Review

Landscape of Germline Mutations in DNA Repair Genes for Breast Cancer in Latin America: Opportunities for PARP-Like Inhibitors and Immunotherapy

Laura Keren Urbina-Jara 1, Augusto Rojas-Martinez 1, Emmanuel Martinez-Ledesma 1, Dione Aguilar 1,2, Cynthia Villarreal-Garza 2,3* and Rocio Ortiz-Lopez 1,*

1 Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey 64710, Mexico
2 Tecnologico de Monterrey, Centro de Cancer de Mama, Hospital Zambrano Hellion, San Pedro Garza Garcia 66278, Mexico
3 Instituto Nacional de Cancerologia, Departamento de Investigacion, Av. San Fernando #22, Tlalpan, Ciudad de Mexico 14080, Mexico

* Correspondence: rortizl@tec.mx; Tel.: +52-81-8888-2270

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Abstract: Germline mutations in BRCA1 and BRCA2 (BRCA1/2) genes are present in about 50% of cases of hereditary breast cancer. Proteins encoded by these genes are key players in DNA repair by homologous recombination (HR). Advances in next generation sequencing and gene panels for breast cancer testing have generated a large amount of data on gene variants implicated in hereditary breast cancer, particularly in genes such as PALB2, ATM, CHEK2, RAD51, MSH2, and BARD1. These genes are involved in DNA repair. Most of these variants have been reported for Caucasian, Jewish, and Asian population, with few reports for other communities, like those in Latin American (LA) countries. We reviewed 81 studies from 11 LA countries published between 2000 and 2019 but most of these studies focused on BRCA1/2 genes. In addition to these genes, breast cancer-related variants have been reported for PALB2, ATM, CHEK2, BARD1, MLH1, BRIP1, MSH2, NBN, MSH6, and PMS2 genes. Some of these variants are unique to LA populations. This analysis may contribute to enhance breast cancer variant characterization, and thus to find therapies and implement precision medicine for LA communities.

Keywords: breast cancer; BRCA1; BRCA2; DNA repair; Latin America; germline; PARP inhibitors therapy

1. Introduction

Breast cancer is the leading cause of cancer death in women worldwide, with about 627,000 deaths in 2018 [1]. About 5–10% of all breast cancer is caused by germline variants in BRCA1/2 [2,3]. Moreover, about 50% of hereditary breast cancer (HBC) cases present germline mutations in BRCA genes [2]. BRCA1/2 pathogenic variants confer more than 50% risk of breast cancer development [4]. Since the identification of breast cancer genes BRCA1/2 in 1994 and 1995, respectively [5–7], a large amount of data on the risks conferred by these genes for breast and other cancers has been generated. These genes play an important role in the repair of double-strand breaks in DNA by homologous recombination (HR) along with a plethora of additional proteins [2,8–10].

About 50–60% of cases of HBC show variants in BRCA1/2 genes. The remaining percentage involves moderate and low penetrance variants in non-BRCA genes [11]. Next generation sequencing (NGS) and other technologies are still identifying variants in genes associated with breast cancer.
Non-BRCA variants have been observed in genes like ATM, PALB2, RAD51, and BARD1 [4,12,13]. Like BRCA genes, these genes codify for proteins participating in DNA repair [14,15].

The National Comprehensive Cancer Network (NCCN) guidelines for genetic assessment in hereditary breast cancer (version 3.2019) recommends genetic evaluation of ATM, CDH1, CHEK2, NBN, NF1, and PALB2 in addition to BRCA1/2 genes. There is accumulative evidence that variants in BARD1, BRIP1, MSH2, MLH1, MSH6, PMS2, RAD51C, and RAD51D are also causative of HBC, although some of these gene products participate in other DNA repair pathways and there is insufficient evidence for establishing management strategies [16]. This generates a paradigm for genetic counseling and assessment. Based on the absence of functional studies evaluating the activity of these genes, genetic advisory is being challenged by patient management.

Notably, most of the data on HBC variants represent Caucasian populations [17]. HBC accounts for about 15% of breast cancer cases in Latin America (LA) [18]. This population, resulting from the combination of Native American, Spanish, African, and other communities, is highly heterogeneous, even within the regions of the different countries where they live [19–21]. This diversity impacts the genetic variation involved in HBC in this large community [20]. Unfortunately, the data on HBC variants for this population is scarce and mainly focused on BRCA1/2; few cumulative reports on these variants have been reported. This information will be required to implement programs of precision medicine for HBC patients belonging to this population, like those that are being implemented for prevention and therapy of BRCA1/2 variants, particularly with Poly-ADP ribose polymerase (PARP) inhibitors [22–27]. Additionally, studies are suggesting that some tumor types with mutations in DNA repair genes are amenable for immunotherapy approaches [28–33]. This review analyzes 81 studies of germline mutations in breast cancer from 11 LA countries published between 2000 and 2019, with the focus on BRCA and non-BRCA genes involved in DNA repair.

2. Materials and Methods

We searched the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) for all breast cancer studies in 21 LA countries. Studies published between 2000 and April 5, 2019 were considered. A total of 7901 studies were retrieved using the following search terms “Breast cancer” and 21 LA countries (“Argentina”, “Belize”, “Bolivia”, “Brazil”, “Chile”, “Colombia”, “Costa Rica”, “Cuba”, “Dominican Republic”, “Ecuador”, “El Salvador”, “Guatemala”, “Honduras”, “Mexico”, “Nicaragua”, “Panama”, “Paraguay”, “Peru”, “Puerto Rico”, “Uruguay”, and “Venezuela”); as well as “BRCA1 and BRCA2”. Studies published in English and Spanish were included. Titles and abstracts were reviewed, and ineligible reports were discarded. The inclusion criteria considered research papers, case reports, and germline mutation data. A diagram showing the process of data acquisition is presented in Figure 1.

Considering the inclusion criteria, 81 studies were selected for extensive analysis [34–114]. Eleven countries reported germline gene variant data in breast cancer (Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Mexico, Peru, Puerto Rico, Uruguay, and Venezuela). Six hundred and ninety-two variants were found in BRCA1/2 genes. Additionally, 126 variants were reported in 43 non-BRCA genes of patients from 7 countries. All variants were investigated in the Catalogue of Somatic Mutations in Cancer (COSMIC) (https://cancer.sanger.ac.uk/cosmic) and the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) databases. The COSMIC database is the largest curated resource, with cancer mutation data from over 32,000 genomes including samples from The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC). ClinVar was used to measure the clinical significance of the reported data.

Among variants in BRCA1/2 genes, 202 were not found in the databases, 316 were classified as pathogenic, 59 as benign, and 115 were classified as “conflicting interpretations”, “uncertain significance”, “likely pathogenic”, and “likely benign”. Regarding the variants in non-BRCA genes, 22 variants were classified as pathogenic, 10 as benign, 57 as “conflicting interpretations”, “uncertain significance”, “likely pathogenic”, “likely benign”, “drug response”, “risk” and “risk factor”, and 37 were not found in the databases. Variants classified as “conflicting interpretations”, “uncertain
significance”, “likely pathogenic”, “likely benign”, “drug response”, “risk”, and “risk factor”, were grouped as variants of unknown significance (VUS) for the purposes of this study.

Figure 1. Study diagram. This diagram shows data acquisition and variant classification. *VUS: conflicting interpretation, uncertain significance, likely pathogenic, likely benign, risk factor, drug response.

3. Results

3.1. The Scope of Germline Mutations in Breast Cancer in LA Countries

From our literature analysis, only 11 out of 21 countries documented germline data for breast cancer cases. Brazil led the list of reports (32), followed by Chile, Mexico, Colombia, and Argentina. Cuba and Venezuela only had one report each (Table 1). No germline data were found for studies performed in Ecuador, Paraguay, Panama, Dominican Republic, El Salvador, Bolivia, Guatemala, Nicaragua, Honduras, and Belize. Most of the data for germline variants in HBC accounts for the BRCA1/2 genes and just a few studies include non-BRCA genes in a few LA countries.

Table 1. BRCA and Non-BRCA genes papers in Latin America (LA).

| Country   | Total Retrieved Papers | Germline Data | BRCA1/2 Papers | Non-BRCA Papers | Total Papers | References |
|-----------|------------------------|---------------|----------------|-----------------|--------------|------------|
| 1 Brazil  | 3290                   | ✓             | 13             | 19              | 32           | [34–65]    |
| 2 Chile   | 455                    | ✓             | 7              | 7               | 14           | [66–79]    |
| 3 Mexico  | 2014                   | ✓             | 8              | 4               | 12           | [80–91]    |
| 4 Colombia| 274                    | ✓             | 5              | 1               | 6            | [92–97]    |
| 5 Argentina| 899                   | ✓             | 4              | 4               | 8            | [98–101]   |
| 6 Peru    | 161                    | ✓             | 2              | 1               | 3            | [102–104]  |
| 7 Puerto Rico | 253                  | ✓             | 2              | 3               | 5            | [105–107]  |
| 8 Uruguay | 126                    | ✓             | 3              | 3               | 6            | [108–110]  |
| 9 Costa Rica | 56                   | ✓             | 2              | 2               | 4            | [111,112]  |
| 10 Cuba   | 142                    | ✓             | 1              | 1               | 2            | [113]      |
| 11 Venezuela | 76                    | ✓             | 1              | 1               | 2            | [114]      |
| Country              | Total Retrieved Papers | Germline Data | BRCA1/2 Papers | Non-BRCA Papers | Total Papers | References |
|----------------------|------------------------|---------------|----------------|-----------------|--------------|------------|
| 12 Ecuador           | 42                     |               |                |                 |              |            |
| 13 Paraguay          | 31                     |               |                |                 |              |            |
| 14 Panama            | 23                     |               |                |                 |              |            |
| 15 Dominican Republic| 18                     |               |                |                 |              |            |
| 16 El Salvador       | 16                     |               |                |                 |              |            |
| 17 Bolivia           | 13                     |               |                |                 |              |            |
| 18 Guatemala         | 8                      |               |                |                 |              |            |
| 19 Nicaragua         | 7                      |               |                |                 |              |            |
| 20 Honduras          | 2                      |               |                |                 |              |            |
| 21 Belize            | 1                      |               |                |                 |              |            |
| Total                | 7901                   | 11            | 48             | 33              | 81           |            |

1 First search combining terms “Breast cancer” versus 21 LA countries (“Argentina”, “Belize”, “Bolivia”, “Brazil”, “Chile”, “Colombia”, “Costa Rica”, “Cuba”, “Dominican Republic”, “Ecuador”, “El Salvador”, “Guatemala”, “Honduras”, “Mexico”, “Nicaragua”, “Panama”, “Paraguay”, “Peru”, “Puerto Rico”, “Uruguay”, “Venezuela”); as well as “BRCA1 and BRCA2”. 2 Second search including papers with germline mutation data and breast cancer.

3.2. Genes reported for HBC in LA countries

The study found 363 variants in BRCA2 and 329 variants in BRCA1 in 11 countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Mexico, Peru, Puerto Rico, Uruguay, and Venezuela). In addition, variants were also observed in 43 non-BRCA genes like ATM, TP53, CHEK2, BARD1, MLH1, PALB2, BRIP1, MSH2, MSH6, NBN, and PMS2 in Chile, Brazil, Colombia, and Mexico (Table 2, Figure S1).

| Gene   | Number of Variants | Argentina | Brazil | Chile | Colombia | Costa Rica | Cuba | Mexico | Peru | Puerto Rico | Uruguay | Venezuela |
|--------|--------------------|-----------|--------|-------|----------|------------|------|--------|------|-------------|---------|-----------|
| BRCA2  | 363                | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| BRCA1  | 329                | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| ATM    | 17                 | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| TP53   | 11                 | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| CHEK2  | 8                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| BARD1  | 6                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| MLH1   | 6                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| PALB2  | 6                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| BRIP1  | 5                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| MSH2   | 4                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| MSH6   | 4                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| NBN    | 4                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| PMS2   | 4                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| APC    | 3                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| ATR    | 3                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| BLM    | 3                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| RAD51C | 3                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| CDKN2A | 2                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| ERCC1  | 2                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| ERCC2  | 2                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| ERCC3  | 2                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| FANCB  | 2                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| FANCI  | 2                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| LIG4   | 2                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
| MUTYH  | 2                  | ✓         | ✓      | ✓     | ✓        | ✓          | ✓    | ✓      | ✓    | ✓           | ✓       | ✓         |
### Table 2. Cont.

| Gene   | Number of Variants | Argentina | Brazil | Chile | Colombia | Costa Rica | Cuba | Mexico | Peru | Puerto Rico | Uruguay | Venezuela |
|--------|---------------------|-----------|--------|-------|----------|------------|------|--------|------|-------------|---------|-----------|
| RAD51B | 2                   | ✓         | ✓      |       | ✓        |            |      |        |      |             |         |           |
| RAD51D | 2                   | ✓         | ✓      |       | ✓        |            |      |        |      |             |         |           |
| XRCC1  | 2                   | ✓         | ✓      |       | ✓        |            |      |        |      |             |         |           |
| CDH1   | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| FANCC  | 1                   | ✓         | ✓      |       | ✓        |            |      |        |      |             |         |           |
| FANCF  | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| FANCL  | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| FANCM  | 1                   | ✓         | ✓      |       | ✓        |            |      |        |      |             |         |           |
| MSH3   | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| NF1    | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| POLH   | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| POLQ   | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| PTEN   | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| RAD50  | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| RAD51  | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| RECQL4 | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| SMAD4  | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| WRN    | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| XPC    | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |
| XRCC3  | 1                   | ✓         | ✓      | ✓     | ✓        |            |      |        |      |             |         |           |

### 3.3. BRCA1 and BRCA2 Genes in LA countries

Studies conducted in some LA countries have established frequent and founder BRCA1/2 mutations in the region. The BRCA1 3450del4, c.5123C>A variant and BRCA2 3034del4 are considered founder mutations in Colombia [67,92,115]. The variants 5382insC in BRCA1 and 6633del5 and 156_157insAlu in BRCA2 are prevalent in Brazil [52,105,115,116]. Three variants observed in the Ashkenazi community, c.66_67delAG and c.5263insC in BRCA1, and c.5946delT in BRCA2 were reported in Argentina [92,98,105]. In Mexico, the BRCA1 ex9–12 deletion is reported as a founder mutation [88], while the variants, 2805_2808delAGAT and 3124_3133delAGCAATATTA in BRCA1, and 2639_2640delTG and 5114_5117delTAAA in BRCA2 are reported as pathogenic [89,105,115]. In Puerto Rico, the variant E1308X in BRCA2 is present in most cases of HBC [105], while in Chile, the variants c.3331_3334delCAAAG and c.3759dupT in BRCA1 and c.4740_4742dupTG, c.5146_5149delTATG in BRCA2 are more prevalent [67]. In Peru, three recurrent mutations were described, 185delAG and 2080delA in BRCA1, and mutation 3034del4 in BRCA2 have been observed [102,116]. In Costa Rica, BRCA2 variants such as the 5531delTT are frequently reported [111,116]. No recurrent mutations in BRCA1/2 genes were found in Venezuela [114,116]. No reports on BRCA1/2 variants were registered for Belize, Bolivia, the Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, and Paraguay. This evidence suggests that some variants are preferentially distributed in particular LA countries.

Some other BRCA1/2 variants are observed in more than one LA country (Table 3), like the pathogenic variant BRCA2 c.2808_2811del variant reported in seven countries (Argentina, Brazil, Colombia, Mexico, Peru, Uruguay, and Venezuela) and the pathogenic BRCA1 variants c.68_69delAG and c.211A>G observed in six countries. Remarkably, the BRCA2 variant c.7469T>C classified as benign in ClinVar was observed in HBC cases in Argentina, Brazil, Colombia, Cuba, Mexico, Uruguay, and Venezuela, prompting a reconsideration of its reclassification. In summary, there are shared and specific BRCA1/2 variants in HBC patients, reflecting the ethnic heterogeneity in Latin America [105].
Table 3. Frequent BRCA1/2 gene variants in LA.

| Gene Variant | rs | Exon | Argentina | Brazil | Chile | Colombia | Costa Rica | Cuba | Mexico | Peru | Puerto Rico | Uruguay | Venezuela |
|--------------|----|------|-----------|--------|-------|----------|------------|------|--------|------|-------------|---------|------------|
| BRCA1 VARIANT |    |      |           |        |       |          |            |      |        |      |             |         |            |
| c.68_69delAG | rs386833395 | 2 (4) | (4) | (2) | (1) | (1) | (1) |
| c.181T>G     | rs28897672  | 5 | (1) | (4) | (1) |
| c.211A>G     | rs80357382  | 5 | (2) | (3) | (1) | (3) | (1) | (1) |
| c.3113A>G    | rs16941     | 11 | (1) | (3) | (2) | (1) |
| c.3548A>G    | rs16942     | 11 | (1) | (3) | (1) | (1) |
| c.1067A>G    | rs1799950   | 11 | 2 | (3) | (1) |
| c.3119G>A    | rs4986852   | 11 | (1) | (3) | (1) | (1) |
| c.2612C>T    | rs799917    | 11 | (1) | (3) | (1) |
| c.3331_3334delCAAG | rs80357701 | 11 | (9) | (3) | (6) |
| c.4308C>T    | rs1060915   | 13 | (1) | (2) | (1) |
| c.4837A>G    | rs1799966   | 16 | (1) | (3) | (1) | (1) |
| c.5123C>A    | rs28897696  | 18 | (1) | (2) | (8) | (3) |
| c.5266dupC   | rs397907247 | 20 | (4) | (16) | (1) | (1) |
| BRCA2 VARIANT |    |      |           |        |       |          |            |      |        |      |             |         |            |
| c.865A>C     | rs766173    | 10 | (1) | (2) | (1) | (1) |
| c.2971A>G    | rs1799944   | 10 | (1) | (2) | (2) | (1) | (1) |
| c.5744C>T    | rs4987117   | 11 | (1) | (2) | (2) | (1) |
| c.2808_2811del | rs80359351 | 11 | (3) | (5) | (2) | (1) | (2) | (1) |
| c.5351dupA   | rs80359507  | 11 | (1) | (2) | (2) |
| c.5946delT   | rs80359550  | 11 | (5) | (4) | (1) |
| c.7469T>C    | rs11571707  | 15 | (2) | (4) | (1) | (1) | (1) |
| c.10234A>G   | rs1801426   | 27 | (1) | (3) | (2) | (1) |

() Number of reporting papers.

There are also reports of large genomic rearrangements (LGR) in BRCA1/2 in LA countries (Table 4). Brazil has reported 18 different LGR in BRCA genes, more than in other LA countries. The deletion of exons 1-2 in BRCA1 was reported in three cases in Brazil and Puerto Rico [56,63,106]. The 6kb duplication in exon 13 in BRCA1 was reported in seven Brazilian patients [51]. In Mexico, the exon 9–12 deletion in BRCA1 is considered as a founder mutation that has been found in 25 cases so far [80,81,84,88]. Interestingly, the LGR g.26826_30318del in BRCA2 found in Brazil was associated with high-risk male breast cancer [35,64]. There are also descriptions of LGRs in BRCA1/2 in breast cancer patients from Peru, Puerto Rico, and Uruguay [104,106,109].

Table 4. Large genomic rearrangements in BRCA1/2.

| Gene | Mutation | Cases | Brazil | Colombia | Mexico | Peru | Puerto Rico | Uruguay | References |
|------|----------|-------|--------|----------|--------|------|-------------|---------|------------|
| BRCA1 | exon 1-2 deletion | 3     | ✓      | ✓       | ✓      | ✓    | ✓           |         | [60,63,106] |
| BRCA1 | exon 3 deletion     | 2     | ✓      | ✓       | ✓      | ✓    |             |         | [60,63]   |
| BRCA1 | exon 4-6 deletion   | 2     | ✓      | ✓       | ✓      | ✓    |             |         | [60,63]   |
| BRCA1 | exon 5-7 deletion   | 2     | ✓      | ✓       | ✓      | ✓    |             |         | [53,60]   |
| BRCA1 | exon 8 deletion     | 2     | ✓      | ✓       | ✓      | ✓    |             |         | [60,63]   |
| BRCA1 | exon 8-13 deletion  | 1     | ✓      | ✓       | ✓      | ✓    |             |         | [104]     |
| BRCA1 | exon 9-11 deletion  | 1     | ✓      | ✓       | ✓      | ✓    |             |         | [80]      |
| BRCA1 | exon 9-12 deletion  | 25    | ✓      | ✓       | ✓      | ✓    |             |         | [80,81,84,88] |
| BRCA1 | exon 9-19 deletion  | 2     | ✓      | ✓       | ✓      | ✓    |             |         | [41,60]   |
| BRCA1 | exon 12 deletion    | 1     | ✓      | ✓       | ✓      | ✓    |             |         | [80]      |
| BRCA1 | exon 14 deletion    | 1     | ✓      | ✓       | ✓      | ✓    |             |         | [109]     |
| BRCA1 | exon 14-16 deletion | 1     | ✓      | ✓       | ✓      | ✓    |             |         | [60]      |
Table 4. Cont.

| Gene   | Mutation                  | Cases | Brazil | Colombia | Mexico | Peru | Puerto Rico | Uruguay | References |
|--------|---------------------------|-------|--------|----------|--------|------|--------------|---------|------------|
| BRCA1  | exon 16-17 deletion       | 2     | ✓      |          |        |      |              |         | [60,65]    |
| BRCA1  | exon 18-19 deletion       | 2     | ✓      | ✓        |        |      |              |         | [60,104]   |
| BRCA1  | exon 19 deletion          | 1     |        |          | ✓      |      |              |         | [60]       |
| BRCA1  | exon 21-23 deletion       | 1     |        |          | ✓      |      |              |         | [60]       |
| BRCA1  | exon 24 duplication       | 1     |        |          | ✓      |      |              |         | [69]       |
| BRCA1  | 6-KB DUP EX13             | 7     |        |          | ✓      | ✓    |              |         | [61]       |
| BRCA2  | exon 1 deletion           | 3     |        |          |        | ✓    |              |         | [80]       |
| BRCA2  | exon 1-14 deletion        | 2     |        |          | ✓      |      |              |         | [94]       |
| BRCA2  | exon 2 deletion           | 1     |        |          | ✓      |      |              |         | [60]       |
| BRCA2  | exon 11 deletion          | 1     |        |          | ✓      |      |              |         | [80]       |
| BRCA2  | exon 13 deletion          | 1     |        |          | ✓      |      |              |         | [60]       |
| BRCA2  | exon 14 deletion          | 1     |        |          | ✓      |      |              |         | [60]       |
| BRCA2  | exon 15-16 deletion       | 1     |        |          | ✓      |      |              |         | [92]       |
| BRCA2  | exon 17 deletion          | 1     |        |          | ✓      |      |              |         | [80]       |
| BRCA2  | exon 22-24 deletion       | 2     |        |          | ✓      |      |              |         | [80]       |
| BRCA2  | exon 23 deletion          | 2     |        |          | ✓      |      |              |         | [80]       |
| BRCA2  | exon 25 deletion          | 1     |        |          | ✓      |      |              |         | [60]       |
| BRCA2  | exon 26 deletion          | 1     |        |          | ✓      |      |              |         | [80]       |
| BRCA2  | g.26826_30318del          | 2     |        |          | ✓      |      |              |         | [35,64]    |

3.4. Non-BRCA Genes Reported in Breast Cancer in LA Countries

Brazil, Chile, Colombia, Mexico, Peru, Puerto Rico, and Uruguay are the only LA countries that have conducted screenings for non-BRCA genes in breast cancer cases. We found 126 variants in 43 non-BRCA genes (Table 5). Variants were found in ATM, TP53, CHEK2, BARD1, MLH1, PALB2, and BRIP1. The most frequent variants of ATM, TP53, CHEK2, and BARD1 are represented in Figure 2 as lollipop plots following published instructions [117,118]. The ataxia telangiectasia mutated (ATM) gene was the most reported in LA breast cancer cases. Seventeen variants were found in ATM in Mexico, Brazil, Chile, and Colombia, 11 variants in TP53 (Brazil, Colombia, and Uruguay) and 8 variants in CHEK2 (Brazil, Chile, Mexico, and Uruguay). Furthermore, six variants in each of the following genes were found in HBC cases: BARD1, MLH1, PALB2 and five variants in BRIP1 (Brazil, Chile, Colombia, Mexico, Peru, and Uruguay). The pathogenic classification of these variants is described according to ClinVar and COSMIC databases in Table S1. The CHEK2 variant c.1100delC reported in Brazil and Chile presents conflicting interpretations of pathogenicity according to ClinVar and is not reported in the COSMIC database. The TP53 variant c.1010G>A (p.R337H) observed in Brazil is considered to be pathogenic by ClinVar, but it is not classified as such by COSMIC [115].

Table 5. Frequent variants in non-BRCA genes in LA.

| Gene   | rs             | Variant   | COSMIC | CLINVAR | Brazil | Chile | Colombia | Mexico | Peru | Uruguay |
|--------|----------------|-----------|--------|---------|--------|-------|----------|--------|------|---------|
| ATM    | NA             | c.634delT | ✓      | x       |        |       |          |        |      |         |
| ATM    | NA             | c.5648_5655del | ✓      | x       |        |       |          |        |      |         |
| ATM    | rs145119475    | c.4060C>A |        |         | x      |       |          |        |      |         |
| ATM    | rs1800056      | c.2572T>C | ✓      | ✓       | x      |       |          |        |      |         |
| ATM    | rs1801516      | c.5557G>A | ✓      | ✓       | x      |       |          |        |      |         |
| ATM    | rs1801673      | c.5558A>T | ✓      | ✓       | x      |       |          |        |      |         |
| ATM    | rs200381392    | c.1703G>T | ✓      |         | x      |       |          |        |      |         |
| Gene | rs          | Variant       | COSMIC | CLINVAR | Brazil | Chile | Colombia | Mexico | Peru | Uruguay |
|------|------------|---------------|--------|---------|--------|-------|----------|--------|------|---------|
| ATM  | rs202173660| c.1444A>C     | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| ATM  | rs2234997  | c.378T>A      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| ATM  | rs2235006  | c.1744T>C     | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| ATM  | rs4986761  | c.2119T>C     | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| ATM  | rs587782153| c.5039C>T     | ✓      | ✓       | x      | ✓    | x        |        |      |         |
| ATM  | rs75862678 | c.241A>G      | ✓      | ✓       | x      | ✓    | x        |        |      |         |
| ATM  | rs759965045| c.7702_7703del| ✓      | ✓       | x      | ✓    | x        |        |      |         |
| ATM  | rs771887195| c.43del       | ✓      | ✓       | x      | ✓    | x        |        |      |         |
| ATM  | rs786203421| c.7000_7003delTACA | ✓      | ✓       | x      | ✓    | x        |        |      |         |
| TP53 | rs1042522  | c.215C>G      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs11540652 | c.743G>A      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs121912664| c.1010G>A     | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs121913344| c.916C>T      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs144386518| c.173C>G      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs1800370  | c.108G>A      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs1800371  | c.139C>T      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs28934576 | c.818G>A      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs55863639 | c.375G>A      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs587782144| c.473G>A      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| TP53 | rs587782620| c.427G>A      | ✓      | ✓       | ✓      | x     | x        |        |      |         |
| CHEK2| NA         | c.1015C>T     | x      | ✓       | x      | ✓    | x        |        |      |         |
| CHEK2| NA         | c.1151delT    | x      | ✓       | x      | ✓    | x        |        |      |         |
| CHEK2| NA         | c.705A>C      | x      | ✓       | x      | ✓    | x        |        |      |         |
| CHEK2| NA         | c.852G>T      | x      | ✓       | x      | ✓    | x        |        |      |         |
| CHEK2| rs155926890?| c.506T>C    | x      | ✓       | x      | ✓    | x        |        |      |         |
| CHEK2| rs555607078 | c.1100delC  | x      | ✓       | x      | ✓    | x        |        |      |         |
| CHEK2| rs587781652 | c.485A>G    | x      | ✓       | x      | ✓    | x        |        |      |         |
| CHEK2| rs864622149| c.846+1G>C   | x      | ✓       | x      | ✓    | x        |        |      |         |
| BARD1| NA         | c.2215dupT    | x      | ✓       | x      | ✓    | x        |        |      |         |
| BARD1| rs143914387 | c.339G>T     | x      | ✓       | x      | ✓    | x        |        |      |         |
| BARD1| rs28997576 | c.1670G>C     | x      | ✓       | x      | ✓    | x        |        |      |         |
| BARD1| rs587781948 | c.1921C>T   | x      | ✓       | x      | ✓    | x        |        |      |         |
| BARD1| rs58972589 | c.334C>T     | x      | ✓       | x      | ✓    | x        |        |      |         |
| BARD1| rs777937955 | c.1622C>A   | x      | ✓       | x      | ✓    | x        |        |      |         |
| MLH1 | NA         | c.1966C>T    | x      | ✓       | x      | ✓    | x        |        |      |         |
| MLH1 | NA         | c.413A>G     | x      | ✓       | x      | ✓    | x        |        |      |         |
| MLH1 | NA         | c.791G>A     | x      | ✓       | x      | ✓    | x        |        |      |         |
| MLH1 | rs148317871| c.2213G>A    | x      | ✓       | x      | ✓    | x        |        |      |         |
| MLH1 | rs63751615 | c.676C>T     | x      | ✓       | x      | ✓    | x        |        |      |         |
| MLH1 | del_exon8  | NA           | x      | ✓       | x      | ✓    | x        |        |      |         |
| PALB2| NA         | c.1861C>A    | x      | ✓       | x      | ✓    | x        |        |      |         |
| PALB2| NA         | c.483C>G     | x      | ✓       | x      | ✓    | x        |        |      |         |
| PALB2| rs150390726 | c.23C>T     | x      | ✓       | x      | ✓    | x        |        |      |         |
| PALB2| rs152451   | c.1676A>G    | x      | ✓       | x      | ✓    | x        |        |      |         |
| PALB2| rs180177100| c.1240C>T    | x      | ✓       | x      | ✓    | x        |        |      |         |
| PALB2| rs45551636 | c.2993C>T    | x      | ✓       | x      | ✓    | x        |        |      |         |
| BRIP1| rs202072866| c.415T>G     | x      | ✓       | x      | ✓    | x        |        |      |         |
| BRIP1| rs28997569 | c.790C>T     | x      | ✓       | x      | ✓    | x        |        |      |         |
| BRIP1| rs371185409 | c.3079G>A   | x      | ✓       | x      | ✓    | x        |        |      |         |
| BRIP1| rs45589637 | c.2220G>T    | x      | ✓       | x      | ✓    | x        |        |      |         |
| BRIP1| rs759031349| c.689C>T     | x      | ✓       | x      | ✓    | x        |        |      |         |

✓ Databases; x Country; NA: Not available.
Figure 2. Mutations in non-BRCA genes reported in LA breast cancer patients. Frequently reported mutations are observed in \textit{ATM}, \textit{TP53}, \textit{CHEK2} and \textit{BARD1} genes. (a) \textit{ATM} likely loss of function and therefore likely oncogenic mutations S214Pfs*16, S1883fs, T2334Qfs*4, and R2568fs; (b) \textit{TP53} likely loss of function and therefore likely oncogenic mutations V143M, R158H, R248Q, R273H, R306*, and R337H; (c) \textit{CHEK2} most reported mutation T367M*; (d) \textit{BARD1} likely loss of function and therefore likely oncogenic mutations R112*, S541*, RG41* and Y739Lfs*. Mutation type: missense (green), truncating (black), in frame (red), other (pink).

Non-BRCA genes with at least two reported variants in LA countries are presented in Figure 3A. Mexico, Brazil, and Colombia are the countries with more reported variants in non-BRCA genes. Non-BRCA genes with only one variant reported in LA are described in Figure 3B. A total of 10 non-BRCA genes with one variant are reported in Mexico [81]. Additionally, only one variant was found in \textit{RAD51}, \textit{XRCC3}, \textit{CDH1}, \textit{MSH3}, \textit{POLQ}, \textit{SMAD4}, and \textit{XPC} genes in Brazil, Chile, and Colombia.

Cock et al. [92] reported germline mutations in non-BRCA genes (\textit{PALB2}, \textit{ATM}, \textit{MSH2}, \textit{PMS2}, \textit{MSH6}, and \textit{TP53}) in Colombia. Among their findings, the mutation c.137G>T in \textit{PMS2} was identified in a patient with early-onset breast cancer (31 years old), an invasive ductal carcinoma, HR-, HER2+, and positive family history. Another patient diagnosed at 36 years with invasive ductal carcinoma HR+, HER2-, had a \textit{PALB2} mutation c.1240C>T. There was another patient diagnosed at 48 years with invasive ductal carcinoma and positive history of familial cancer carrying the \textit{ATM} c.43del variant. VUS were also reported in patients carrying \textit{PMS2}, \textit{BARD1}, \textit{RAD51C}, \textit{BRIP1}, \textit{MSH6}, and \textit{MSH2} variants [92]. A previously study of Mexican patients carried out by Quezada et al. describes variants in DNA
repair genes including ATM, ERCC3, FANCI, ATR, MLH1, NBN, RAD51C, non-BRCA genes (54%) and BRCA1/2 (46%) [81].

![Figure 3. Non-BRCA gene variants reported from breast cancer patients in 7 LA countries. (a) Reported number of germline genes variants in breast cancer by country in LA; (b) Unique gene variants reported in LA countries.]

4. Biallelic Cases, Double Heterozygosity and Young Women in LA Countries

In addition to cancer-associated variants in BRCA1/2 and non-BRCA genes in breast cancer, there have been reports of biallelic mutations in Australia, Italy, Denmark, Spain, Korea, and other Caucasian populations [119]. Mutations in FANCM, ATM, FANCE, and PALB2 contribute to locus heterogeneity, besides BRCA1/2 [120]. Cases harboring biallelic and double heterozygosity are listed in Table 6. The study performed in Colombia by Cock et al. found cases caused by locus heterogeneity involving BRCA1, MSH6, RAD51, PMS2, PALB2, BRCA2, and SMAD4 [92]. Interestingly, patients with double heterozygosity presented a familial cancer history and were diagnosed at early ages (before 40 years) [92]. In addition, HBC cases caused by biallelic variants in BRCA1/2 genes affecting young patients were reported in Brazil, Mexico, and Venezuela [63,87,114]. Notoriously, a 12-year old Argentinian patient with a triple-negative breast tumor was double heterozygous for BRCA1 and BRCA2 variants classified as benign, although she also carried some other non-reported variants [101]. Studies in communities like those described here may help to define the clinical phenotypes of HBC cases caused by locus heterogeneity.

![Table 6. Biallelic and locus heterogeneity mutations reported in LA breast cancer cases.]

- **Patient ID**: NA, 15, 8
- **Gene 1**: BRCA1: c.1674del (pathogenic), PALB2: c.1240C>T (pathogenic), BRCA2: c.5616-5620del (not reported)
- **Gene 2**: MSH6: c.2419G>A (uncertain significance), PMS2: c.2395C>T (uncertain significance), SMAD4: c.677C>T (conflicting interpretations)
- **Age Onset**: 15, 36, 35
- **Country**: Colombia
- **Family History**: YES
- **Reference**: [92]
Table 6. Cont.

| Patient ID | Gene 1 | Gene 2 | Age | Country | Family History | Subtype | Reference |
|------------|--------|--------|-----|---------|----------------|---------|-----------|
| NA         | BRCA1: c.4357+1G>T (pathogenic) | BRCA2: c.6405_6409delTTAA (pathogenic) | 38   | Brazil  | NA             | ipsilateral BC | [63]       |
| NA         | BRCA1: LGR (deletion of exons 4–6) | BRCA2: c.9004C>A (conflicting interpretation) | 43   | Brazil  | NA             | NA       | [63]       |
| NA         | BRCA2: c.8878C>T (pathogenic), c.9699_9702delTATG (pathogenic) | | 52   | Brazil  | NA             | NA       | [63]       |
| CM001      | BRCA1: c.1129_1135insA (not reported), c.4063_4065delAAT (conflicting interpretations) | | 37   | Venezuela | YES | ER+, PR+ | [114] |
| CM055      | BRCA1: c.1129_1135insA (not reported), c.4063_4065delAAT (conflicting interpretations) | | 48   | Venezuela | YES | ER-, PR- | [114] |
| CM031      | BRCA2: c.1282T>C (not reported), c.3479G>A (conflicting interpretations) | | 49   | Venezuela | YES | NA       | [114] |
| 5          | BRCA2: c.865A>C (benign), c.2971A>G (benign), c.8851G>A (benign) | | 33   | Mexico   | NA             | ductal  | [87]       |
| 12         | BRCA1: c.2245G>T (uncertain significance) | BRCA2: p.Ile3412Val (benign) | 34   | Mexico   | NA             | ductal  | [87]       |
| 7          | BRCA1: c.442-34C>T (benign) | BRCA2: c.865A>C (benign), c.2971A>G (benign) | 34   | Mexico   | NA             | ductal  | [87]       |
| 17         | BRCA1: c.3548A>G (benign), c.442-34C>T (benign) | | 30   | Mexico   | YES | ER+, PR+, HER2- | [89] |
| A11        | BRCA1: c.4308T>C (benign), c.442-34C (not reported), c.5152+66G>A (benign), c.548-58delT (benign) | BRCA2: c.426+67A>C (not reported), c.426-99T>C (benign), c.7435+53C>T (benign) | 12   | Argentina | YES | TNBC, Secretry Carcinoma | [101] |
| A17        | BRCA1: c.4308T>C (benign), c.5152+66G>A (benign), c.548-58delT (benign) | | 25   | Argentina | NO | PR+, ER+, HER2+, infiltrating ductal carcinoma | [101] |
| A18        | BRCA1: c.442-34T>C (not reported) | BRCA2: c.7469T>C (benign), c.6811+56C>T (benign), c.7242A>G (benign) | 21   | Argentina | NO | ER+, PR+ HER2-, infiltrating lobular carcinoma | [101] |

() Pathogenicity: ClinVar; NA: Not Available; LGR: Large Genomic Rearrangements.

Nowadays, a plethora of commercial testing panels are available including “Breast Next” from Ambry Genetics, “OncoGeneDx” from GeneDx, “My Risk” from Myriad Genetics, and others. These panels along with NGS and exome analysis provide a large amount of data yet to be analyzed for
breast cancer risk and its management [121]. According to the NCCN guidelines, genetic evaluation of genes like BRCA1/2, ATM, CDH1, CHEK2, NBN, NF1, and PALB2 is recommended for HBC prevention. Other genes associated to breast cancer risk included in the NCCN guidelines are BARD1, BRIP1, MSH2, MLH1, MSH6, PMS2, RAD51C, and RAD51D, but they are not considered for breast cancer management and assessment [16]. The growing number of genes and variants associated with HBC is a challenge to the standardized systems used for clinical testing, including the re-evaluation of the variants of unknown significance (VUS). VUS are not rare, for example, there are thousands of VUS reported for BRCA1/2 genes [122,123]. The increased number of VUS in BRCA genes correlates with the discovery of new variants in non-Caucasian ethnic groups. In individuals of European ancestry across the United States, VUS account for approximately 5–6% of the variants reported in clinical tests, and up to 21% in patients with African-American ancestry. Recent studies show a higher rate of VUS in BRCA1/2 for non-Caucasians (36%) than in Caucasians (27%) [124]. Testing laboratories in Europe estimate that up to 15% of alterations in BRCA1/2 are VUS [123]. Furthermore, reported variants in non-BRCA genes increase the complexity of pathogenicity classification and genetic counseling.

Information on non-BRCA gene variants in LA is scarce due to the low coverage for genetic testing in the health systems of the region, among other reasons [92,125]. This hinders the identification of new variants, their evaluation for clinical significance, and the risk management assessment.

5. Therapy Recommendation for DNA Repair Related Genes

DNA double-strand breaks (DSB) are among the first procedures that take place in cancer formation and progression because of endogenous and exogenous factors [126]. With DSB, two main mechanisms may be activated during the repair process, HR and non-homologous end joining (NHEJ) [127]. Most of the non-BRCA genes frequently reported in breast cancer participate in different DNA repair pathways. Reported DSB repair variants in breast cancer comprise PALB2, NBN, RAD51, ATM, CHEK2, ATR, RAD50, and WRN [128]. Likewise, reported variants include genes participating in mismatch repair (MMR) such as MSH2, MSH6, PMS2, and MLH1 [129] and genes participating in the Fanconi Anemia repair pathway like FANCM, FANCI, FANCB, FANCC, FANCL [130]. In addition to these pathways, variants in XPC, ERCC1, ERCC2 and ERCC3 genes relate to nucleotide excision repair. Variants in XRCC1 and MUTYH participate in base excision repair [131].

DNA repair genes display high mutation incidence in cancer, when DNA repair pathways are compromised, mutation rate arises because alternative error-prone repair pathways are used by the cell [11,132]. The study of the repair pathway mechanisms has identified new targets for therapy that might be useful in some types of cancer. For instance, PARP inhibitors such as Olaparib are used for ovarian cancer treatment based on the concept of synthetic lethality and are currently being studied in breast, prostate and gastrointestinal cancers. Besides PARP, there are other key components with potential for targeted therapy; ATR and ATM are major targets for inhibition as well as CHEK1/2 and DNA-PKs. For instance, M6620, the first inhibitor of ATR has been tested and ATM inhibitors such as M3541 are currently in clinical trials [133,134].

A different therapy approach that displays promising results in cancer treatment is immunotherapy with PD-1 and PD-L1 inhibitors [30,135]. High expression of PD-L1 on tumor cells or tumor-infiltrating lymphocytes (TILs) results in exhaustion of T cells and an attenuated tumor-specific immunity that promotes tumor progression [136]. Diverse studies show a possible relationship between altered DNA repair pathways that increase the mutational burden and immunotherapy response. For example, colorectal cancer patients with altered MMR pathways display high microsatellite instability, expression of PD-L1, as CD3+, CD8+ TILs and tumor-associated macrophages located at invasive fronts of the tumor. The mutational burden was associated with mutations in ATM, MMR deficiency, and therefore loss of expression in MLH1, MSH2, MSH6, and PMS2 [35]. In addition, patients with tumor DNA repair deficiencies such as POLE and POLD mutations, are considered good candidates for checkpoint immunotherapy [137,138]. In non-small cell lung cancer (NSCLC), a study by Chae et al. [28] showed that tumors with altered HR genes, MMR genes or POLE contained higher mutational load than tumors
with wildtype DNA repair genes. These tumors also contained higher infiltration of T cells and other cells that perform anti-tumor activity. The best treatment responses were observed in patients with high mutational burden with PD-1 inhibitors. The group of better responder patients displayed a neoantigen load and mutations in POLE, POLD1, and MSH2. Based on the premise that DNA repair loss results in elevated anti-tumor immune response, improved clinical outcomes were observed in patients with DNA repair gene mutations. Therefore, mutations in DNA repair genes in lung cancer were linked to increased TILs as CD4+ and CD8+ in the tumor. For patients with higher mutational burden, there is a greater likelihood of the formation of immunogenic epitopes expressed only in cancerous cells [28]. Similarly, in high-grade ovarian cancer altered BRCA1/2 results in a higher mutational load, therefore, tumors harbor more tumor-specific neoantigens, increased TILs including CD3+ and CD8+ and PD-1 and PD-L1 expression [29,136]. Strickland et al. found that tumors with altered HR repair show higher neoantigens along with improved overall survival. They inferred that high grade serous ovarian cancer with mutations in BRCA1/2 may be more sensitive to immune checkpoint inhibitors PD-1 and PD-L1 in comparison with tumors proficient in HR repair [29].

Breast cancer patients with compromised DNA repair mechanisms display high-risk tumor characteristics such as changes in cell morphology that promote invasion [139]. When HR is compromised, alternative error-prone DNA repair pathways are used and thus there is a chance that errors will occur, such as indels in the cell [140,141]. There are frequently mutated DNA repair genes in breast cancer and their analysis is fundamental to determine the tumor phenotype and clarify if a high mutational load is due to deficient DNA repair performance. PARP inhibitors are approved for some breast cancer cases, Olaparib was approved by the FDA for germline BRCA-mutated metastatic breast cancer on January 12, 2018 [142]. Similarly, Talazoparib was approved for germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer by the FDA in October, 2018 [143]. Moreover, several studies in Clinical Trials (https://clinicaltrials.gov/ct2/home) are focused on DNA repair genes. For instance, the study NCT03495544 focuses on the association between germline DNA repair genes mutations and PD-L1 expression level in breast cancer. Studies for PARP inhibitors such as Rucaparib have been completed, studies for Niraparib are still recruiting for Phase I and Phase III trials, and BMN673 is being tested in advanced breast cancer. On the other hand, immunotherapy studies in breast cancer like the one conducted by Schmid et al. [144] for triple-negative breast cancer (TNBC) showed that the combination of PD-L1 inhibitor Atezolizumab with nab-paclitaxel resulted in improvement in overall survival with a median of 9.5-month (HR 0.62, 95% CI 0.45–0.86) in patients with PD-L1 positive immune infiltration [144]. Another combined therapy for TNBC of Pembrolizumab an anti-PD-1 with chemotherapy increased the pathological complete response rates [145]. The potential for immunotherapy in breast cancer is promising, suggesting combination therapies for future clinical trials [146].

Even though novel cancer treatment strategies are appearing, in Latin America the availability of these therapies is challenging [147]. Over the last five years, about 64% of medicine newly released to the market was sold exclusively in the US, 24% of these new drugs were sold in Western Europe and 7% in Japan. Therefore, the remaining 5% is distributed in the rest of the world [147]. Between 2009 and 2013, 37 new cancer drugs were launched worldwide and only 17 of them are available in Mexico and 10 in Brazil [148], and access to high-cost cancer drugs is a barrier in the LA region [149]. In LA countries, use of novel drugs differs widely by insurance type, therefore, one promising solution to improve access to these therapies is participation in clinical research [148,149]. For breast cancer, chemotherapy with anthracyclines is accepted in the region, however, targeted therapy drugs such as Trastuzumab is not accessible to all patients. Restrictions to access new drugs leaves patients with few therapeutic alternatives, disease progression, and consequently, poor outcomes [150]. Therefore, one option for new drugs to be available in LA countries is through participation in clinical trials. Some of these countries are currently participating in clinical trials that are focused on PARP inhibitors and immune checkpoint inhibitors. Velaparib, Talazoparib, and Olaparib are PARP inhibitors and currently, active clinical trials NCT01506609, NCT02595905, and NCT02163694 are testing Velaparib
in combination with Carboplatin, Paclitaxel, and Cisplatin in breast cancer patients harboring BRCA mutations in Argentina, Brazil, Chile, Colombia, Puerto Rico, Mexico. Similarly, a phase 3 study NCT01945775 in Brazil is currently testing Talazoparib in patients with metastatic breast cancer and BRCA mutations. In addition, Olaparib is currently being tested in metastatic breast cancer patients with germline BRCA1/2 mutation in Peru and Mexico in a phase 3 study (NCT02000622). Also, some immunotherapy agents are currently in clinical trials in Latin America countries. Pembrolizumab, a PD-1 inhibitor, is being tested (NCT02447003) in metastatic TNBC in Puerto Rico. Pembrolizumab in combination with chemotherapy (NCT03036488) is being tested in Colombia and Brazil. Clinical trial NCT03797326 is studying Pembrolizumab in combination with lenvatinib in Chilean TNBC patients. Clinical trial NCT03725059 is currently recruiting patients in Brazil and Colombia to test neoadjuvant chemotherapy in combination with Pembrolizumab in early stage ER positive, HER2 negative breast cancer. The PD-1 inhibitor Nivolumab is being tested in combination with Pembrolizumab in TNBC patients in Puerto Rico. Pembrolizumab in combination with chemotherapy (NCT03125902) is being tested in Mexico, Colombia, Brazil, Argentina, and Chile. Similarly, clinical trials NCT03498716, NCT03197935, and NCT03125902 are recruiting TNBC patients in Mexico, Peru, Brazil, and Argentina to test Pembrolizumab in combination with chemotherapy, Anthracyclines, Taxanes, Paclitaxel.

Based on the reported mutation data for LA countries, we consider that breast cancer patients might benefit from novel targeted therapies like PARP-inhibitors and immunotherapy. In the same way, patients with germline mutations in DNA repair genes like PALB2, NBN, RAD51, ATM, CHEK2, ATR, and RAD50, might benefit from PARP inhibitors. In Latin America countries, germline mutations in BRCA and non-BRCA genes have been reported mostly in patients with early onset, advanced disease or TNBC. With this in mind, PARP inhibitors and immunotherapy might be a good strategy for breast cancer patients harboring these previously mentioned mutations. Consequently, further studies focusing on DNA repair gene mutations and their role as novel predictive markers are needed for immunotherapy response and targeted therapy in the DNA damage response (DDR) pathway [28]. We hypothesize that breast cancer patients in Latin America that have mutations in the DNA repair pathway could benefit from these kinds of therapies.

In this study, several BRCA1/2 variants that are considered susceptible to PARP inhibitors were found according to the JAX Clinical Knowledgebase (JAX-CKB) (https://ckb.jax.org) and the Clinical Interpretations of Variants in Cancer database (https://civicdb.org/home). In these databases, seventeen variants in each BRCA1 and BRCA2 genes are considered to be sensitive to PARP inhibitors due to loss of function or predicted loss of function. These variants were reported in some LA countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Peru, Uruguay, and Venezuela). Interestingly, some variants such as c.211A>G and c.68_69delAG in BRCA1 were each reported in six countries (Argentina, Brazil, Chile, Colombia, Mexico, Peru, and Uruguay); and for BRCA2, variant c.5946delT was observed in five countries (Argentina, Brazil, Chile, Costa Rica, and Peru).

For non-BRCA genes like ATM, PARP inhibitors are suggested for inactivating mutations or loss of function variants; in the same way as for BARD1, CHEK2, MSH2, NBN, and PALB2 genes. Consequently, we consider that patients in different LA countries harboring these variants could benefit from PARP inhibitors therapies.

In this work, even though rare variants are often reported and counted as mutations, most of them have not been tested in functional analysis. Herein, variants that have been reported in at least two countries for breast cancer are included, suggesting that they may have biological significance.

6. Conclusions

Understanding germline mutations in BRCA and non-BRCA genes in Latin American communities is necessary to improve screening strategies and to implement and develop viable precision medicine practices. This study shows that more information and analyses are required to define the prevalence of gene variants involved in HBC in LA, to define their pathogenicity and for reclassifying VUS.
and variants of conflicting interpretation in this population. This information will facilitate the implementation of HBC screening programs and targeted therapies in Latin America, particularly of those treatments that address DNA repair mechanisms.

The importance of more breast cancer studies, including non-BRCA genes, is to analyze the DNA repair capacity status for a better understanding of the relationship between DNA repair and breast cancer tumor aggressivity, potential biomarkers for prognosis along with immunotherapy recommendations and possible novel targets in DDR. Therefore, patients with mutations in DNA repair genes might also be candidates for targeted therapy in order to improve their outcome. Future studies focusing on non-BRCA genes, mainly DNA repair genes, will be of great benefit for LA breast cancer patients.

7. Take Home Messages

- **BRCA1/2** are the most analyzed and studied genes in LA countries, few studies report non-BRCA gene status in breast cancer.
- In addition to **BRCA1/2**, non-BRCA genes provide information about the DNA repair capacity status.
- Targeted therapy such as immunotherapy and mainly PARP inhibitors are focused on DNA repair gene status for better response.
- Studies focusing on non-BRCA genes are needed in LA countries.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/2073-4425/10/10/786/s1, Figure S1: **BRCA1/2** and non-BRCA gene variants reported from breast cancer cases in LA countries, Table S1: Frequent variants in non-BRCA genes in LA and their pathogenic classification.

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