Mutations in BRCA1, BRCA2 and other breast and ovarian cancer susceptibility genes in Central and South American populations

Lilian Jara1,3*, Sebastian Morales1, Tomas de Mayo1,2,3, Patricio Gonzalez-Hormazabal1, Valentina Carrasco1 and Raul Godoy1

Abstract
Breast cancer (BC) is the most common malignancy among women worldwide. A major advance in the understanding of the genetic etiology of BC was the discovery of BRCA1 and BRCA2 (BRCA1/2) genes, which are considered high-penetrance BC genes. In non-carriers of BRCA1/2 mutations, disease susceptibility may be explained by a small number of mutations in BRCA1/2 and a much higher proportion of mutations in ethnicity-specific moderate- and/or low-penetrance genes. In Central and South American populations, studies have focused on analyzing the distribution and prevalence of BRCA1/2 mutations and other susceptibility genes that are scarce in Latin America as compared to North America, Europe, Australia, and Israel. Thus, the aim of this review is to present the current state of knowledge regarding pathogenic BRCA variants and other BC susceptibility genes. We conducted a comprehensive review of 47 studies from 12 countries in Central and South America published between 2002 and 2017 reporting the prevalence and/or spectrum of mutations and pathogenic variants in BRCA1/2 and other BC susceptibility genes. The studies on BRCA1/2 mutations screened a total of 5956 individuals, and studies on susceptibility genes analyzed a combined sample size of 11,578 individuals. To date, a total of 190 different BRCA1/2 pathogenic mutations in Central and South American populations have been reported in the literature. Pathogenic mutations or variants that increase BC risk have been reported in the following genes or genomic regions: ATM, BARD1, CHECK2, FGFR2, GSTM1, MAP3K1, MTHFR, PALB2, RAD51, TOX3, TPS3, XRCC1, and 2q35.

Keywords: Hereditary and early onset breast cancer, Susceptibility genes, Pathogenic point mutations, Large genomic rearrangements, Ethnic composition

Background
Breast cancer (BC) is the most common malignancy among women worldwide. Each year, 1.15 million new cases are diagnosed, representing 23% of all cancer diagnoses among women [1, 2], and one in eight women will develop BC during their lives [3]. The greatest challenge currently facing clinical researchers, therefore, is identifying prevention strategies that would reduce the morbidity and mortality associated with the disease.

Breast cancer (BC) is a complex disease, with both sporadic and familial presentations, as in most cancers. Inherited genetic risk factors contribute to BC susceptibility in both familial and sporadic BC.

The discovery of tumor suppressor genes BRCA1 (MIM 113705) and BRCA2 (MIM 600185) [4, 5] was a major advance in elucidating the genetic etiology of BC. A mutation that inactivates the BRCA proteins increases the risk for breast, ovarian, and other cancers. These genes are now considered high-penetrance dominant autosomal genes for BC susceptibility. Germline mutations in BRCA1 and BRCA2 are responsible for about 25% of the risk for familial BC [6–8] and therefore 5–10% of all BC cases [9]. Retrospective studies [10–19], suggest an estimated cumulative risk of breast cancer to 70 years
of age of 40–87% for \textit{BRCA1} carriers and 27–84% for \textit{BRCA2} carriers. The corresponding ovarian cancer risks are 16–68% for \textit{BRCA1} carriers and 11–30% for \textit{BRCA2} carriers. Disease-causing mutations are distributed throughout the entire coding regions of both genes. Since the identification of \textit{BRCA1}/2 as the principal genes responsible for inherited BC \cite{5,20}, over 3781 distinct DNA sequence variants have been added to the BIC database (http://research.nhgri.nih.gov/bic/). Of these, 3079 are classified as pathogenic, including 1598 truncating mutations (1197 frameshift and 387 nonsense) and 14 splicing alterations. The frequency of \textit{BRCA1}/2 mutations varies significantly according to geographic region and ethnicity.

There is a consensus that mutations in genes \textit{BRCA1}/2 and TP53 are responsible for on average 16–20% of the risk for familial BC \cite{6,7}. Genome-wide linkage analyses using large samples of \textit{BRCA1}/2-negative families have not mapped any other high-penetrance susceptibility loci to date \cite{21}. Therefore, a large part of the genetic component remains unidentified. How can the remaining ~80% of familial BC risk be explained? Ford et al. \cite{15} proposed that other susceptibility alleles, called moderate- or low-penetrance, could be responsible for a significant percentage of BC in \textit{BRCA1}/2-negative families. Currently, BC risk variants can be classified into three categories of penetrance (high, moderate, and low) that reflect the probability of developing the disease \cite{22}. Therefore, in non-carriers of \textit{BRCA1}/2 mutations, disease susceptibility may be explained by mutations in other high-, moderate- or low-penetrance genes, interactions between alleles involved in the same pathways, or environmental factors. Sporadic BC is the result of serial stepwise accumulation of acquired and uncorrected mutations in somatic genes that are yet to be identified \cite{23}. Nevertheless, in cases without a family history of BC (sporadic BC), certain combinations of low-penetrance alleles that are associated with a high polygenic risk score (PRS) have been shown to contribute to BC susceptibility \cite{22}.

Screening for \textit{BRCA1} and \textit{BRCA2} mutations provides potentially significant health benefits. Armed with genetic results, physicians may offer risk-reducing options for mutation carriers who have, thus far, not developed cancer, such as prophylactic mastectomy and oophorectomy, prophylactic tamoxifen, or surveillance \cite{24–28}.

Research evaluating the distribution and prevalence of \textit{BRCA1}/2 mutations in Central and South American populations has been quite limited as compared to the number of studies in North America, Europe, Australia and Israel. Moreover, some of the studies performed in Latin America have analyzed hereditary BC, while others have evaluated early-onset BC or cohorts unselected for family history. Furthermore, because Central and South American populations are of mixed ethnic origin, the distributions of recurrent mutations vary by region and country. Published data regarding other BC susceptibility genes is even scarcer than data on \textit{BRCA1}/2 mutations. Therefore, the aim of this review is to provide a report on the current state of knowledge regarding pathogenic point mutations and large genomic rearrangements (LGRs) in \textit{BRCA1} and \textit{BRCA2}, as well as mutations in other BC susceptibility genes, in Central and South American populations.

**Methods**

PubMed, EBSCO, and SciELO databases were searched for all studies involving \textit{BRCA1} and \textit{BRCA2} mutations in Central and South American individuals with breast cancer. Moreover, we searched for pathogenic mutations or variants in other susceptibility genes in the same populations. The search terms included “hereditary breast cancer,” “South America,” “Latin America,” and other terms associated with Central or South American countries; and “\textit{BRCA1} and \textit{BRCA2}” and “genes and breast cancer risk.” Manuscripts published through February 28, 2017 were considered. Only papers published in English or Spanish were reviewed. Non-human studies, in vitro or in vivo studies, and studies focused on topics other than breast/ovarian cancer were excluded.

The inclusion criteria varied significantly among the selected studies; therefore, we classified the articles into three categories: cohorts that included cases with hereditary BC (cohort A), cases with early-onset (≤40 years) BC (cohort B), and cases unselected for family history of BC (cohort C). We classified a cohort as hereditary BC (cohort A) if the inclusion criteria met one or more of the following criteria, as established in the literature: (1) At least two first-degree relatives with BC and/or ovarian cancer diagnosed at any age; (2) at least two first- or second-degree relatives with BC diagnosed before the age of 50 years; (3) at least three first- or second-degree relatives with BC with at least one diagnosed before the age of 40; (4) at least one relative with BC diagnosed before the age of 50 and at least one relative with ovarian cancer diagnosed at any age; (5) at least one male relative with BC diagnosed at any age and at least one female relative diagnosed with BC at any age; (6) at least one relative diagnosed with BC before the age of 30 and one other first- or second-degree relative diagnosed with BC at any age; and (7) at least one relative with bilateral BC and one other first- or second-degree relative with BC. A cohort was classified as early-onset BC (cohort B) if the cohort was made up entirely of BC patients diagnosed at or before 40 years of age. We classified a cohort as unselected for
family history (cohort C) if none of the criteria for hereditary BC were applied in the case selection.

Pathogenic mutations are base substitutions, deletions, or duplications that inactivate the BRCA proteins. “Recurrent” refers to mutations present in several cases in at least one cohort.

The scope of BRCA1 and BRCA2 mutations in Central and South American countries

We conducted a literature review of reports on BRCA1 and BRCA2 pathogenic point mutations and LGRs in 12 Central and South American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Paraguay, Peru, Uruguay and Venezuela). Between January 2002 and February 2017, there were 28 published reports on BRCA mutations in these countries. Figure 1 shows that studies were performed in nine countries: Argentina, Brazil, Colombia, Costa Rica, Chile, Mexico, Peru, Uruguay and Venezuela. There were no reports on BRCA mutations in Bolivia, Ecuador or Paraguay. Collectively, the 28 studies screened 5956 individuals and identified 190 different pathogenic mutations (Additional file 1: Table S1; Tables 1, 2).

Additional file 1: Table S1; Tables 1 and 2 show the cohort size, inclusion criteria, and BRCA pathogenic point mutations, LGR(s) and recurrent mutations detected in cohorts A, B and C, respectively. Additional file 1: Table S1 show that in hereditary BC, 118 different BRCA point mutations were detected in 9 countries (68 in BRCA1 and 50 in BRCA2). Recurrent mutations were detected in Argentina, Chile, Brazil, Colombia and Costa Rica. Table 1 shows that in early-onset BC, 21 different BRCA mutations were detected in Brazil and Mexico (13 in BRCA1 and 8 in BRCA2). The c.5266dupC and c.548-?_4185+?del mutations were recurrent in Brazil and Mexico, respectively. Table 2 shows that in cohorts unselected for family history, 51 different BRCA mutations (29 in BRCA1 and 22 in BRCA2) were detected in Brazil, Colombia, Mexico and Peru. Large genomic rearrangements were reported in Argentina, Brazil, Chile, Mexico and Peru.

When the results were analyzed separately for each country, we found that 57 different BRCA mutations were detected in Argentina (32 in BRCA1 and 25 in BRCA2), all in hereditary BC cohorts (n = 40), including 4 recurrent mutations (2 in BRCA1 and 2 in BRCA2). Four LGRs were reported in BRCA1 but none in BRCA2 [29].

In Brazil, 6 studies that collectively screened 1151 individuals with hereditary BC reported 34 different BRCA mutations (24 in BRCA1 and 10 in BRCA2) [30–35], including 7 recurrent mutations (5 in BRCA1 and 2 in BRCA2) (Additional file 1: Table S1). In cohort B, a study by Carraro et al. [36] (n = 54) detected another 5 mutations (2 in BRCA1 and 3 in BRCA2), including the recurrent mutation c.5266dupC (3.7%), which was also a recurrent mutation in hereditary BC (Additional file 1: Table S1). Another 3 mutations not seen in cohorts A or B were detected in cohort C (n = 402) (1 in BRCA1 and 2 in BRCA2), including the recurrent mutation c.6405_6409delCTTAA (0.5%) [37]. Therefore, 42 different pathogenic point mutations in BRCA were described in the cohorts A, B and C in Brazil. All patients positive for BRCA mutations had a family history of BC (Additional file 1: Table S1; Tables 1, 2). Four different LGRs...
| Country | Cohort size | Inclusion criteria | Number of mutations detected | Pathogenic mutation in BC patients | Recurrent mutation (frequency %) | Large genomic rearrangements | References |
|---------|-------------|--------------------|-----------------------------|-----------------------------------|---------------------------------|-----------------------------|------------|
| Brazil  | 54          | a) Young female patient with BC diagnosed at < 35 year of age, b) Women with a family history of BC | 6 | c.181T>G, c.560+2T>A | c.2808_2811delACAA, c.2494C>T | ND NS NS | Carraro et al. [13] |
| Mexico  | 32          | Early-onset BC patients (≤ 35 years) reporting no first or second-degree relatives with BC or OC | 1 | c.560+2T>A, c.2405_2406delTG | c.4968insGT, c.5190T>A | ND NS NS | Ruíz-Flores et al. [48] |
| Mexico  | 22          | Early-onset BC patients (≤ 35 years) with a family history of BC | 1 | c.560+2T>A, c.2405_2406delTG | c.4968insGT, c.5190T>A | ND NS NS | Ruíz-Flores et al. [48] |
| Mexico  | 810         | Early-onset BC patients (≤ 40 years) reporting no first or second-degree relatives with BC or OC | 6 | c.548-7_4185+7delAG, c.2396-2297deletAG | c.1796-1800delT, c.4111C>T | ND NS | Torres-Mejia et al. [50] |

ND not detected, NS not studied, BC breast cancer
Table 2  Cohort characteristics and pathogenic BRAC1 and BRAC2 mutation in unselected breast cancer cases in Central and South American populations

| Country | Cohort size | Inclusion criteria | Number of mutation detected | Pathogenic mutation in BC patients | Recurrent mutation (frequency %) | Large genomic rearrangements (frequency %) | References |
|---------|-------------|--------------------|-----------------------------|------------------------------------|----------------------------------|-------------------------------------------|------------|
|         |             |                    | BRCA1 | BRCA2 | Exon | Mutation | BRCA1 | BRCA2 | Exon | Mutation | BRCA1 | BRCA2 | BRCA1 | BRCA2 | BRCA1 | BRCA2 | BRCA1 | BRCA2 |
| Brazil  | 402         | Unselected, but all of the patients positive for a BRCA mutation had a family history of BC | 2 | 2 | 11 | c.3228_3229delAG | 11 | c.5946delT | 11 | c.640_6409delCTAA | 1.2% | 0.5% |
|         |             |                    | 2 | 2 | 20 | c.5266dupC | NS | NS | Gomes et al. [37] |
| Colombia | 766         | Unselected for family history | 2 | 1 | 11 | c.3331_3334delCAAG | 11 | c.2808_2811delACAG | 11 | c.3331_3334delCAAG | 1.6% | 1.3% |
|         |             |                    | 2 | 1 | 11 | c.5123C>A | ND | ND | Torres et al. [44] |
| Colombia | 96          | Unselected for family history | 3 | 2 | 11 | c.3331_3334delCAAG | 11 | c.6024dupG | 11 | c.3331_3334delCAAG | ND | ND |
|         |             |                    | 3 | 2 | 11 | c.1674_1674delIA | 11 | c.6024dupG | ND | ND | Rodríguez et al. [42] |
| Colombia | 244         | Unselected for family history | 2 | 1 | 11 | c.3331_3334delCAAG | 11 | c.5616_5620delAGTAA | ND | ND | Hernández et al. [43] |
|         |             |                    | 2 | 1 | 18 | c.5123C>A | ND | ND | |
| Mexico  | 188         | Unselected for family history | 14 | 6 | 2 | 70insAG | 10 | 1803insA | 11 | c.68_69delAG | ND | ND |
|         |             |                    | 14 | 6 | 2 | c.68_69delAG | 11 | 2900delICT | 11 | c.211A>G | ND | ND |
|         |             |                    | 14 | 6 | 5 | c.211A>G | 11 | C.6024dupG | 5 | c.212+1G>A | ND | ND |
|         |             |                    | 14 | 6 | 11 | c.798_799delTT | 11 | c.6486_6489delACAG | 11 | c.3853_3861delITGAG | 6.9% | 1.1% |
|         |             |                    | 14 | 6 | 11 | 803delIA | 11 | c.4065_4068delITCAG | 11 | c.815_824dupAGCCATGG | ND | ND |
|         |             |                    | 14 | 6 | 11 | 2009delICT | 11 | c.4065_4068delITCAG | 11 | c.815_824dupAGCCATGG | ND | ND |
|         |             |                    | 14 | 6 | 11 | 803delIA | 11 | c.4065_4068delITCAG | 11 | c.815_824dupAGCCATGG | ND | ND |
|         |             |                    | 14 | 6 | 11 | 2009delICT | 11 | c.4065_4068delITCAG | 11 | c.815_824dupAGCCATGG | ND | ND |
|         |             |                    | 14 | 6 | 11 | 803delIA | 11 | c.4065_4068delITCAG | 11 | c.815_824dupAGCCATGG | ND | ND | Villarreal-Garza et al. [51] |
| Country | Cohort size | Inclusion criteria | Number of mutation detected | Pathogenic mutation in BC patients | Recurrent mutation (frequency %) | Large genomic rearrangements (frequency %) | References |
|---------|-------------|--------------------|-----------------------------|-----------------------------------|---------------------------------|---------------------------------------------|------------|
|         |             |                    | BRCA1 BRCA2                 | BRCA1 Exon Mutation               | BRCA1 Exon Mutation             | BRCA1 Exon Mutation                        |            |
| Mexico  | 810         | Unselected [85.3% with sporadic BC and 67.7% with early-onset BC (< 50 years of age)] | 8 11 | 9_12 c.5487_41857del | 10 | c.1796_1800del ITT TAT (I1%) | ns ns Torres-Mejia et al. [50] |
|         |             |                    |                             |                                   | c.1796_1800del ITT TAT (I1%)    |                                   |            |
|         |             |                    |                             |                                   | c.2808_2811del IACAA            |                                   |            |
|         |             |                    |                             |                                   | c.5487_41857del I1       |                                   |            |
|         |             |                    |                             |                                   | c.1796_1800del ITT TAT(0.37%)  |                                   |            |
|         |             |                    |                             |                                   | c.2433del (0.25%)              |                                   |            |
|         |             |                    |                             |                                   | c.4111C>T (0.25%)              |                                   |            |
|         |             |                    |                             |                                   | c.3123C>A (0.5%)               |                                   |            |
| Peru    | 266         | Unselected for family history | 4 1               | 2 c.68_69del IAG               | 11 | c.2808_2811del IACAA (2.6%) | ns ns Abugattas et al. [52] |
|         |             |                    |                             |                                   | c.1961_1962del IA (0.75%)     |                                   |            |
|         |             |                    |                             |                                   | c.815_824dupAGCCATG TGG       |                                   |            |
|         |             |                    |                             |                                   | c.1961_1962del IA (0.75%)     |                                   |            |
|         |             |                    |                             |                                   | c.3759_3706del ITA             |                                   |            |
| Peru    | 124         | Unselected, but 39.39% of patients had a positive family history of BC and/or OC | 5 2               | 2 c.211A>G                  | 11 | c.2455C>T                  | nd nd Gonzalez-Rivera et al. [53] |
|         |             |                    |                             |                                   | c.7673_7674del                 |                                   |            |
|         |             |                    |                             |                                   | c.1961_1962del IA (0.75%)     |                                   |            |
|         |             |                    |                             |                                   | c.4041_4042del                 |                                   |            |
|         |             |                    |                             |                                   | c.4065_4068de ITC AA           |                                   |            |
|         |             |                    |                             |                                   | c.5074_1G>T                    |                                   |            |
|         |             |                    |                             |                                   | c.5091_5092del                 |                                   |            |

ND not detected, NS not studied, BC breast cancer

* A panel of BRCA1 and BRCA2 mutation was used

* Only mutations previously described by Torres et al. [41] were studied

* A panel of 96 Hispanic BRCA mutation was used
(3 in BRCA1 and 1 in BRCA2) were also reported, all in hereditary BC, one of which was recurrent (Additional file 1: Table S1).

In Chile, 19 BRCA mutations were reported (9 in BRCA1 and 10 in BRCA2), all in hereditary BC. Of these, 9 were recurrent (4 in BRCA1 and 5 in BRCA2) (Additional file 1: Table S1) [38, 39]. Furthermore, 2 LGRs were detected in cohort A [40]. No BRCA mutations were reported in cohorts B or C.

The only study on patients with hereditary BC in Costa Rica (n = 53) described 6 BRCA mutations (2 in BRCA1 and 3 in BRCA2) in a hereditary BC cohort (n = 111), including the recurrent mutation c.5303_5304delTT (1.8%) [45].

In Mexico, 17 different BRCA mutations were reported in hereditary BC (10 in BRCA1 and 7 in BRCA2). Three LGRs were also described. The authors did not report recurrent mutations [46, 47]. In cohort B, 11 mutations were described (7 in BRCA1 and 4 in BRCA2) [48–50]. Of these, 4 mutations in BRCA1 (c.548-?_4185+del, c.2296–2297delAG, c.3598C>T and c.4327C>T) and 3 in BRCA2 (c.5946delT and c.6024dupG) and one in BRCA2 (c.2808_2811delA) were recurrent, and 2 LGRs were also detected (Table 2) [52, 53]. The third publication tested for LGRs in 16 hereditary BC patients but did not test for pathogenic point mutations. The authors detected only one LGR, in BRCA1 (exon 7 amplification) [54].

In Uruguay, only one study described BRCA1 mutations, in a cohort of 53 patients with hereditary BC. Seven mutations were detected (2 in BRCA1 and 5 in BRCA2), and no LGR testing was performed [55].

In Venezuela, only one study reported BRCA mutations, again in patients with hereditary BC (n = 51). The authors described 6 different mutations (3 in BRCA1 and 3 in BRCA2). No recurrent mutations were reported, and no LGR testing was performed [56].

Table 4 shows BRCA1/2 mutations common in more than one Central or South American country, including a total of 21 mutations (14 in BRCA1 and 7 in BRCA2). The most common mutations were found in exons 2, 5, 11, 13, 18 and 20 in BRCA1 and in exons 3 and 11 in BRCA2. Seven mutations were present in 3 or more countries: c.68_69delAG, c.211A>G, c.3331_3334delAAAG and c.5123C>G in BRCA1 and c.145G>T, c.2808_2811delA and c.5946delT in BRCA2. The c.68_69delAG mutation, also known as 185delAG (BRCA1 exon 2), was described in Argentina, Brazil, Chile, Mexico and Peru and was reported as a recurrent mutation in Brazil (0.3%), Chile (0.6%) and Peru (2.6%). The mutation c.211A>G (BRCA1 exon 5) was detected in Argentina, Brazil, Mexico and Peru and was reported as a recurrent mutation in hereditary BC in Argentina (1.17%). The c.3331_3334delAAAG was present in BC patients from Brazil, Chile and Colombia and was a recurrent mutation in Chile (0.9%) and Colombia (9.4%). The mutation c.5123C>A (BRCA1 exon 18) was detected in Argentina (cohort A), Brazil (cohort A), Colombia (cohort A and C) and Mexico (cohort A, B and C) and was a recurrent mutation in Colombia (5.7%) and Mexico (0.5%). In BRCA2, 6 mutations in exon 11 (c.2808_2811delA, c.3264dupT, c.4740_4741insTG, c.535dupA, c.5946delT and c.6024dupG) and one in exon 3 (c.145G>T) were detected in more than one country; c.2808_2811delA was a recurrent mutation in Argentina (0.64%), Colombia (3.8%) and Peru (0.75%), and c.145G>T was a recurrent mutation in Chile (2.6%).

Other BC susceptibility mutations in Central and South American countries

There is a consensus that BC risk is attributable to susceptibility alleles in many different genes. In patients negative for BRCA1/2 mutations, inherited variations in other genes explain up to 20% of familial BC [8]. However, 51% of breast cancer families do not show mutations in BRCA1/2 or other known susceptibility genes and
are therefore classified as BRCAX families. These families may carry a mutation in a moderate-penetrance BC gene yet to be identified. Alternatively, a truly polygenic model may underlie these cases, with susceptibility conferred by the collective actions of several low-penetrance loci [57–60]. We carried out a literature review of reports on pathogenic mutations or variants in other susceptibility genes in Central and South American countries and found 19 publications between January 2002 and February 2017 in 5 Central or South American countries: Brazil, Chile, Ecuador, Mexico and Peru (Fig. 1). Pathogenic mutations or variants that increase BC risk were reported in the following genes or genomic regions: ATM, BARD1, CHECK2, FGFR2, GSTM1, MAP3K1, MTHFR, PALB2, RAD51, TOX3, TP53, XRCC1 and 2q35.

ATM is frequently implicated in hereditary BC as a low-penetrance susceptibility gene. The ATM kinase has an essential role maintaining genomic integrity, as a key activator of cellular responses to DNA double-strand breaks [61]. In Chile and Mexico, association studies were performed to evaluate the relationship between common ATM variants and familial BC [62, 63]. The same variants were studied in both countries: IVS24-9delT and IVS38-8T>C. Both reports concluded that these variants are associated with increased risk of BC (Table 5). In Chile, the authors studied the variant 5557G>A, which was also found to increase BC risk [62].

Germline and somatic mutations in the BARD1 gene are reportedly associated with susceptibility to a subset of breast and ovarian cancers [64]. BARD1 participates in important cellular processes such as DNA repair, RNA processing, transcription, cell cycle regulation and apoptosis [65]. Studies on BARD1 were performed in Chile and Peru (Table 5) [53, 66]. Gonzalez-Hormazabal et al. [66] reported that in Chilean women negative for BRCA1/2 mutations, BARD1 Cys557Ser was associated with increased risk of BC. In Peru, one pathogenic mutation (c.334C>T) was reported in one of the triple-negative BC patients studied (0.95%).

CHEK2 is a gene involved in DNA damage and replication checkpoint responses and has been suggested as a BC susceptibility gene. The CHEK2 1100delC variant, which is associated with increased BC susceptibility among familial BC cases not attributable to mutations in BRCA1/2 [67], was studied in Brazilian (n = 120) [31] and Chilean (n = 196) patients with hereditary BC [67].

| Table 3 Mutations present in more than one cohort |

| Country | Mutation | Exon | Hereditary BC | Early-onset BC | Unselected BC |
|---------|----------|------|---------------|----------------|---------------|
| BRCA1   |          |      |               |                |               |
| Brazil  | c.5266dupC | 20   | ✔️            | ✔️             | ✔️            |
| Brazil  | c.560+2T>A | 7    | ✔️            | ✔️             | ✔️            |
| Brazil  | c.3331_3334delCAAG | 11 | ✔️             | ✔️             | ✔️            |
| Brazil  | c.5251C>T | 20   | ✔️            | ✔️             | ✔️            |
| Colombia| c.3331_3334delCAAG | 11 | ✔️ ✔️          | ✔️             | ✔️            |
| Colombia| c.5123C>A | 18   | ✔️ ✔️          | ✔️             | ✔️            |
| Mexico  | c.5487_4185del | 9_12 | ✔️ ✔️          | ✔️             | ✔️            |
| Mexico  | c.4065_4068delTCAG | 11 | ✔️ ✔️          | ✔️             | ✔️            |
| Mexico  | c.2296-2297delAG | 11 | ✔️             | ✔️             | ✔️            |
| Mexico  | c.433delC | 11   | ✔️            | ✔️             | ✔️            |
| Mexico  | c.3598C>T | 11   | ✔️ ✔️          | ✔️             | ✔️            |
| Mexico  | c.4327T>C | 13   | ✔️ ✔️          | ✔️             | ✔️            |
| Mexico  | c.5123C>A | 18   | ✔️ ✔️          | ✔️             | ✔️            |
| Mexico  | c.211 A>G | 5    | ✔️             | ✔️             | ✔️            |
| Mexico  | c.3759_3760delTA | 11 | ✔️ ✔️          | ✔️             | ✔️            |
| BRCA2   |          |      |               |                |               |
| Brazil  | c.2808_2811delACAA | 11 | ✔️             | ✔️             | ✔️            |
| Colombia| c.2808_2811delACAA | 11 | ✔️ ✔️          | ✔️             | ✔️            |
| Mexico  | c.2808_2811delACAA | 11 | ✔️ ✔️          | ✔️             | ✔️            |
| Mexico  | c.1796-1800delTTTAT | 10 | ✔️             | ✔️             | ✔️            |
| Mexico  | c.4111C>T | 11   | ✔️             | ✔️             | ✔️            |

BC breast cancer
✔️ = Mutation present
* Recurrent mutation
Only one of the Brazilian patients carried this mutation (0.83%), and it was not present in any of the Chilean cases (n = 196). Therefore, this variant is not a common mutation in these two populations (Table 5).

Glutathione S-transferases (GSTs) play an important role in carcinogen detoxification and metabolism of various bioactive compounds [68]. The GST family is composed of six classes of isoenzymes, including GSTM1 [69]. The GSTM1 gene is polymorphic in humans and has three known alleles: GSTM1*A, GSTM1*B and GSTM1O (null), which is the most common variant. The null variant results in undetectable expression of the gene product [70], leading to excessive accumulation of reactive oxygen species and consequently higher susceptibility to carcinogenic events due to DNA damage [71]. Three studies in Mexican and Brazilian populations evaluated the association between the null genotype and BC risk. Two reports concluded that GSTM1O is associated with BC risk in patients from northeastern Mexico [72] and Guadalajara [69]. In Brazil, a study by Possuelo et al. [73] also reported an association between the null GSTM1 genotype and BC risk.

The MTHFR enzyme, encoded by the MTHFR gene, is responsible for catalyzing the irreversible conversion of 5,6-methylenetetrahydrofolate to 5-methyltetrahydrofolate. The latter molecule is involved in DNA methylation, an important mechanism in regulation of gene expression. Alterations in DNA methylation due to MTHFR polymorphisms may be associated with the development of cancer [74–76]. Association studies on MTHFR C677T polymorphisms and BC risk were performed in Brazil [77] and Ecuador [78] (Table 5). In both reports, the authors found a significant association between this SNP and BC risk.

RAD51 is a gene that plays a key role in repairing DNA double-strand breaks through homologous DNA recombination, forming complexes with other proteins involved in DNA repair such as BRCA2 [79, 80]. Variants or pathogenic mutations in this gene were studied in Chile [81] and Peru [53]. In Chile, no mutations were detected in the exon or splice-boundaries regions of the RAD51 gene. The same study also evaluated the RAD51 5′UTR variant 135 G>C, which is associated with an increased risk of familial BC in BRCA1/2-negative women and early-onset BC (age < 50 years at diagnosis). In Peru, the pathogenic mutation c.694C>T was detected in triple-negative BC patients (n = 105), with a frequency of 0.95% (Table 5).

Mutations in the TP53 tumor suppressor gene also play a significant role in cancer risk, as impaired p53 function may contribute to the multistep process of carcinogenesis [82]. The p53 protein is important in cell-cycle regulation and maintenance of genome stability. The most notable property of p53 is its action as a transcription factor [83]. We found three articles that studied variations in TP53, all in Brazilian populations [31, 84, 85]. These articles studied the c.1010G>A (p.R337H) mutation, which occurs at a high frequency in southern and southeastern Brazil [86–90]. Silva et al. [31] reported a frequency of 2.5% for this variant and suggested that all BRCA-negative female BC patients with clinical criteria for hereditary breast-ovarian cancer should be tested for the c.1010G>A variant. Giacomazzi et al. [84] reported that the prevalence of p.R337H was higher in women diagnosed with BC at or before 45 years of age (12.1%) than in those diagnosed at 55 or older (5.1%). An article by Andrade et al. [85] suggested that screening for the germline TP53 p.R337H mutation should be recommended for young females with no family history of cancers associated with Li-Fraumeni syndrome. The three authors agree that inheritance of the c.1010G>A variant may significantly contribute to the high incidence of BC in Brazil.

The XRCC1 gene encodes a protein involved in DNA base excision repair. Therefore, mutations or polymorphisms in this gene may be involved in the genetic etiology of BC. The only study on the association between the XRCC1 gene and BC risk was performed in a Mexican population [91]. Macias-Gomez et al. [91] studied Arg194Trip and Arg399Gln, reporting a significant association between BC risk and the 399Gln polymorphism but no significant association with the Arg194Trip polymorphism.

Variations in the FGFR2 gene were studied in Chile [92] and Mexico [93]. The genes or genomic regions in MAP3K, TOX3, PALB2, 2q35 and 8q24 were studied only in Chile (Table 5) [92, 94, 95].

Fibroblast Growth Factor Receptor 2 (FGFR2) and mitogen-activated protein kinase-kinase-1 (MAP3K1) have been proposed as low-penetrance BC susceptibility genes [57]. A study by Jara et al. [92] used a case–control design to evaluate the association of BC with the FGFR2 SNPs rs2981582, rs2420946 and rs121648 and the MAP3K1 SNP rs889312 in BRCA1/2-negative Chilean BC cases. All of the SNPs studied were significantly associated with increased BC risk in familial BC and non-familial early-onset BC, in a dose-dependent manner. In Mexico, a study by Murillo-Zamora et al. [93] reported that rs2981582 was associated with BC risk (p = 0.007) (Table 5).

In the TOX3/LOG643714 (also known as TNRC9) locus, several SNPs associated with BC risk were identified. Among these, rs380362 is the most strongly correlated with disease [57]. The SNPs rs13387042 (2q35) and rs13281615 (8q24), located in non-coding regions,
### Table 4  Common BRCA ½ mutation found in multiple Central and South American countries

| Exon | Mutation | Country | Hereditary | Early-onset BC | Unselected BC | Frequency of recurrent mutation (%) |
|------|----------|---------|------------|----------------|---------------|-------------------------------------|
| 2    | c.68_69delAG | Argentina ✔ | ✔ | ✔ | ✔ | 0.33% |
|      | Brazil ✔ | ✔ | ✔ | ✔ | 0.6% |
|      | Chile ✔ | ✔ | ✔ | ✔ | 0.6% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 0.6% |
|      | Peru ✔ | ✔ | ✔ | ✔ | 2.6% |
| 5    | c.181T>G | Argentina ✔ | ✔ | ✔ | ✔ | 0.64% |
|      | Brazil ✔ | ✔ | ✔ | ✔ | 0.64% |
| 5    | c.211A>G | Argentina ✔ | ✔ | ✔ | ✔ | 1.17% |
|      | Brazil ✔ | ✔ | ✔ | ✔ | 1.17% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 1.17% |
|      | Peru ✔ | ✔ | ✔ | ✔ | 1.17% |
| 11   | c.798_799delTT | Argentina ✔ | ✔ | ✔ | ✔ | 9.4% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 9.4% |
| 11   | c.815_824dupAGCCATGTGG | Mexico ✔ | ✔ | ✔ | ✔ | 5.7% |
|      | Peru ✔ | ✔ | ✔ | ✔ | 5.7% |
| 11   | c.2568T>G | Argentina ✔ | ✔ | ✔ | ✔ | 9.4% |
|      | Uruguay ✔ | ✔ | ✔ | ✔ | 9.4% |
| 11   | c.3228_3229delAG | Argentina ✔ | ✔ | ✔ | ✔ | 9.4% |
|      | Brazil ✔ | ✔ | ✔ | ✔ | 9.4% |
| 11   | c.3331_3334delCAAG | Brazil ✔ | ✔ | ✔ | ✔ | 0.9% |
|      | Chile ✔ | ✔ | ✔ | ✔ | 0.9% |
|      | Colombia ✔ | ✔ | ✔ | ✔ | 0.9% |
| 11   | c.3858_3861delTGAG | Mexico ✔ | ✔ | ✔ | ✔ | 9.4% |
|      | Peru ✔ | ✔ | ✔ | ✔ | 9.4% |
| 11   | c.3858_3861delTGAG | Chile ✔ | ✔ | ✔ | ✔ | 9.4% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 9.4% |
| 11   | c.4065_4068delTCAA | Mexico ✔ | ✔ | ✔ | ✔ | 2.5% |
|      | Peru ✔ | ✔ | ✔ | ✔ | 2.5% |
| 13   | c.4327>T | Argentina ✔ | ✔ | ✔ | ✔ | 0.25% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 0.25% |
| 18   | c.5123C>A | Argentina ✔ | ✔ | ✔ | ✔ | 5.7% |
|      | Brazil ✔ | ✔ | ✔ | ✔ | 5.7% |
|      | Colombia ✔ | ✔ | ✔ | ✔ | 5.7% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 5.7% |
| 20   | c.5266upC | Argentina ✔ | ✔ | ✔ | ✔ | 2.5% |
|      | Brazil ✔ | ✔ | ✔ | ✔ | 2.5% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 2.5% |
|      | Peru ✔ | ✔ | ✔ | ✔ | 2.5% |
|      | Venezuela ✔ | ✔ | ✔ | ✔ | 2.5% |

**Mutation in BRCA 2**

| 3    | c.145G>T | Argentina ✔ | ✔ | ✔ | ✔ | 3.7% |
|      | Chile ✔ | ✔ | ✔ | ✔ | 3.7% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 3.7% |
| 11   | c.2808_2811delACAA | Argentina ✔ | ✔ | ✔ | ✔ | 0.64% |
|      | Brazil ✔ | ✔ | ✔ | ✔ | 0.64% |
|      | Colombia ✔ | ✔ | ✔ | ✔ | 0.64% |
|      | Mexico ✔ | ✔ | ✔ | ✔ | 0.64% |
|      | Peru ✔ | ✔ | ✔ | ✔ | 0.64% |
|      | Venezuela ✔ | ✔ | ✔ | ✔ | 0.64% |
were also associated with BC risk [57, 60]. In a Chilean population, Elematore et al. [94] evaluated the association between rs380362 (TOX3), rs13387042 (2q35) and rs13281615 (8q24) and BC risk in 344 BRCA1/2-negative BC cases and 801 controls. Two SNPs, rs380362 and rs13387042, were significantly associated with increased BC risk in familial BC and non-familial early-onset BC. The risk of BC increased in a dose-dependent manner with the number of risk alleles (p-trend < 0.0001 and 0.0091, respectively). Other studies reported an additive effect of the rs380362 and 2q35 rs1387042 alleles on BC risk. There was no association between rs13281615 (8q24) and BC risk (Table 5).

The PALB2 (partner and localizer of BRCA2) protein interacts with BRCA2, stabilizing the intracellular accumulation of the BRCA2 protein at sites of DNA damage [96]. PALB2 is also recruited by BRCA1 in response to DNA damage and serves as a linker between BRCA1 and BRCA2 and is necessary for BRCA2-mediated homologous-recombination repair [97, 98]. Thus, BRCA1, BRCA2 and PALB2 are key BC susceptibility genes that work together in the same DNA damage response pathway [99, 100]. Leyton et al. [95] studied 100 BRCA1/2-negative Chilean cases with familial BC, identifying 3 PALB2 variants. Using a case–control design, the authors evaluated the association of the identified variants with BC risk. Two of the variants, PALB2 c.1676A>G(rs152451A>G) and c.2993C>T (rs45551636C>T), were significantly associated with increased BC risk only in cases with a strong family history of BC (Table 5).

The relationship of BRCA1/2 mutations and other BC susceptibility variants to the demographic composition of Central and South American countries

Genetic factors play an important role in the development of BC. The most widely-accepted model of BC oncogenesis, known as the polygenic model, attributes BC susceptibility to a small number ethnicity-specific mutations in high-penetrance genes (BRCA1, BRCA2 and TP53) and a much larger number of variants in moderate- or low-penetrance genes [7, 101], as well as interactions among these genetic variants and exposure to environmental factors [102]. Both BRCA1 and BRCA2 confer susceptibility to breast and ovarian cancer. About 5–7% of all BC diagnosed are associated with germline mutations in BRCA1 and BRCA2 [8, 15], and an even larger proportion of familial BC cases are associated with BRCA1 and BRCA2 variations; collectively, germline mutations in the two major susceptibility genes BRCA1 and BRCA2 account for ~20% of familial BC cases [8, 103]. The spectrum of mutations in BRCA1 and BRCA2 genes and other susceptibility alleles varies considerably by ethnic group and geographic region.

South America has a complex demographic history shaped by multiple migration and admixture events in pre- and post-colonial times [104], including settlement by Native Americans, European colonization and the African slave trade [104]. Moreover, the continental ancestry of the admixed populations in South America is not homogenous. For example, the Argentine population is a mixture of European (0.673), Native American (0.277), West African (0.036) and East Asian (0.014).
### Table 5 Mutations or variations in other breast cancer susceptibility genes in Central and South American populations

| Country | Cohort size | Selection criteria | BC susceptibility gene | Mutation or variant | References |
|---------|-------------|--------------------|------------------------|---------------------|------------|
| Brazil  | 874         | a) Family history of BC  
             b) Unselected for family history | TP53 | c.1010G>A (pathogenic mutation)  
Frequency: 8.23% | Giacomazzi et al. [85] |
| Brazil  | 120         | a) BC diagnosed at \( \leq \) 45 years of age (no family history of BC)  
             b) BC diagnosed at \( \leq \) 45 years of age; at least 1 close blood relative with breast/ovarian/fallopian tube/primary peritoneal cancer diagnosed at any age  
             c) BC diagnosed at \( \leq \) 50 years of age; at least 1 blood relative with breast/ovarian/fallopian tube/primary peritoneal cancer diagnosed at \( \leq \) 50 years  
             d) BC diagnosed at \( > \) 50 of age; at least 1 blood relative with breast/ovarian/fallopian tube/primary peritoneal cancer diagnosed at any age  
             e) At least 2 relatives with primary BC diagnosed at \( < \) 50 years of age  
             f) BC with a history of ovarian/fallopian tube/primary peritoneal cancer diagnosed at any age  
             g) Ethnicity associated with a higher mutation frequency (e.g., Ashkenazi Jewish)  
             h) Personal history of ovarian/fallopian tube/primary peritoneal cancer  
             i) Personal history of male BC | TP53 | c.1010G>A (pathogenic mutation)  
Frequency: 2.5%  
c.1100delC Frequency: 0.83% | Silva et al. [31] |
| Brazil  | 348         | Female with BC diagnosed at \( < \) 45 years of age; no family history of the disease | TP53 | c.1010G>A (pathogenic mutation)  
Frequency: 12% | Andrade et al. [78] |
| Brazil  | 100         | Patient with BC; no family history of the disease | MTHFR | MTHFR c.677T (rs1801133) associated with increased BC risk | Zara-Lopes et al. [77] |
| Brazil  | 49          | a) Women with family history of BC  
             b) Women with no family history of BC | GSTM1 | Null GSTM1 associated with increased BC risk | Possuelo et al. [73] |
| Chile   | 143         | a) At least 2 first-degree relatives with BC and/or OC diagnosed at any age (46.1%)  
             b) At least 2 first- or second-degree relatives with BC diagnosed at \( < \) 50 years of age (22.7%)  
             c) At least 1 relative with BC diagnosed at \( < \) 30 of age years (11.3%)  
             d) At least 1 relative with bilateral BC  
             e) At least 3 first- or second-degree relatives with BC; at least 1 diagnosed at \( < \) 40 years of age (5.7%)  
             f) 3 or more different cancers (female or male BC, OC, prostate, pancreatic or larynx in non-smoking individuals) (5.7%)  
             g) At least 1 relative with male BC diagnosed at any age; at least 1 relative with female BC diagnosed at any age | RAD51 | RAD51 135G>C associated with increased BC risk in BRCA1/2 negative women with a family history of BC and diagnosis at \( < \) 50 years of age | Jara et al. [81] |
| Country | Cohort size | Selection criteria | BC susceptibility gene | References |
|---------|-------------|---------------------|------------------------|------------|
| Chile   | 137         | a) At least 2 relatives with BC  
b) At least 2 relatives with BC; at least 1 with diagnosis at < 40 years of age  
c) At least 2 relatives with BC; at least 1 with bilateral BC  
d) At least 3 relatives with BC  
e) At least 3 relatives with BC; at least 1 with diagnosis at < 40 years of age  
f) At least 3 relatives with BC; at least 1 male relative with BC  
g) At least 3 relatives with BC; at least 1 male relative with BC  
h) Two family members with BC; at least one with both BC and OC  
i) At least 1 relative with BC diagnosed at < 31 years of age; male & BC  | ATM | IVS24-9delT IVS38-5557G>A all associated with increased BC risk | González-Hormazabal et al. [67] |
| Chile   | 322         | a) At least 3 relatives with BC and/or OC  
b) 2 relatives with BC and/or OC  
c) At least 1 relative with BC diagnosed at ≤ 35 years of age  
d) At least 1 relative with BC diagnosed at ≤ 36–50 years of age  | BARD1 | BARD1 Cys557Ser associated with increased BC risk | González-Hormazabal et al. [66] |
| Chile   | 351         | a) At least 3 relatives with BC and/or OC  
b) 2 relatives with BC and/or OC  
c) At least 1 relative with BC diagnosed at ≤ 35 years of age  
d) At least 1 relative with BC diagnosed at ≤ 36–50 years of age  | FGFR2 MAP3K1 | rs2981582, rs2420946 and rs1219648 All associated with increased BC risk  
rS889312 Associated with increased BC risk | Jara et al. [92] |
| Chile   | 347         | a) At least 3 relatives with BC and/or OC  
b) 2 relatives with BC and/or OC  
c) At least 1 relative with BC diagnosed at ≤ 35 years of age  
d) At least 1 relative with BC diagnosed at ≤ 36–50 years of age  | TOX3 | rs3803662 associated with increased BC risk  
rS13387042 Associated with increased BC risk | Elematore et al. [94] |
| Chile   | 436         | a) At least 3 relatives with BC and/or OC  
b) 2 relatives with BC and/or OC  
c) At least 1 relative with BC diagnosed at ≤ 35 years of age  
d) At least 1 relative with BC diagnosed at ≤ 36–50 years of age  | PALB2 | rs152451 and rs4551636 associated with increased BC risk in cases with strong family history of BC | Leyton et al. [95] |
| Chile   | 196         | BC patients belonging to a high-risk family | CHEK2 1100delC | Not detected | González-Hormazabal et al. [67] |
| Ecuador | 114         | Unselected for family history of cancer | MTHFR | MTHFR c.677T (rs1801133) associated with increased BC risk | López-Cortes et al. [78] |
| Mexico  | 397         | Unselected for family history of cancer | XRCC1 | Arg399Gln associated with increased BC risk | Macías-Gómez et al. [91] |
| Mexico  | 559         | Unselected for family history of cancer | GSTM1 | Null GSTM1 associated with increased BC risk | Soto-Quintana et al. [69] |
| Mexico  | 243         | Unselected for family history of cancer | GSTM1 | Null GSTM1 associated with increased BC risk | Jaramillo-Rangel et al. [72] |
| Mexico  | 94          | Familial and/or early-onset BC | ATM | IVS24-9delT IVS38-5557G>A all associated with increased BC risk | Gilderón-Zúñiga et al. [63] |
| Mexico  | 687         | Unselected for family history of cancer | FGR2 | rs2981582 associated with increased BC risk | Murillo-Zamora et al. [93] |
| Peru    | 105         | a) Triple-negative BC  
b) Unselected for family history of cancer or age at diagnosis (but 39.39% had a family history of breast or ovarian cancer) | BARD1 | c.334C>T (pathogenic) Frequency: 0.95% | González-Rivera et al. [53] |

Note: The table continues as described in the original text.
components, while the proportions in the Peruvian population are European (0.26), Native American (0.683), West African (0.032) and East Asian (0.025) [104]. Uruguay is unique among South American countries in that it has almost no communities of Native American or African descent [105]. Therefore, South American countries should not be analyzed as a monolithic group without regard for specific regional genetic ancestry, as the ethnic differences between South American populations suggests that medically-relevant genetic variations may differ according to population and region.

Mexico and Costa Rica were the only Central American populations with data on BRCA mutations. Central America was included in this review as it was also colonized by Spaniards. The Costa Rica population is a mixture of European (0.61), Native American (0.31) and African (0.06) components, with variations by region [106]. For example, a recent study on the genetic and population structure in Guanacaste, Costa Rica, which is heavily admixed, reported a mixture of predominantly European (0.425), Native American (0.383) and African (0.152) ancestry, although the authors could not exclude an Asian component (0.04) [107].

The Mexican population also harbors great ethnic diversity [108] as confirmed by numerous studies on the admixture in Mexico. Amerindian ancestry is the largest component (0.51–0.56) in the general population, followed by European (0.40–0.45), while the African component is small (0.02–0.05). When analyzed by region, however, there is significant variation. For example, European is the largest component in the north (at 0.5 in Chihuahua, 0.62 in Sonora and 0.55 in Nueva Leon) [105].

An overview of the literature indicates a marked Amerindian influence in Mexican and Peruvian populations, while European ancestry is more prevalent in Costa Rica, Argentina and Uruguay. The proportions of European, Amerindian and African components are roughly equal in Venezuela. In Colombia and Brazil, there is significant interpopulation variability. The ethnic distribution in Brazil follows a geographical pattern, with the European influence more prevalent in the southeast and south, African in northeast and Amerindian in the north. In Chile, the Amerindian and European components are 0.6 and 0.4, respectively [105].

**Genetic testing for breast cancer**

Genetic testing for BRCA1 and BRCA2 mutations may provide significant public health benefits for cancer patients and high-risk individuals, who could be offered targeted treatment and prevention strategies [109]. The feasibility of providing widespread genetic screening for BRCA1/2 mutations in Central and South America depends on knowledge of mutations present in these regions, given the varied ethnic composition of the populations. To develop a test that might be useful throughout the region and therefore sufficiently cost-effective, it is first necessary to determine which BRCA1/2 mutations are common in multiple countries. Public insurance coverage for genetic testing is also crucial. Finally, it is important to identify pathogenic mutations or variants in other moderate- or low-penetration susceptibility genes that increase BC risk, as the use of panel testing is growing more common.

**Conclusions**

The BRCA1/2 gene mutation spectrum varies widely throughout different Central and South American populations, likely due to the patterns of ethnic diversity in these countries. These complex ethnic patterns are associated with various migration and settlement events. Even populations within a given country are not necessarily homogeneous, and each subgroup may have a distinct ethnic composition and genetic structure. Because the same genetic composition cannot be extrapolated across diverse sub-populations, genetic screening tests for breast cancer in these regions should not be based on a single genetic test with a defined gene variant panel to detect mutational events. This guideline is even more categorical for screening approaches designed to test more than one population in Central and or South American countries.

A significant percentage of high-risk families with hereditary breast cancer are negative for mutations in BRCA1/2 genes. The genetic etiology of BC in these subjects may be attributable to variations in other moderate- or low-penetration susceptibility alleles and/or variations in specific chromosomal regions. Data on variants in these genes and/or chromosomal regions in Central and South American populations are even scarcer than studies involving high-penetration alleles. Given the importance of these variants in the etiology of hereditary BC, elucidating the distribution of these mutations and variations is crucial for advancing population studies and screening approaches in high-risk families with a hereditary breast cancer profile.

Appropriate inclusion criteria are also of vital importance when conducting these studies, given the considerable variability observed in the reported studies.

**Additional file**

Additional file 1: Table S1. Cohort characteristics and pathogenic BRCA1 and BRCA2 mutations in hereditary breast cancer in Central and South American populations.
Abbreviations
BCRA1: breast cancer type 1 susceptibility protein; BCRA2: breast cancer type 2 susceptibility protein; LGRs: large genomic rearrangements; ATM: ataxia telangiectasia mutated gene; BARD1: BCRA1 associated ring domain 1; CHEK2: Checkpoint kinase 2; G5STs: glutathione S-transferases; MTHFR: methylenetetrahydrofolate reductase; RAD51: BCRA1/BCRA2-containing complex, subunit 5; TP53: phosphoprotein P53; XRCC1: X-ray repair cross-complementing protein 1; FGF2: fibroblast growth factor receptor 2; MAP3K1: mitogen-activated protein kinase-kinase-kinase 1; TOX3/LOG643714: TOX high mobility group box family member 3; PALB2: partner and localizer of BCRA2.

Authors’ contributions
LJ conceived the study and wrote the paper. RG, PGH and VC participated to draft the literature and the manuscript. SM and TDM contribute with the box family member 3; PALB2: partner and localizer of BRCA2.

References
1. Parkin DM, Fernandez LM. Use of statistics to assess the global burden of breast cancer. Breast J. 2006;12(Suppl 1):S70–80. doi:10.1111/j.1075‑1105.2006.00205.x
2. Oldenburg RA, Meijers‑Heijboer H, Connelisse Cj, Develee P. Genetic susceptibility for breast cancer: how many more genes to be found? Crit Rev Oncol Hematol. 2007;63(2):125–49. doi:10.1016/j.critrevonc.2006.12.004.
3. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59(4):223–45. doi:10.3322/caac.20062.
4. Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q21–23. Science. 1994;265(5181):2088–90.
5. Tavtigian SV, Simard J, Rommens J, Couch F, Shattuck‑Eidens D, Neuhausen S, et al. The complete BCRA2 gene and mutations in chromosome 13q‑linked kindreds. Nat Genet. 1996;12(3):333–7. doi:10.1038/ng0396e‑333.
6. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population‑based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer. 2000;83(10):1301–8. doi:10.1054/bjoc.2000.1407.
7. Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. Nat Genet. 2008;40(11):17–22. doi:10.1038/ng.2007.53.
8. Melchor L, Benitez J. The complex genetic landscape of familial breast cancer. Hum Genet. 2013;132(8):845–63. doi:10.1007/s00439‑013‑1299‑y.
9. Claus EB, Schildkraut JM, Thompson WD, Risch N. The genetic attributable risk of breast and ovarian cancer. Cancer. 1996;77(11):2318–24. doi:10.1002/(SICI)1097‑0142(19960601)77:11<2318:AID‑CNCR21>3.0.CO;2‑Z.
10. Antoniou AC, Pharoah PD, Narod S, Risch HA, Easton DF, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2006;78(5):597–601. doi:10.1086/501540.
11. Antoniou AC, Cunningham AP, Peto J, Evans DG, Lalloo F, Narod SA, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer. 2008;98(8):1457–66. doi:10.1038/sj.bjc.6600350.
12. Begg CB, Halle RW, Berg A, Malone KE, Concannon P, Thomas DC, et al. Variation of breast cancer risk among BRCA2 carriers. JAMA. 2008;299(2):194–201. doi:10.1001/jama.2007.55‑a.
13. Brohet RM, Velhuizen ME, Hogervorst FB, Meijers‑Heijboer HE, Seynaeve C, Collee MJ, et al. Breast and ovarian cancer risks in a large series of clinically ascertained families with a high proportion of BRCA1 and BRCA2 Dutch founder mutations. J Med Genet. 2014;51(2):98–107. doi:10.1136/jmgene.2013‑101974.
14. Chen S, Iversen ES, Friebel T, Finkelstein D, Weber BL, Eisen A, et al. Characterization of BRCA1 and BRCA2 mutations in a large United States sample. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(6):863–71. doi:10.1200/JCO.2005.03.6772.
15. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The breast cancer linkage consortium. Am J Hum Genet. 1996;59(3):676–89.
16. Gabai‑Kapara E, Lahad A, Kaufman B, Friedman E, Segov S, Renbaum P, et al. Population‑based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci USA. 2014;111(13):4920–5. doi:10.1073/pnas.1415979111.
17. Hopper JL, Southey MC, Czitrom FS, Dite G, Giles GG, McCredie MR, et al. Population‑based estimate of the average cumulative risk of breast cancer for a defined set of protein‑truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidemiol Biomark Prev Pub Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 1999;8(7):741–7.
18. Milne RL, Ostorio A, Caijal TR, Vega A, Llort G, de la Hoya M, et al. The average cumulative risks of breast and ovarian cancer for carriers of mutations in BRCA1 and BRCA2 attending genetic counseling units in Spain. Clin Cancer Res Off J Am Assoc Cancer Res. 2008;14(9):2861–9. doi:10.1158/1078‑0432.CCR‑07‑4436.
19. Evans DG, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting. risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. BMC cancer. 2008;8:155. doi:10.1186/1471‑2407‑8‑155.
20. Miki Y, Swensen J, Shattuck‑Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266(5182):66–71. doi:10.1126/science.8007164.
21. Smith P, McGuffog L, Easton DF, Mann GJ, Pupo GM, Newman B, et al. A genome wide linkage search for breast cancer susceptibility genes. Genes Chromosom Cancer. 2006;45(7):646–55. doi:10.1002/gcc.20330.
22. Mavaddat N, Pharoah PD, Michailidou K, Tyer J, Brook MN, Bolla MK, et al. Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst. 2015;107(5). doi:10.1093/jnci/djv036.
23. Kenemans P, Verstraeten RA, Verheijen RH. Oncogenic pathways in hereditary and sporadic breast cancer. Maturitas. 2008;61(1‑2):141–50.
24. Metcalfe KA, Snyder C, Seidel J, Hanna D, Lynch HT, Narod S. The use of preventive measures among healthy women who carry a BRCA1 or BRCA2 mutation. Fam Cancer. 2005;4(2):97–103. doi:10.1007/s10549-005-4215-3.

25. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. Nat Rev Cancer. 2004;4(9):665–76. doi:10.1038/nrc1431.

26. Warner E, Causer PA. MRI surveillance for hereditary breast-cancer risk. Lancet. 2005;365(9473):1747–9. doi:10.1016/S0140-6736(05)6620-8.

27. Weitzel JN, Buys SS, Sherman WH, Daniels A, Ursin G, Daniels JR, et al. Reduced mammographic density with use of a gonadotropin-releasing hormone agonist-based chemoprevention regimen in BRCA1 carriers. Clin Cancer Res Off J Am Assoc Cancer Res. 2007;13(2 Pt 1):654–8. doi:10.1158/1078-0432.CCR-06-1902.

28. Tutt A, Robinson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376(9737):235–44. doi:10.1016/S0140-6736(10)60892-6.

29. Solano AR, Cardoso FC, Romano V, Perazzo F, Bas C, Recondo G, et al. Spectrum of BRCA1/2 variants in 940 patients from Argentina including novel, deleterious and recurrent germline mutations: impact on healthcare and clinical practice. Oncotarget. 2016. doi:10.18632/oncotarget.10814.

30. Ewald IP, Cossio SL, Palmero EI, Pinheiro M, Nascimento IL, Machado RC, et al. Genomic rearrangements of the BRCA1 and BRCA2 genes in breast cancer patients with positive family history. Sao Paulo Med J Rev Bras. 2009;42(5):453–7.

31. Silva FC, Lisboa BC, Figueiredo MC, Torrezan GT, Santos EM, Krepschi AC, et al. Hereditary breast and ovarian cancer: assessment of point mutations and copy number variations in Brazilian patients. BMC Med Genet. 2014;15:55. doi:10.1186/1471-2350-15-55.

32. Felix GE, Abe-Sandres C, Machado-Lopes TM, Bonfim TF, Guindalini RS, Santos VC, et al. Germline mutations in BRCA1, BRCA2, CHEK2 and TP53 in patients at high-risk for HBOC: characterizing a Northeast Brazilian Population. Hum Genet. 2014;133(4):401–22. doi:10.1007/s00439-013-1431-2.

33. Dufloth RM, Carvalho S, Heinrich JK, Shinzato JY, dos Santos CC, Vitorino Krepischi AC, et al. Hereditary breast and ovarian cancer: assessment of point mutations and copy number variations in Brazilian patients. BMC Med Genet. 2014;15:55. doi:10.1186/1471-2350-15-55.

34. Esteses VF, Thuler LC, Amendola LC, Kofman RJ, Kofman S, Frankel PP, et al. Prevalence of BRCA1 and BRCA2 gene mutations in families with medium and high risk of breast and ovarian cancer in Brazil. Braz J Med Biol Res. 2009;42(5):453–7.

35. Ewald IP, Ismaiel P, Vargas FR, Moreira MA, Moreira AS, Moreira-Filho CA, et al. Prevalence of the BRCA1 founder mutation c.5266dup in Brazilian individuals at-risk for the hereditary breast and ovarian cancer syndrome. Hered Cancer Clin Pract. 2011;9:12. doi:10.1186/1477-2559-9-12.

36. Carraro DM, Kozie Folgueira MA, Garcia Lisboa BC, Ribeiro Olivieri EH, Vtto S, Krepschi AC, de Carvalho AF, et al. Comprehensive analysis of BRCA1/2, CHEK2 and TP53 gene mutations and tumor characterization, a portrait of early-onset breast cancer in Brazil. PLoS ONE. 2013;8(3):e57581. doi:10.1371/journal.pone.0057581.

37. Gomes MC, Costa MM, Borjevic R, Monteiro AN, Veira R, Kofman S, et al. Prevalence of BRCA1 and BRCA2 mutations in breast cancer patients from Brazil. Breast Cancer Res Treat. 2007;103(3):349–55. doi:10.1007/s10549-006-9378-6.

38. Gonzalez-Hormazabal P, Gutierrez-Fabrace O, et al. Full-exon pyrosequencing screening of BRCA germline mutations in Mexican women with inherited breast and ovarian cancer. PLoS ONE. 2012;7(15):e37432. doi:10.1371/journal.pone.0037432.

39. Nahleh Z, Otoukesh S, Dwivedi AK, Mallawaarachchi I, Sanchez L, Saldivar JS, et al. Clinical and pathological characteristics of Hispanic BRCA-associated breast cancers in the American-Mexican border city of El Paso, TX. Am J Cancer Res. 2015;5(1):466–71.

40. Puente JS, Herrera LA, Castello D, et al. Significant clinical impact of recurrent BRCA1 and BRCA2 mutations in Mexican women with breast cancer. Cancer Epidemiol Biomark Prev. 2012;21(6):1945–54. doi:10.1158/1055-9965.EPI-11-0980.

41. Villarreal-Garza C, Alvarez-Gomez RM, Perez-Plasencia C, Herrera LA, Herzog J, Castillo D, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature. 2007;447(7148):1087–93. doi:10.1038/nature05887.

42. Rodriguez AO, Llacuachaqui M, Pardo GG, Royer R, Llacuachaqui M, et al. Prevalence of BRCA1 and BRCA2 mutations among ovarian cancer patients from Colombia. Gynecol Oncol. 2012;124(2):236–43. doi:10.1016/j.ygyno.2011.10.027.

43. Hernandez JE, Llacuachaqui M, Palacio GV, Figueroa JD, Madrid J, Lema M, et al. Prevalence of BRCA1 and BRCA2 mutations in unselected breast cancer patients from medellin, Colombia. Hered Cancer Clin Pract. 2014;12(1):11. doi:10.1186/1475-2091-12-11.

44. Torres D, Umana A, Robledo JP, Caicedo JJ, Quintero E, Orozco A, et al. Estudio de factores genéticos para cáncer de mama en Colombia. Univ Med Bogotá. 2005;50(3):297–301.

45. Gutierrez-Espelta GA, Llacuachaqui M, Garcia-Jimenez L, Aguilar Herrera M, Lopiccia Vega K, Ortiz A, et al. BRCA1 and BRCA2 mutations among familial breast cancer patients from Costa Rica. Clin Genet. 2012;85(5):484–8. doi:10.1111/j.1399-0004.2011.01774.x.

46. Vaca-Parraguirre F, Alvarez-Gomez RM, Fragoso-Ontriveros V, Vidal-Millan S, Herrera LA, et al. Full-exon pyrosequencing screening of BRCA germline mutations in Mexican women with inherited breast and ovarian cancer. PLoS ONE. 2012;7(15):e37432. doi:10.1371/journal.pone.0037432.

47. Nahleh Z, Otoukesh S, Dwivedi AK, Mallawaarachchi I, Sanchez L, Saldivar JS, et al. Clinical and pathological characteristics of Hispanic BRCA-associated breast cancers in the American-Mexican border city of El Paso, TX. Am J Cancer Res. 2015;5(1):466–71.

48. Puente JS, Herrera LA, Castello D, et al. Significant clinical impact of recurrent BRCA1 and BRCA2 mutations in Mexican women with breast cancer. Cancer Epidemiol Biomark Prev. 2012;21(6):1945–54. doi:10.1158/1055-9965.EPI-11-0980.

49. Calderon-Garciduenas AL, Ruiz-Flores P, Cerda-Flores RM, Barrera-Saldana HA. Clinical follow up of Mexican women with early onset of breast cancer and mutations in the BRCA1 and BRCA2 genes. Salud Publica Mex. 2005;47(2):297–301.

50. Delgado L, Fernandez M, Grotiuz G, Cataldi S, Gonzalez A, Lluveras-Tovar C, et al. Clinical and pathological characterization of Hispanic breast cancer patients from Medellin, Colombia. Hered Cancer Clin Pract. 2014;12(1):11. doi:10.1186/1897-4287-12-11.

51. Villarreal-Garza C, Alvarez-Gomez RM, Perez-Plasencia C, Herrera LA, Herzog J, Castillo D, et al. Significant clinical impact of recurrent BRCA1 and BRCA2 mutations in Mexican women with breast cancer. Cancer Epidemiol Biomark Prev. 2012;21(6):1945–54. doi:10.1158/1055-9965.EPI-11-0980.
59. Rosa-Rosa JM, Pita G, Urioste M, Llorá G, Brunet J, Lazaro C, et al. Genome-wide linkage scan reveals three putative breast-cancer-susceptibility loci. Am J Hum Genet. 2009;84(2):115–22. doi:10.1016/j.ajhg.2008.12.013.

60. Stacey SN, Manolescu A, Sulem P, Thorlacius S, Gudjonsson SA, Jonssons GF, et al. Common variants on chromosome 8p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet. 2008;40(6):703–6. doi:10.1038/ng.113.

61. Lavin MF, Birrell G, Chen P, Kozlov S, Scott S, Gueven N. ATM signaling and genomic stability in response to DNA damage. Mutat Res. 2005;569(1–2):123–32. doi:10.1016/j.mrfmmm.2004.04.020.

62. Gonzalez-Hormazabal P, Bravo T, Blanco R, Valenzuela CY, Gomez F, Waugh E, et al. Association of common ATM variants with familial breast cancer in a South American population. BMC Cancer. 2008;8:117. doi:10.1186/1471-2407-8-117.

63. Calabró-Zuniga Filde C, Ofacio-Gomez G, Lopez-Marquez FC, Recio-Vega R, Serrano-Gallardo LB, Ruiz-Flores P. ATM polymorphisms rs24-9delet, rs639847T-C, and SS57S>A in Mexican women with familial and/or early-onset breast cancer. Salud Publica Mex. 2014;56(2):206–12.

64. Irminger-Finger I. BARD1, a possible biomarker for breast and ovarian cancer. Gynecol Oncol. 2010;117(2):211–5. doi:10.1016/j.ygyno.2009.10.079.

65. Karpinnen SM, Barkardottir RB, Backenhorn K, Sydenham T, Syrjakoski K, Schluchter L, et al. Nordic collaborative study of the BARD1 Cys557Ser allele in 3956 patients with cancer: enrichment in familial BRCA1/BRCA2 mutation-negative breast cancer but not in other malignancies. J Med Genet. 2006;43(11):856–62. doi:10.1136/jmg.2006.041731.

66. Gonzalez-Hormazabal P, Reyes JM, Blanco R, Bravo T, Carrera I, Peralta O, et al. The BARD1 Cys557Ser variant and risk of familial breast cancer in a South-American population. Mol Biol Rep. 2012;39(9):8091–8. doi:10.1007/s11033-012-1656-2.

67. Gonzalez-Hormazabal P, Castro VG, Blanco R, Gomez F, Peralta O, Waugh E, et al. Absence of CHEK2 1100delC mutation in familial breast cancer cases from a South American population. Breast Cancer Res Treat. 2008;110(3):543–5. doi:10.1007/s10549-007-9743-0.

68. Coles BF, Kadiubaf FB. Detoxification of electrophilic compounds by glutathione S-transferase catalysis: determinants of individual response to chemical carcinogens and chemotherapeutic drugs? BioFactors. 2003;17(1):41–130.

69. Soto-Quintana O, Zuniga-Gonzalez GM, Ramirez-Patino R, Ramos-Silva A, Figuera LE, Carrillo-Moreno DI, et al. Association of the GSTM1 null polymorphism with breast cancer in a Mexican population. Genet Mol Res GMR. 2015;14(4):13066–75. doi:10.4238/2015.October.26.2.

70. Wang T, Yu HT, Wang W, Pan YY, He LX, Wang ZY. Genetic polymorphisms of cytochrome P450 and glutathione S-transferase and/or early-onset breast cancer. Salud Publica Mex. 2014;56(2):206–12.

71. Possuelo LG, Peraca CF, Eisenhardt MF, Dotto ML, Cappelletti L, Foletto C, et al. Polymorphisms of the XRCC1 gene and breast cancer risk in the Mexican population. Fam Cancer. 2013;12(2):291–4. doi:10.1007/s10689-012-9788-y.

72. Seidinger AL, Mastellaro MJ, Paschoal Fortes F, Godoy Assumpcao J, Arendt AL, Mustafa MI. TP53 mutations as biomarkers for cancer epidemiology in Latin America: current knowledge and perspectives. Mutat Res. 2005;589(3):192–207. doi:10.1016/j.mrfmmm.2005.01.002.

73. Levine AJ, Oren M. The first 30 years of p53: growing ever more complex. Nat Rev Cancer. 2009;9(10):749–58. doi:10.1038/nrc2723.

74. Giacomazzi J, Graudenz MS, Osorio CA, Koehler-Santos P, Palmero EI, Zagonel-Oliveira M, et al. Prevalence of the TP53 p.R337H mutation in breast cancer patients in Brazil. PLoS ONE. 2014;9(6):e98993. doi:10.1371/journal.pone.0098993.

75. Andrade KC, Santiago RM, Fortes FP, Mamberti LL, Nobrega AF, Achatz MI. Early-onset breast cancer patients in South and Southeast of Brazil should be tested for the TP53 p.R337H mutation. Breast Cancer Res. 2016;39(2):199–202. doi:10.1186/s13555-014-0343-9.

76. Ribeiro RC, Sandrini F, Figueiredo B, Zambetti GP, Michalkiewicz E, Lafferty AF, et al. An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. Proc Natl Acad Sci USA. 2001;98(16):9330–5. doi:10.1073/pnas.161479898.

77. Achatz MI, Olivier M, Le Calvez F, Martel-Planche G, Lopes A, Rossi BM, et al. The TP53 mutation, R337H, is associated with Li-Fraumeni and Li-Fraumeni-like syndromes in Brazilian families. Cancer Lett. 2007;245(1–2):96–102. doi:10.1016/j.canlet.2007.10.044.

78. Custodio G, Parise GA, Kiesel Filho N, Komechen H, Sabbaga CC, Rosati R, et al. Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenal cortical tumors. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(20):2619–26. doi:10.1200/JCO.2012.46.3711.

79. Seidinger AL, Mastellaro MJ, Paschoal Fortes F, Godoy Assumpcao J, Aparecida Cardinalli I, Aparecida Ganazza M, et al. Association of the highly prevalent TP53 R337H mutation with pediatric choroid plexus carcinoma and osteosarcoma in southeast Brazil. Cancer. 2011;117(10):2288–95. doi:10.1002/cncr.25826.

80. Macias-Gomez NM, Peralta-Leal V, Meza-Espinoza JP, Gutierrez-Angulo M, Duran-Gonzalez J, Ramirez-Gonzalez JM, et al. Polymorphisms of the XRCC1 gene and breast cancer risk in the Mexican population. Fam Cancer. 2015;14(3):349–54. doi:10.1007/s10689-015-9787-y.

81. Jara L, Gonzalez-Hormazabal P, Cerceno K, Di Capua GA, Reyes JM, Blanco R, et al. Genetic variants in FGFR2 and MAP3K1 are associated with the risk of familial and early-onset breast cancer in a South American population. Breast Cancer Res Treat. 2013;137(2):559–69. doi:10.1007/s10549-012-2359-z.
93. Murillo-Zamora E, Moreno-Macias H, Ziv E, Romieu I, Lazcano-Ponce E, Angeles-Llerenas A, et al. Association between rs2981582 polymorphism in the FGFR2 gene and the risk of breast cancer in Mexican women. Arch Med Res. 2013;44(6):459–66. doi:10.1016/j.arcmed.2013.08.006.

94. Elmetature I, Gonzalez-Hormazabal P, Reyes JM, Blanco R, Bravo T, Peralta O, et al. Association of genetic variants at TOX3, 2q35 and 8q24 with the risk of familial and early-onset breast cancer in a South-American population. Mol Biol Rep. 2014;41(6):3715–22. doi:10.1007/s11033-014-3236-0.

95. Leyton Y, Gonzalez-Hormazabal P, Blanco R, Bravo T, Fernandez-Ramires R, Morales S, et al. Association of PALB2 sequence variants with the risk of familial and early-onset breast cancer in a South-American population. BMC Cancer. 2015;15:30. doi:10.1186/s12885-015-1033-3.

96. Xia B, Sheng Q, Nakanishi K, Ohashi A, Wu J, Christ N, et al. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell. 2006;22(6):719–29. doi:10.1016/j.molcel.2006.05.022.

97. Sy SM, Huen MS, Chen J. PALB2 is an integral component of the BRCA complex required for homologous recombination repair. Proc Natl Acad Sci USA. 2009;106(17):7155–60. doi:10.1073/pnas.0811159106.

98. Zhang F, Ma J, Wu J, Ye L, Cai H, Xia B, et al. PALB2 links BRCA1 and BRCA2 in the DNA-damage response. Curr Biol CB. 2009;19(6):524–9. doi:10.1016/j.cub.2009.02.018.

99. Zhang F, Fan Q, Ren K, Andreassen PR. PALB2 functionally connects the breast cancer susceptibility proteins BRCA1 and BRCA2. Mol Cancer Res MCR. 2009;7(7):1110–8. doi:10.1158/1541-7786.MCR-09-0123.

100. Sy SM, Huen MS, Zhu Y, Chen J. PALB2 regulates recombinational repair through chromatin association and oligomerization. J Biol chem. 2009;284(27):18302–10. doi:10.1074/jbc.M109.016717.

101. Pharoah PD, Antoniou A, Bobrow M, Zimmern RL, Easton DF, Ponder BA. Polygenic susceptibility to breast cancer and implications for prevention. Nat Genet. 2002;31(1):33–6. doi:10.1038/ng853.

102. Nathanson KL, Wooster R, Weber BL. Breast cancer genetics: what we know and what we need. Nat Med. 2001;7(5):552–6. doi:10.1038/87876.

103. Wooster R, Weber BL. Breast and ovarian cancer. New Engl J Med. 2003;348(23):2339–47. doi:10.1056/NEJMra012284.

104. Homburger JR, Moreno-Estrada A, Gignoux CR, Nelson D, Sanchez E, Ortiz-Tello P, et al. Genomic insights into the ancestry and demographic history of South America. PLoS Genet. 2015;11(12):e1005602. doi:10.1371/journal.pgen.1005602.

105. Salzano FM, Sans M. Interethnic admixture and the evolution of Latin American populations. Genet Mol Biol. 2014;37(1 Suppl):151–70.

106. Morera B, Barrantes R, Marin-Rojas R. Gene admixture in the Costa Rican population. Ann Hum Genet. 2003;67(Pt 1):71–80.

107. Wang Z, Hildesheim A, Wang SS, Herrera R, Gonzalez P, Burdette L, et al. Genetic admixture and population substructure in Guanacaste Costa Rica. PLoS ONE. 2010;5(10):e13336. doi:10.1371/journal.pone.0013336.

108. Moreno-Estrada A, Gignoux CR, Fernandez-Lopez JC, Zakaria F, Sikora M, Contreras AV, et al. Human genetics. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science. 2014;344(6189):1280–5. doi:10.1126/science.1251688.

109. Alter BP, Rosenberg PS, Brody LC. Clinical and molecular features associated with biallelic mutations in FANCD1/BRCA2. J Med Genet. 2007;44(1):1–9. doi:10.1136/jmg.2006.043257.