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Founder and Recurrent Mutations in *BRCA1* and *BRCA2* Genes in Latin American Countries: State of the Art and Literature Review

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Key Words. Breast cancer • *BRCA1* • *BRCA2* • Latin America • Hereditary cancer • Hispanics

Abstract

Background. Numerous epidemiological factors affect the probability of developing breast or ovarian cancer, but no predictor is as determinant as inheriting a mutation in *BRCA1* or *BRCA2*. The concept of the founder effect explains the reduced genetic variability in some populations, according to the theory that new populations can be formed from a reduced number of individuals, so the new population would carry only a small fraction of the genetic variability of the original population. The main purpose of this review is to provide an update on the state of the art in founder mutations and some recurrent mutations that have recently been described in Latin America.

Methods. A literature search was performed in the electronic databases of PUBMED, EMBASE, LILACS, and BIREME using the terms *BRCA1*, *BRCA2*, founder mutation, Latin American population, and Hispanic. Sixty-two papers were identified, of which 38 were considered relevant for this review. Each result is shown per country.

Results. In Latin America, clear founder effects have been reported in Mexico (*BRCA1* del exons 9–12), Brazil (*BRCA1* 5382insC and *BRCA2* c.156_157insAlu), and Colombia (*BRCA1* 3450del4, A1708E, and *BRCA2* 3034del4) and in Latinas residing in Southern California (*BRCA1* 185delAG, IVS5+1G>A, S955x, and R1443x). Of these, mutation *BRCA1* 3450del4 has also been reported in Brazil and Chile, whereas mutation *BRCA2* 3034del4 has been reported in Argentina and Peru. These data support the idea that although most Hispanic populations are the result of a mixture between Europeans, Africans, and Amerindians, the relative proportion of each genetic component varies throughout the Hispanic populations, making it necessary to identify the mutations characteristic of each population to generate mutation profiles adjusted to each one of them.

Conclusion. In Latin American countries, and even among regions of the same country, there is great heterogeneity of ancestors. Therefore, Latinas should not be analyzed like other population groups without taking into account their genetic ancestry. The presence of founder mutations in specific population groups represents a cost-effective analysis. The importance of determining the founder mutations lies mainly in the decrease in costs. If we manage to decrease costs, screenings could be offered more widely and cover a larger number of women. ***The Oncologist*** 2016;21:832–839

Implications for Practice: Hispanic and African-American populations are four to five times less likely than other populations worldwide to receive screening for *BRCA* mutations, a main reason being the high costs of these tools. The present study seeks to identify the prevalent mutations and the founder effect in the *BRCA* gene in the Hispanic population to address specific panels for this population group in the future and develop strategies for population screening.

Introduction

Although the genetic predisposition to cancer is considered mostly heterogeneous, founder mutations in genes with high penetrance have been identified in certain population groups through the observation of hundreds of different alterations in the genomic sequence that cause disease. As a consequence of their location in genomic regions with linkage disequilibrium, these mutations are segregated as a unit. Haplotype analysis gives the possibility to discriminate between a variant originating from a single mutation event (founder mutation) and a variant that results from an independent mutational event. A recurrent mutation is the first indication that we are facing a founder mutation, but not all carriers of recurrent pathogenic variants are expected to share a common ancestor, which means that not all recurrent mutations are founder

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mutations. Thus, the analysis of haplotypes in families with the same mutation is recommended to determine whether the high frequency of a given number of alleles has migrated from one linked geographic area to another or whether the alleles originated independently [1]. The concept of founder effects was described by Ernst Mayr to explain the reduced genetic variability in some populations through the theory that new populations can be formed from a reduced group of individuals, so the new population would carry only a small fraction of the genetic variability of the original population. Founder alleles represent most mutations in that population, with very little probability of other nonfounder alleles explaining the same disease [2]. For this reason, these founder mutations are inherited and are frequently restricted to one or few populations or geographical regions that fulfill certain characteristics.

Almost 20 years have passed since the genes responsible for increased susceptibility to breast cancer and ovarian family cancer were characterized. This remains the most significant discovery for the genetics of hereditary cancer in humans, in part demonstrated by the fact that almost all ethical-legal debates regarding patents are focused on *BRCA1* and *BRCA2* genes, with few cases of debate about other genes for cancer susceptibility [3, 4]. A woman with a mutation in *BRCA1/2* has a risk of up to 87% of developing breast cancer in her lifetime and up to 50% of developing ovarian cancer, but the risk can vary according to the mutation, country of residence, and family history [5, 6]. Additionally, mutations in the *BRCA1/2* genes confer a higher risk for the development of a second primary cancer compared with non-mutation carriers, particularly among women who are diagnosed young ($\leq$45 years) [7]. Therefore, the classification of highly penetrant mutations in these genes has significant implications for both the affected women and their family members.

Several epidemiologic factors affect the probability of developing breast cancer or ovarian cancer, but no predictor is as determinant as inheriting a mutation in *BRCA1/2*. Therefore, the analysis of these two genes in particular has gained great acceptance worldwide, not only because of the increased availability of prevention options in healthy women bearing a mutation, but also because of the development of new and personalized cancer therapies [8, 9]. However, genetic tests remain expensive and inaccessible for most women in developing countries. Analysis of the *BRCA1/2* genes has been available in North America and Western Europe since 1996. In recent years, Eastern Europe and some Latin American countries have begun the introduction of genetic testing of *BRCA1/2* mutations, in part because of the presence of founder mutations [1, 10]. The presence of founder mutations, which explains reduced genetic variability in a gene or group of genes in a specific population, allows the probability of focusing on the analysis of them because of the very low possibility that other nonfounder alleles explain the same disease.

In Hispanic populations, a limited number of studies have focused on analysis of the distribution and prevalence of mutations in *BRCA1* and *BRCA2* genes (Fig. 1). However, founder mutations in these genes have been described in this population group. The main purpose of this review is to provide an update on the state of founder mutations (variants originated from a single mutation event) and some recurrent mutations (variants that have not been proved to share a common ancestor) that have been recently described in Latin America.

Argentina

Only the three mutations characteristic of the Ashkenazi Jewish population have been reported as founder mutations in Argentina. Solano et al. [11] performed a sequencing analysis in 134 patients with breast and ovarian cancer, selected by diagnosis age or family history. The study included 40 Ashkenazi Jews who were analyzed only for the three founder mutations characteristic of this population (c.66_67delAG and c.5263insC in *BRCA1* and c.5946delT in *BRCA2*), observing a high recurrence of these mutations, with a mutation frequency of 42.5% (17/40). The most recurrent founder mutation was *BRCA2* 6174delT (8/17), followed by *BRCA1* 185delAG (7/17). A less recurrent mutation was *BRCA1* 5382insC (2/17). In the second population group (non-Ashkenazi) (57/134), 24 deleterious mutations were identified; 16 in *BRCA1* and 8 in *BRCA2*, but none of them were identified in more than 1 nonrelated patient. However, among the nonrecurrent mutations identified in *BRCA2*, the 3034del4 mutation had been previously reported as founder in a Colombian population by Torres et al. [12].

Brazil

Two founder mutations have been reported in Brazil: *BRCA1* 5382insC, which is characteristic of Ashkenazi Jews, and *BRCA2* c.156_157insAlu. The *BRCA1* 5382insC mutation, the second most recurrent mutation in *BRCA1* according to the Breast Cancer Information Core (BIC) (http://research.nhgri.nih.gov/bic/), with high prevalence in eastern and central Europe, was also reported in seven nonrelated Brazilian patients with hereditary breast cancer [13], in whom haplotype analysis revealed a founder effect [14]. The genomic rearrangement *BRCA2* c.156_157insAlu (consisting of the insertion of an Alu sequence in exon 3 of gene *BRCA2*) was identified as a founder mutation by Machado et al. [15] in 17/210 (8%) Portuguese families with a high risk of developing breast or ovarian cancer. *BRCA1/2* were fully screened for mutations (by polymerase chain reaction [PCR], reverse-transcriptase PCR, and direct sequencing) in 168 Brazilian women with breast cancer who reported having a strong history of familial cancer and having lived in Brazil for at least 3 generations. The *BRCA2* c.156_157insAlu mutation was identified in three nonrelated subjects. Using genotypification, a common haplotype was observed for two of the markers used (D13S260 and D13S171), with sizes comparable to those described in Portuguese families. However, the size of the alleles for marker D13S1246 agreed in only two of the three families analyzed, suggesting that this haplotype could be present in only a subgroup of families as the result of two probable recombination events that occurred for this marker [15]. In fact, this mutation is highly prevalent in the center of Portugal and in Portuguese individuals established in the south of Brazil [16].

Recurring mutations have also been reported in Brazil. Esteves et al. [17] analyzed 612 Brazilian patients from the five geographical regions of the country (central-western, northeast, north, southeast, and south) with medium and high risk of developing breast or ovarian cancer. In total, 21/612 (3.4%) deleterious mutations were identified by sequencing, 18 (2.9%) in *BRCA1* and 3 (0.5%) in *BRCA2*. Of the mutations identified in *BRCA1*, four were recurrent (ins6Kb, 5382insC, 326+delGinsCC, and 185delAG). However, haplotype analyses

Figure 1. Countries with studies of founder or recurrent mutations in Latin America reported to date.

were not performed in the carriers of mutations ins6Kb or 2156delGinsCC; thus, the founder effect could not be confirmed in these patients. Gomes et al. [14] performed a screening of *BRCA1/2* in 402 women diagnosed with breast cancer, who were not selected because of family background (ethnicity or family history of cancer). They used the protein truncation test (PTT), fluorescent multiplex denaturing gradient gel electrophoresis (DGGE), and denaturing high performance liquid chromatography (DHPLC), and all variants identified were confirmed by direct DNA sequencing. In total, nine deleterious mutations were identified, including three in the *BRCA2* gene. Of these, two corresponded to mutation 6633del5 reported in two nonrelated women. Recently, Felix et al. [18] reported two new recurrent mutations in gene *BRCA1* identified in 106 patients from the north of Brazil, mutation c.211A>G (p.R71G) followed by mutation 3450del4, which was previously reported as a founder in the Colombian population by Torres et al. [12].

Chile

Six recurrent mutations (identified using single-strand conformation polymorphism gel electrophoresis [SSCP] and sequencing) have been described in the Chilean population by Jara et al. [19]: three in *BRCA1* (187delAG, 2605delTT, and 3450del4) and three in *BRCA2* (4969insTG, 5374del4, and 6503delTT). Among these, *BRCA1* 3450del4 and *BRCA2* 6503delTT have also been reported, the first as a founder and the second as recurrent in the Colombian population, by Torres et al. [12]. In a second study in the Chilean population performed by Gallardo et al. [20], a group of 54 families with high risk of breast/ovarian cancer were evaluated (using SSCP, heteroduplex analysis, PTT, and sequencing analysis),

identifying two mutations not previously reported: *BRCA1* c.308_309insA and *BRCA2* c.4970_4971insTG. However, none of them were found recurrently; thus, the founder effect could not be established.

Colombia

Torres et al. [12] performed an analysis of mutations in the *BRCA1/2* genes (using a range of techniques, including DHPLC, SSCP, and PTT, followed by direct DNA sequencing). They included 53 patients with breast cancer selected by family history and reported the identification of 3 founder mutations: 2 in *BRCA1* (A1708E and 3450del4) and 1 in *BRCA2* (3034del4). Using haplotype analysis, it was concluded that each one of these mutations originated from a common ancestor. Recently, Hernández et al. [21] established the mutation frequency in the *BRCA1/2* genes with Hispanel (115 Hispanic mutations panel), in patients with breast cancer not selected by family history from a region of Medellín. In total, 3 (1.2%) deleterious mutations were identified in 244 patients analyzed, of which 2 (67%) corresponded to mutations previously reported as founders in gene *BRCA1* by Torres et al. [12] (3450del4 in exon 11 and A1708E in exon 18). Rodríguez et al. [22] performed a *BRCA1/2* study, also using Hispanel, in 96 women diagnosed with ovarian cancer. In total, 15 (16.6%) deleterious mutations were identified; 13 in *BRCA1* and 2 in *BRCA2*. The founder mutation 3450del4 was observed in 11 of the 13 women identified with a mutation in *BRCA1*, with the conclusion that approximately 84% of the cases with ovarian cancer in the region of Bogota are attributable to a single founder mutation. Additionally, founder mutation *BRCA1* A1708E was identified in this cohort, but not in a recurrent way.

Costa Rica

Gutiérrez Espeleta et al. [23] published the first study in a Costa Rican population of a group of 111 patients with diagnosis of breast cancer and family history of cancer. Only exon 10 of *BRCA1* and exons 10 and 11 of *BRCA2* (which covers approximately 65% of the coding region of both genes) were screened by PTT and sequencing. The three common mutations, *BRCA1* 185delAG and 5382insC and *BRCA2* 6174delT, which are most commonly seen in Ashkenazi Jews, were evaluated using a rapid multiplex method. In total, four mutations were identified, one in *BRCA1* (C3522T) and three in *BRCA2* (5531delTT, C5507G, and 6174delT), with a mutation frequency of 4.5%. Mutation *BRCA2*:5531delTT was identified in two nonrelated patients. The lack of haplotype analysis did not allow confirmation of the presence of a founder effect for this mutation.

Cuba

In the study performed by Rodriguez et al. [24], the entire coding sequence of *BRCA1* and *BRCA2* was screened using a combination of PTT, DGGE, and sequencing analysis. Additionally, all samples were screened for four common mutations, *BRCA1* 185delAG and 5382insC and the *BRCA2* 6174delT mutations common to Ashkenazi Jews and others of eastern European ancestry, in a cohort of 307 patients with breast cancer. In total, eight mutations were identified (2.6%): one in *BRCA1* and seven in *BRCA2*. Mutation c.3394C>T was observed in two nonrelated patients. However, according to the authors' conclusions, this mutation does not represent an example of a founder effect.

Mexico

In a recent study by Villarreal-Garza et al. [25] performed at the National Cancer Institute of Mexico, 188 patients not selected by family history (92 cases of ovarian cancer and 96 cases of breast cancer) were analyzed for the presence of deleterious mutations based on Hispanel. In total, 26 mutations were observed in 92 patients with ovarian cancer (28%) and 14 mutations in 96 patients with breast cancer (15%). Interestingly, the study found that 33% of the patients analyzed had the mutation *BRCA1* del exon 9–12, which represents a clear example of the founder effect in this population. Vidal-Millán et al. [26], in a group of 40 patients selected by family history and/or diagnostic age, reported a mutation rate of 5% (using DHPLC and sequencing), without the presence of recurrent mutations. Vaca-Paniagua et al. [27], in a group of 39 patients with family history of cancer (using massive parallel pyrosequencing), identified four deleterious mutations (10.2%), two in *BRCA1* (c.2805_2808delAGAT and c.3124_3133delAGCAATATTA) and two in *BRCA2* (c.2639_2640delTG and c.5114_5117delTAAA), but none was observed recurrently.

Peru

Identifying the prevalence of mutations in *BRCA1* and *BRCA2* genes in patients with breast cancer had not been performed in Peru until 2014, when Abugattas et al. [28] reported the first study there. The study included 266 women, not selected by age or family history, in which the panel of 115 Hispanic's mutations (Hispanel) in *BRCA1/2* genes was analyzed. In total, 13/114 (5%) deleterious mutations were identified: 11 in *BRCA1* and 2 in *BRCA2*. Mutation *BRCA1* 185delAG was the most prevalent, observed in 7 (54%) of the 13 mutation carriers, and is the most common founder mutation in the Ashkenazi Jewish population. It has also been reported in other population groups living in Mexico, Chile, and the Bahamas [19, 29, 30]. The frequency observed in Peru (54%) is the highest yet reported in nonselected populations in Latin America. Additionally, three of the carriers of this mutation were self-identified as descendants of indigenous people from South America. *BRCA1* 2080delA and mutation *BRCA2* 3034del4 were two other recurrent mutations, and each one was identified in two nonrelated women. The latter mutation was reported in Colombia as a founder mutation [12] and is also one of the most frequent mutations in Spain.

Uruguay

In the study performed by Delgado et al. [31], 42 families with at least 3 cases of female breast cancer or 2 cases and subcriteria (paternal transmission, ovarian cancer, bilateral breast cancer, male breast cancer, Ashkenazi Jewish ancestry) in the same lineage, at least 1 diagnosed before age 50, were screened for *BRCA* germline mutations. In total, seven different truncating mutations in seven families were identified, two in *BRCA1* (5583insT and 2687T>G) and five in *BRCA2* (4359ins6d, 5579insA, 3829insTdel35, 4088delA, and 1617delAG), but none were recurrent.

Venezuela

No founder mutations have been described in Venezuela to date. Lara et al. [32] evaluated 58 high-risk families (using SSCP and sequencing) and found a positive rate of 17.2%, including 6 patients with mutations in *BRCA1* (10.3%) and 4 in *BRCA2* (6.9%), but none were recurrent.

Guatemala, El Salvador, Honduras, Nicaragua, Panama, Bolivia, Ecuador, and Paraguay

There are no reports of population studies on mutations in *BRCA1* or *BRCA2* genes in these countries.

Materials and Methods

A literature search was performed in the electronic databases of PUBMED, EMBASE, LILACS (Latin American and Caribbean Health Sciences Literature), and BIREME using the terms *BRCA1*, *BRCA2*, founder mutation, Latin American population, and Hispanic. These words were crossed with each of the Latin American countries (e.g., Colombia, Mexico). The search was performed in Spanish, English, and Portuguese. In some cases, the research groups related with the subject were contacted by e-mail in search of preliminary data or more information.

A total of 62 papers were identified, 38 of which were selected because they were considered relevant for this review. Each result is shown per country.

Discussion

The term "Hispanic/Latino" refers to a diverse ethnic group inhabiting Latin America native from other parts of the world, originating from groups of people who migrated to that region of the continent. Hispanics/Latinos now have a complex population structure with significant genetic contributions from indigenous Americans and European populations [33] (mainly immigrants from the Iberian Peninsula and southern Europe), along with West African populations that came to the Americas in the transatlantic slave route [34, 35].

It has been observed that the risk of breast cancer in Latin women is associated with a larger proportion of European ancestry. This association was demonstrated in a study performed by Fejerman et al. [36], in which a greater proportion of European ancestry in Mexican women residing in Mexico was associated with an increased risk of breast cancer. When the percentages of European ancestry were compared, it was observed that the risk considerably increased in those with higher percentages. Women who were 51%–75% and 76%–100% European had odds ratios of 1.35 (95% confidence interval [CI], 0.96–1.91) and 2.44 (95% CI, 0.94–6.35), respectively. For every increase of 25 percentage points of European ancestry, an increase of 20% was observed in the risk of breast cancer (95% CI, 1.03–1.41; $p = .019$).

Precarious socioeconomic conditions, such as low income, lack of health system coverage, and limited access to counseling and genetic testing, and certain ethnic/racial groups are associated in general with a significant increase in cancer incidence. Breast cancer is the most commonly diagnosed cancer in Hispanic women and the main cause of death by cancer. Although the incidence of breast cancer is lower in Hispanic women than in non-Hispanic white women, prevalence studies of mutations in the *BRCA1* and *BRCA2* genes suggest that these mutations can explain a greater proportion of breast cancer than in other populations [37].

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The large sizes of the *BRCA1/2* genes, together with the great variety of described mutations along them, means that analysis—at least in Latin America and other regions of the world—remains expensive and complex and therefore inaccessible to a high proportion of the women at risk. The presence of founder mutations (reduced genetic variability explaining a disease) in a population provides the opportunity to design economically feasible tests with the probability of increasing the detection rate in the population group with which they are identified [38].

The best example of the founder effect is the one observed in the Ashkenazi Jewish population, in which the genetic predisposition for ovarian or breast cancer is much higher than in the general population because of the presence of three founder mutations. Mutation *BRCA1* 185delAG has been found with a 1% frequency and contributes to 16%–20% of the cases of breast cancer diagnosed before age 50. Mutations *BRCA1* 5382insC and *BRCA2* 6174delT have been identified at frequencies of 0.13% and 1.5%, respectively, in this population. The overall rate of these three founder mutations is 2.6% (1/40) compared with the rate of 0.2% (1/500) of mutation carriers in *BRCA1/2* in the general population [1]. Interestingly, these three founder mutations represent 79% of all BRCA1/2 mutations found in the Jewish Ashkenazi population [39].

Founder mutations are not always specific to a certain population. Mutation *BRCA1* 5382insC, for example, is the second most recurrent mutation reported in the *BRCA1* gene according to the BIC and has been identified in several countries, such as Russia, Poland, the Czech Republic, Lithuania, Hungary, Greece, Germany, France, Italy, Canada, and Spain, suggesting that this mutation could have existed before the Jewish diaspora [2]. In Latin America, the same mutation has been identified as a founder in Argentina and Brazil, so it is believed that this mutation likely originated in the Baltic zone at least 38 generations ago, with a gradual descent from East to West, according to haplotype analyses indicating a single founder effect for this mutation that occurred for both Europe and North America [40]. Mutation *BRCA1* 185delAG has been reported as a founder in Argentinian people, whereas it has also been reported as recurrent in Brazil, Chile, and recently Peru and Mexico. Mutation *BRCA2* 6174delT is also a founder in Irish people [41] and has been reported as a founder in Argentinian people.

Founder mutations in *BRCA1/2* have been identified in countries such as Norway [42], Finland [43], Sweden [44], France [45], Holland [46], Italy [47], Canada [48], Pakistan [49], Japan [50], China [51], Malaysia [52], and the Philippines [53]. This has led to a more cost-effective approach in these

Table 1. Recurrent and founder mutations in *BRCA1* and *BRCA2* genes described in Latin America

	Recurrent mutations		Founder mutations			
Country	***BRCA1***	***BRCA2***	***BRCA1***	***BRCA2***	**Mutation detection method**	**Reference**
Argentina		3034del4	185delAG, 5382insC	6174delT	Direct DNA sequencing	Solano et al., 2012 [11]
Brazil	185delAG, ins6Kb, 3450del4, 2156delGinsCC, and c.211A>G	6633del5	5382insC	c.156_157insAlu	PCR, reverse-transcriptase PCR, PTT, DGGE, and DHPLC; all variants identified were confirmed by direct DNA sequencing	Da Costa et al., 2008 [13]; Gomes et al., 2007 [14]; Machado et al., 2007 [15]; Esteves et al., 2009 [17]; Felix et al., 2014 [18]
Chile	185delAG, 2605delTT, and 3450del4	4969insTG, 5374del4, and 6503delTT			SSCP; all variants identified were confirmed by direct DNA sequencing	Jara et al., 2006 [19]
Colombia		6076del4 and 6503delTT	A1708E and 3450del4	3034del4	DHPLC, SSCP, and PTT, followed by DNA sequencing analysis	Torres et al., 2007 [12]
Costa Rica		5531delTT			Only exon 10 of BRCA1 and exons 10 and 11 of BRCA2 were screened by PTT; all mutations were confirmed by direct sequencing	Gutiérrez Espeleta et al., 2012 [23]
Cuba		c.3394C>T			DGGE and PTT followed by DNA sequencing analysis	Rodríguez et al., 2008 [24]
Mexico			del exon 9–12		Hispanel screening of 115 recurrent BRCA1/2 Hispanic mutations; all mutations were confirmed by direct sequencing	Villarreal-Garza et al., 2015 [25]
Peru	2080delA	3034del4	185delAG		Hispanel screening and direct DNA sequencing	Abugattas et al. 2015 [28]

Abbreviations: DGGE, denaturing gradient gel electrophoresis; DHPLC, denaturing high-performance liquid chromatograpy; PCR, polymerase chain reactin; PTT, protein truncation test; SSCP, single-strand conformation polymorphism gel electrophoresis.

populations, where the initial analysis of these genes focuses on the most recurrent mutations [54]. The complete evaluation of *BRCA1* and *BRCA2* is necessary only in cases where there is strong family history and none of the corresponding founder mutations is identified. This approach requires previous knowledge of the prevalence of the mutations in the population of interest.

Clear founder effects have been reported (Table 1) in Mexico (*BRCA1* del exons 9–12), Brazil (*BRCA1* 5382insC and *BRCA2* c.156_157insAlu), and Colombia (*BRCA1* 3450del4, *BRCA1* A1708E, and *BRCA2* 3034del4) and in Latinas residing in Southern California (*BRCA1* 185delAG, IVS5+1G>A, S955x, and R1443x) [53]. Of these, mutation *BRCA1* 3450del4 has also been reported in Brazil and Chile, whereas mutation *BRCA2* 3034del4 has been reported in Argentina and Peru. These data imply that although Hispanic populations share common genetic ancestry components (European, African, and Amerindian), they are genetically heterogeneous.

Therefore, Latinas should not be analyzed as a whole, and it becomes necessary to identify the mutations characteristic of each population and the founder effects in each region to develop local cost-effective mutation screening guidelines.

In some Latin American countries, a wide spectrum of mutations in both genes has been identified, along with some founder or recurrent mutations. In these cases, it is necessary to analyze whether it is really more cost beneficial to first study the recurrent/founder mutations and then perform a complete study of both genes in the negative cases. Unfortunately, there are hardly any studies on the prevalence of *BRCA1/2* in different countries to determine the best strategy in the clinical setting.

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Germinal mutations in the *BRCA1/2* genes significantly contribute to the development of breast and/or ovarian cancer, but the penetrance (mutation-specific risk) can vary among mutations. In Latin America, there are no systematic studies of the penetrance of the *BRCA* mutations identified. It would be very interesting to determine the genotype/phenotype relationships of the founder/recurrent mutations described up to this date.

Some of the studies mentioned report very low mutation rates in the *BRCA1/2* genes, owing in part to the limited number of mutations analyzed in these genes. Additionally, the use of indirect mutation detection methods (SSCP, conformation-sensitive gel electrophoresis [CSGE], PTT, and

DHPLC) [55] could restrict the search of mutations and detect only a fraction of the variants present in the sample screened. The sensitivity of SSCP ranges from 50% to 96%, whereas CSGE and PTT are estimated to detect only 75% and 76% of the *BRCA1* and *BRCA2* variants, respectively [55]. To establish the real prevalence of all mutations in the *BRCA1* and *BRCA2* genes in a population, ideally a complete *BRCA* analysis (i.e., complete sequencing and study of large rearrangements) should be performed. The prevalence of rearrangement variants varies significantly in different populations [56]. Large genomic rearrangements may account for up 21.4% of the variants in high risk patients from Latin America and the Caribbean [57]. The development of clinically useful *BRCA* mutation panels will require a deep knowledge of the mutation spectrum and prevalence in each Latin American country.

Some of the difficulties found in this review include the different techniques used for the processing of samples, the type of mutations analyzed, and the lack of haplotype analyses in most of them. These difficulties did not allow us to differentiate the presence or absence of a founder effect in the recurrent mutations (without haplotype analysis it is not possible to distinguish whether a variant has migrated from a geographic area or is the result of an independent mutational event) and limited the final conclusions of the study.

Conclusion

The risks associated with mutations in the *BRCA1* and *BRCA2* genes are different in geographically and historically defined groups, highlighting the importance of evaluating the risk for each patient regarding their own genetic and environmental context. It is important to highlight that among Latin American countries and even among regions of the same country, there is great heterogeneity in ancestors. Therefore, Latinas should not be analyzed as one population group without taking into account their genetic ancestry.

The presence of founder mutations in specific populations can lead to a cost-effective alternative of panel testing, given that a rapid and inexpensive test can increase the detection of mutations in these population groups. However, it is necessary to first determine the prevalence of such mutations in the population under study.

The range of possibilities now available for the treating physician, the patient, and the health care system in making appropriate and timely decisions in hereditary breast and ovarian cancer has caused a daily increase in the demand of mutation analyses for the *BRCA1/2* genes. Therefore, it is necessary to genetically characterize the affected populations to establish mutation screening guidelines and more adequate and appropriate treatments for each population. The importance of identifying founder mutations lies mainly in the decrease in costs. If we are able to achieve this by focusing first on founder mutations, screening could be offered more widely and could cover a larger number of women, by establishing criteria for testing patients from a population with founder mutations to be less strict than for populations that do not have them.

Even though *BRCA1/2*-founder mutations associated with increased risk of breast and other cancers have been identified in some Latin American countries, several other founder mutations may exist that have not yet been identified because of the limited number of investigations performed to date. Further studies need to be done in Latin America considering the economic advantages that bring the analysis of founder mutations in contrast to full gene sequencing testing, especially for countries with limited economic resources.

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Conception/Design: Carlos Andrés Ossa, Diana Torres
Provision of study material or patients: Carlos Andrés Ossa, Diana Torres
Collection and/or assembly of data: Carlos Andrés Ossa, Diana Torres
Data analysis and interpretation: Carlos Andrés Ossa, Diana Torres
Manuscript writing: Carlos Andrés Ossa, Diana Torres
Final approval of manuscript: Carlos Andrés Ossa, Diana Torres

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