amplification assay (MLPA) for HISPANEL negative cases. *BRCA* mutation prevalence was calculated and correlated with histology and tumor receptor status, and HISPANEL sensitivity was estimated.

Results—*BRCA* mutations were detected in 28% (26/92) of ovarian cancer cases and 15% (14/96) of breast cancer cases overall and 27% (9/33) of triple negative breast cancer. Most breast cancer cases were diagnosed with locally advanced disease. The Mexican founder mutation (*BRCA1* ex9-12del) accounted for 35% of the *BRCA*-associated ovarian cancer cases and 29% of the *BRCA*-associated breast cancer cases. At 2% of the sequencing and MLPA cost, the HISPANEL detected 68% of all *BRCA* mutations.

Conclusion—In this study, we found a remarkably high prevalence of *BRCA* mutations among ovarian and breast cases not selected for family history, and *BRCA1* ex9-12del explained one third of the total. The remarkable frequency of *BRCA1* ex9-12del in Mexico City supports a nearby origin of this Mexican founder mutation and may constitute a regional public health problem. The HISPANEL presents a translational opportunity for cost-effective genetic testing to enable breast and ovarian cancer prevention.

Keywords

BRCA1; *BRCA2*; Genetics; Breast Cancer; Ovarian Cancer; Mexico; Hispanics; HISPANEL; Puebla

Introduction

Approximately 5% of breast cancer cases and 10–15% of ovarian cancer cases are attributable to germline *BRCA1* or *BRCA2* (*BRCA*) mutations among non-Hispanic white women.[1–3] However, a lack of access to clinical *BRCA* gene analysis in some countries like Mexico has limited the implementation of prevention efforts and the scope of comparative studies of genetic factors that influence breast and ovarian cancer risk within Hispanic populations. Breast cancer patients in Mexico have shown an earlier age at onset of disease (<50 years)[4–6] and a high prevalence of triple negative breast cancer,[5] both features suggestive of hereditary etiology and the possibility that deleterious *BRCA* mutations may account for a higher proportion of breast cancers in this population. Our studies demonstrating that *BRCA* mutations are prevalent among high-risk Hispanics in the United States support this hypothesis.[7] A pattern of multiple recurrent mutations was observed in a large study (n=746) of Mexican-Americans,[8] and this led to the development of an inexpensive Hispanic mutation panel (HISPANEL) assay as a screening strategy.

The purpose of this study was to use the HISPANEL and additional analyses to characterize the pattern and frequency of *BRCA* mutations in Mexican breast and ovarian cancer patients, unselected for family history, and to examine the association between *BRCA* mutations and breast/ovarian cancer phenotypes.

Materials & Methods

A blood sample was obtained after written informed consent from participants in two IRB-approved prospective clinical trials: one designed to assess response to cisplatinum in newly diagnosed advanced ovarian cancer patients between January 2008 and December 2012, and the other was a neoadjuvant treatment trial for patients with triple negative breast cancer or hormone receptor positive cases < 50 years old, between January 2005 and March 2008. None of the cases were selected for family cancer history. Histology was analyzed in ovarian cancer cases, and tumor receptor status was analyzed in breast cancer cases. The participants' age at diagnosis and state of origin in Mexico were obtained, as was any family history of breast or ovarian cancer that was recorded in the medical record. DNA was extracted from each sample. A 114 *BRCA* mutation panel (HISPANEL) was developed based on our data from U.S. Hispanics,[7, 8] other published data on *BRCA* mutations among Spanish, Hispanic or South American populations,[9–16] and entries citing Hispanic ancestry in the Breast Cancer Information Core (http://research.nhgri.nih.gov/projects/bic/Member/index.shtml). The assay was designed to detect insertions/deletions and point mutations on the Sequenom® (San Diego, CA 92121) MassARRAY platform (MALDI-TOF MS). Mutation positive samples cluster on the center axis of the Call Cluster Plot, while wild-type samples cluster at the corners. Quality control criteria were developed, including a requirement that >97% of the specified loci provided an unambiguous reading. Comprised of 5 multiplex assays and run in duplicate, the HISPANEL has a capacity of 154 samples per run, and robotics is used to load samples on the SpectroCHIP. DNA extraction, amplification and HISPANEL analysis can be completed within 72 hours from sample collection (data not shown). All samples were analyzed by PCR for the presence of the *BRCA1* ex9-12del Mexican founder mutation, as described.[17]

In addition, complete pyrosequencing of all *BRCA1* and *BRCA2* translated exons and adjacent intronic regions was performed on all breast cancer cases and all HISPANEL-negative ovarian cancer cases using the *BRCA* MASTR Dx kit from Multiplicom (Belgium) on the Roche 454 GS Junior. Finally, all HISPANEL-negative and sequencing-negative cases were analyzed for large deletions/duplications in *BRCA1* by multiplex ligation-dependent probe amplification (MLPA) (MRC-Holland, Amsterdam).

Results

The sample consisted of 92 ovarian cancer and 96 breast cancer cases from the Instituto Nacional de Cancerologia (INCan). The mean age of diagnosis of ovarian cancer was 53 years (range 23 to 83 years) and of breast cancer was 40 years (range 26 to 83) (Table 1). At least 67% of breast cancer cases were diagnosed with locally advanced disease (stage III). Most cases (30%) originated in the Distrito Federal (DF) or nearby regional states (92% in Central States, including the DF). A family history of breast or ovarian cancer was reported in the medical record in less than 10% of cases.

Overall, a *BRCA* mutation was detected in 21% (40/188) of the cases (Table 2). *BRCA* mutations were detected in 28% (26/92) of ovarian cancer cases and 15% (14/96) of breast cancer cases. Representing 33% (13/40) of *BRCA* mutations overall (35% and 29% for

ovarian and breast cancer, respectively), the Mexican founder mutation *BRCA1* ex9-12del was detected in 7% (13/188) of these unselected breast and ovarian cancer patients.

Papillary serous carcinoma (n=49) was the most common ovarian cancer histology and had the highest prevalence (31%) of *BRCA* mutations, as shown in Table 3. None of the 3 cases with unknown histology had a *BRCA* mutation. The majority of mutations were *BRCA1* (88%) and just three (12%) were *BRCA2*. *BRCA1* ex9-12del accounted for 9 of 26 (35%) *BRCA*-associated ovarian cancers. Including the 5 *BRCA1* mutations detected by MLPA, 14/26 (54%) mutations detected in the ovarian cancer cases were large rearrangements, not detectable by sequencing. Most breast cancer cases, (88/96; 92%) were younger than 50 years old, and 11/88 (13%) cases harbored a *BRCA* mutation (8 *BRCA1* mutations and 3 *BRCA2* mutations). Estrogen receptor/progesterone receptor/Her2 *neu*-negative breast cancer (triple negative breast cancer) represented 33/96 (34%) of the breast cancer cases, and 9/33 (27%) carried a *BRCA1* mutation (Table 4). *BRCA1* ex9-12del accounted for 3/9 (33%) *BRCA*-associated triple negative breast cancers.

The HISPANEL detected 77% (27/35) of *BRCA* mutations compared to sequencing, and 68% overall (including the 5 additional large rearrangement mutations detected by MLPA among the ovarian cancer cases).

Discussion

Few studies have assessed the prevalence of *BRCA* mutations among Mexican cancer patients, and all included a limited number of high-risk cases.[18–20] The current study demonstrates a remarkably high prevalence of *BRCA* mutations among breast and ovarian cancer cases not selected for family history (15% and 28%, respectively) in Mexico, which is higher than expected compared to previous data obtained from a population-based breast cancer registry series in the U.S., where the *BRCA1* prevalence was 3.5% among Hispanics (n=393) aged <65, and 8.9% for patients <35 years.[21] Only our recently published high-risk clinic-based population (n=746) study had a higher prevalence (25%).[8]

Similarly, our observation of *BRCA* mutations in 28% of the ovarian cancer cases not selected for family history is much greater than the 18% prevalence reported for a series of 360 unselected largely Caucasian ovarian cancer cases from the University of Washington, Seattle,[22] or the 13% observed in an Ontario population-based study.[1] Similar to other reports, papillary serous carcinoma was the most common ovarian cancer histology associated with *BRCA* mutations.[23]

BRCA mutations accounted for 13% of the breast cancers < 50 years in our study, which represented 92% of the cases. This is particularly relevant in Mexico where the mean age of breast cancer diagnosis is 50 years.[24, 25] Moreover, 23% of incident breast cancer cases present at an age younger than 45 years,[26] which is the threshold for recommending *BRCA* testing in the National Comprehensive Cancer Center Network Guidelines.[27]

We found that a higher proportion (27%) of triple negative breast cancer patients carried a *BRCA1* mutation than previous reports (11–20%).[28–30] In a highly selected series of hereditary cancer clinic patients, *BRCA1* prevalence was 20% among Hispanic triple

negative breast cancer patients.[31] The observed prevalence of *BRCA* mutations in this study may explain in part the higher proportion of triple negative cancer in Mexican patients compared to Caucasians.[5]

It is noteworthy that 67% of the breast cancer patients in our study had locally advanced breast cancer at diagnosis. While the prevalence of younger triple negative breast cancer cases in our study might have influenced the stage distribution, it has been previously reported that 56 to 80% of breast cancer cases present at advanced stages in Mexico.[32] The high prevalence of *BRCA*-associated disease has significant clinical implications. It is conceivable that the use of genetic cancer risk assessment with *BRCA* testing and application of risk-appropriate screening and prevention interventions could result in shift toward more limited stage disease and reduced breast and ovarian cancer incidence. There was a remarkable prevalence of *BRCA1* ex9-12del, which constituted 29% and 35% of all mutations for breast cancer and ovarian cancer, respectively, in this Mexico City regional sample. If the founder mutation is omitted, the prevalence of *BRCA* mutations in the breast and ovarian cancer cases was 10% and 18%, respectively, which are closer to prevalence estimates for *BRCA*-associated disease in other populations.[1, 22] This Mexican founder mutation (*BRCA1* ex9-12del) comprised ~10% of *BRCA1* mutations in a Mexican American sample.[8, 17] An independent report from a commercial vendor in North America noted that it comprises 1/3 of all large rearrangements in Latin American/Caribbean patients.[33]

BRCA1 ex9-12del is clinically significant and one of the most frequent population-specific large rearrangement mutations in the world and is not detectable by standard *BRCA* gene sequencing approaches. We have speculated that the Mexican founder mutation, estimated to have first arisen 74 generations or 1,480 years ago (95% CI, 920 to 2,260 years),[8] may have originated around Puebla. Puebla is in close proximity to the study center in Mexico City, which serves as the main referral center from patients from Central and Southern Mexico. Supporting this hypothesis is our observation that the Mexican founder mutation represented 33% of the *BRCA*-positive cases at the study center, and just 10% of the *BRCA1* mutations among a heterogeneous Mexican-American population.[8] We believe this mutation is a significant public health issue and that Mexican high-risk patients should be screened for its presence. Interestingly, the Jewish founder mutation, *BRCA1* 185delAG, was only detected once (2.5% of *BRCA* mutations) in the current study, compared to 10% of all *BRCA* mutations detected in the Mexican-American high-risk clinic study.[8] Since Mexico is a setting with wide variability in dietary intake, lifestyle and genetic admixture (large contrast between northern and southern parts of Mexico),[34, 35] further studies of the genetic epidemiology of breast cancer in different areas of Mexico are needed. Cost has been a barrier to genetic cancer risk assessment access among Hispanics, with access particularly limited in low- and middle-income countries such as Mexico. The observation of recurrent *BRCA* mutations among Hispanics led to the development of the HISPANEL as an economical *BRCA* screening platform. The HISPANEL detected 27 of 40 *BRCA* mutations (68%) at a cost of ~$25 USD/assay; in contrast with pyrosequencing, which detected an additional 8 mutations (Table 2) at a cost of $1,500/assay, and MLPA with the identification of 5 additional mutations at a cost of $50/assay. Thus, the HISPANEL detected 27 mutations for $4,700, while full sequencing cost $241,500 to detect an additional 8 mutations. We

demonstrate here that the HISPANEL, which includes a specific assay for the Mexican founder mutation, is 77% sensitive compared to full sequencing (68% compared to sequencing and *BRCA1* large rearrangement screening). Although this level of sensitivity is less than optimal for a screening tool, this is by far better than not having access at all for genetic testing, since at the moment testing is not available or covered within the public health system in Mexico, which provides care to more than 85% of the population. Unless and until next generation sequencing(NGS)-mediated clinical grade testing, with complete sequencing and rearrangement studies, costs substantially less than the currently cheapest available commercial testing (~$900), it will not be affordable in the context of competing priorities and needs in the Mexican health care system. We are optimistic that the rapidly evolving NGS technologies will drive the price low enough to obviate even the economical HISPANEL. However, as stated by Voltaire, "The perfect is the enemy of the good,"[36] so in the interval, implementing testing with the HISPANEL has the potential to enable the prevention of many cancers and save the lives of women in these families now, while catalyzing the integration of genetic cancer risk assessment in clinical practice in Mexico. We believe the benefits of its implementation in current practice will rapidly enable preventive and therapeutic interventions for patients and families. The patients identified as *BRCA* mutation carriers in the current study and in other ongoing projects will receive risk-appropriate follow-up care, including risk reduction salpingo-oophorectomies (RRSO) for cancer patients who are identified to have high-risk for additional primary breast and ovarian cancer diagnoses. RRSO is a relatively economical procedure[37] that has been documented to decrease new primary breast and ovarian cancer risk, and decrease all cause mortality.[38, 39]

Limitations of the current study include the possibility of potential ascertainment bias based on the fact that INCan is a National referral center, though 92% of the cases resided in the central states, including the DF. Median age of breast cancer diagnosis in our study was 40 years, in comparison with the general age of diagnosis among Mexican women (50 years), which may partially explain the mutation prevalence.[40] *BRCA2* large genomic rearrangement screening was not performed, so some mutations could have been missed. However, most studies indicate that >80% of all large genomic rearrangements are in *BRCA1*, given the high concentration of Alu sequences.[33, 41, 42] Another limitation is that family history was abstracted from the medical record in this study, and this is generally an inadequate source of family history information, typical of a non-genetic service consultation.[2, 43] Lack of detailed family history did not permit the application of mutation probability models. However, the high prevalence of *BRCA* mutations found in this study, regardless of family history, suggests that genetic testing should be guided more by early age at onset and/or cancer type (e.g., triple negative breast cancer or ovarian cancer) rather than by family history, and that risk assessment should be established for other identified risk factors. The frequency of *BRCA* mutations might be even higher among high-risk populations selected for family history of cancer.

Conclusion

In this study, we found a remarkably high prevalence (28%) of *BRCA* mutations among ovarian and breast cases not selected for family history, and the *BRCA1* ex9-12del Mexican founder mutation explained one third of the total. Both in the US Hispanic populations and

in Mexico, the Mexican founder mutation prevalence makes it a significant public health issue.

The HISPANEL, which includes recurrent *BRCA* mutations found in women of Hispanic ancestry, appears to have high sensitivity and thus is likely to have clinical utility while dramatically reducing overall genotyping cost among underserved women in Mexico and presents an opportunity for cost-effective genetic testing strategies to enable breast and ovarian cancer prevention. Further studies are needed to validate the sensitivity of the HISPANEL in different areas in Mexico and among U.S. Hispanics, and to explore the geographic population distribution of *BRCA1* ex9-12del.

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Table 1

Demographics

Breast Cancer n=96		Ovarian Cancer n=92	
Age			
Range	26–63	Range	23–83
Mean	40	Mean	54
Stage			
I	1%	I	0%
II	27%	II	0%
III	67%	III	53%
IV	2%	IV	42%
Unknown	3%	Unknown	5%
Histology			
Ductal	81%	Serous	53%
Lobular	12%	Adenocarcinoma-nos	25%
Ductal/Lobular	3%	Mucinous	1%
Other	2%	Carcinosarcoma	1%
Unknown	1%	Mixed/Other	16%
Cancer Subtype			
Hormone receptor+, HER2-	26%	-	-
HER2 positive	39%	-	-
Triple negative	34%	-	-
Unknown	1%	-	-
State of Origin			
Chiapas	2%	Chiapas	3%
Distrito Federal	39%	Distrito Federal	21%
Guanajuato	25%	Guanajuato	1%
Guerrero	1%	Guerrero	0%
Hidalgo	10%	Hidalgo	10%
Jalisco	0%	Jalisco	1%

Breast Cancer n=96			Ovarian Cancer n=92		
Michoacán		2%	Michoacán		5%
Morelos		7%	Morelos		7%
Oaxaca		3%	Oaxaca		1%
Puebla		1%	Puebla		9%
Queretaro		2%	Queretaro		0%
State of Mexico		1%	State of Mexico		3%
Tlaxcala		4%	Tlaxcala		28%
Veracruz		0%	Veracruz		1%
Zacatecas		1%	Zacatecas		3%
Unknown		1%	Unknown		1%
Region in Mexico					
Central		92%	Central		85%
North		1%	North		3%
South		6%	South		5%
Unknown		1%	Unknown		1%
Family History					
Breast cancer	Yes	6%	Breast cancer	Yes	7%
	No	94%		No	83%
Ovarian cancer	Yes	1%	Ovarian cancer	Yes	0%
	No	99%		No	90%
Other cancer	Yes	1%	Other cancer	Yes	2%
	No	99%		No	88%

Table 2

BRCA mutations detected among 188 Ovarian/Breast Cancer Patients.

Mutation		Ovarian cancer (n=92)	Breast cancer (n=96)	Total (n=188)
BRCA1 (85%)	ex9-12del	9 (35%)	4 (29%)	13 (33%)
	IVS5+1G>A	2	0	2
	3977del4*	0	1	1
	R1699W*	1	0	1
	803delA*	1	0	1
	70insAG*	1	0	1
	A1708E	1	1	2
	4184del4	1	0	1
	R71G	1	0	1
	917delTT	0	1	1
	943ins10	1	0	1
	2925del4	0	1	1
	3878delTA	0	1	1
	185delAG	0	1	1
	R1443X	0	1	1
BRCA1 Large Rearrangements (*BRCA1*)**	ex8-9dup	2	0	2
	ex18-19del	2	0	2
	ex8-10del	1	0	1
BRCA2 (15%)	9463delG	1	0	1
	6244delG*	1	0	1
	2900delCT*	1	0	1
	6714del4*	0	1	1
	1803insA*	0	1	1
	6252insG	0	1	1
Total		26 (28%)	14 (15%)	40 (21%)

*Mutations detected by pyrosequencing;

**detected by MLPA

Table 3

Frequency of *BRCA* mutations in patients with ovarian cancer by tumor histology.

Category Tumor Histology	No. *BRCA* Positive			Total No. of cases*
	BRCA1	***BRCA2***	**Total**	
Serous	15	0	15	49
Carcinosarcoma	0	1	1	1
Adenocarcinoma-nos	4	1	5	23
Mucinous	1	0	1	1
Mixed/Other	3	1	4	15
All tumors	23	3	26	89

*Excluded 3 cases with unknown tumor histology

Table 4

Frequency of *BRCA* gene mutations according to triple negative breast cancer (TNBC) status.

ER/PR/Her2 TNBC vs. non (any+)	No. (%) *BRCA* positive			Total No. of cases*
	BRCA1	*BRCA2*	Total	
TNBC cases	9	0	9 (27%)	33
Non-TNBC	2	3	5 (8%)	62
All cases	11	3	14 (15%)	95

ER: estrogen receptor, PR: progesterone receptor, TNBC: triple negative breast cancer.

* Excluded one case with unknown tumor receptor status.