Review

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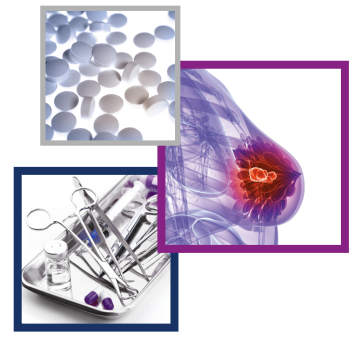
Breast Cancer Management



Genetics, tumor features and treatment response of breast cancer in Latinas

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Practice points

- Latinas with breast cancer have been associated with lower prevalence and higher mortality rates.
- The access to healthcare system for Latinas has been described as lower than for white women.
- Rates of grade III and triple-negative phenotype breast cancer are higher for Latinas than for white women.
- BRCA mutation prevalence appears to be higher in Latinas than white women in the American population.
- Distribution of BRCA mutation differs by country in Central, Latin America or Caribbean and recurrent mutations have been described in Mexico.
- Finally, evaluated information about treatment efficacy and toxicity in Latinas with breast cancer indicate similar effects than in the white race.

Breast cancer is a heterogeneous and genetic disease that has variability according to ethnicity and race with respect to incidence, clinical characteristics and prognosis. The incidence of breast cancer is lower but mortality is higher in Latinas than Caucasians in the US series. Risk factors appear to have different prevalence and impact in Latinas. Breast cancer in Latinas has particular clinic-pathological features including younger age, higher rates of triple-negative subtype and advanced stages. Molecular studies find that Latinas from every region have a specific *BRCA* incidence and a recurrent mutation, as well as differences in activity of molecular pathways. Treatment response rates and toxicity have also been compared, and no difference was found between Latinas and other ethnic groups.

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Keywords: *BRCA* • breast • cancer • Latinas • response • toxicity • treatment

Breast cancer (BC) is a heterogeneous disease that has important variability in incidence, clinical characteristics and prognosis according to ethnicity. Latino population living in Latin America and the Caribbean represent 10% of the developing countries [1]. Inside the USA, they represent the largest (17% of the US population), youngest and fastest-growing minority [2].

Latinas are originally from Mexico, the Caribbean and Central and South America. Their genetic admixture is from Native Americans (NA), Europeans (Iberian Peninsula) and African ancestries, and are combined in different proportion for every region. NAs belonged to different pre-Columbian civilizations and included Incas in the Andes and Mayas in Mesoamerica [3]. European ancestries have Spanish group as the main genetic contributor, but also include Iberians, Celts, Greeks, Romans, Arabs, Gypsies and Sephardic Jews [4]. Finally, different African tribes were brought from interior and coastal regions of Africa and were carried in different proportion to different territories in the New Continent, being the highest Colombia, Brazil and the Caribbean (depending of conquer policies and native population density of every region). Ancestry proportion differs even inside countries, as 50% of

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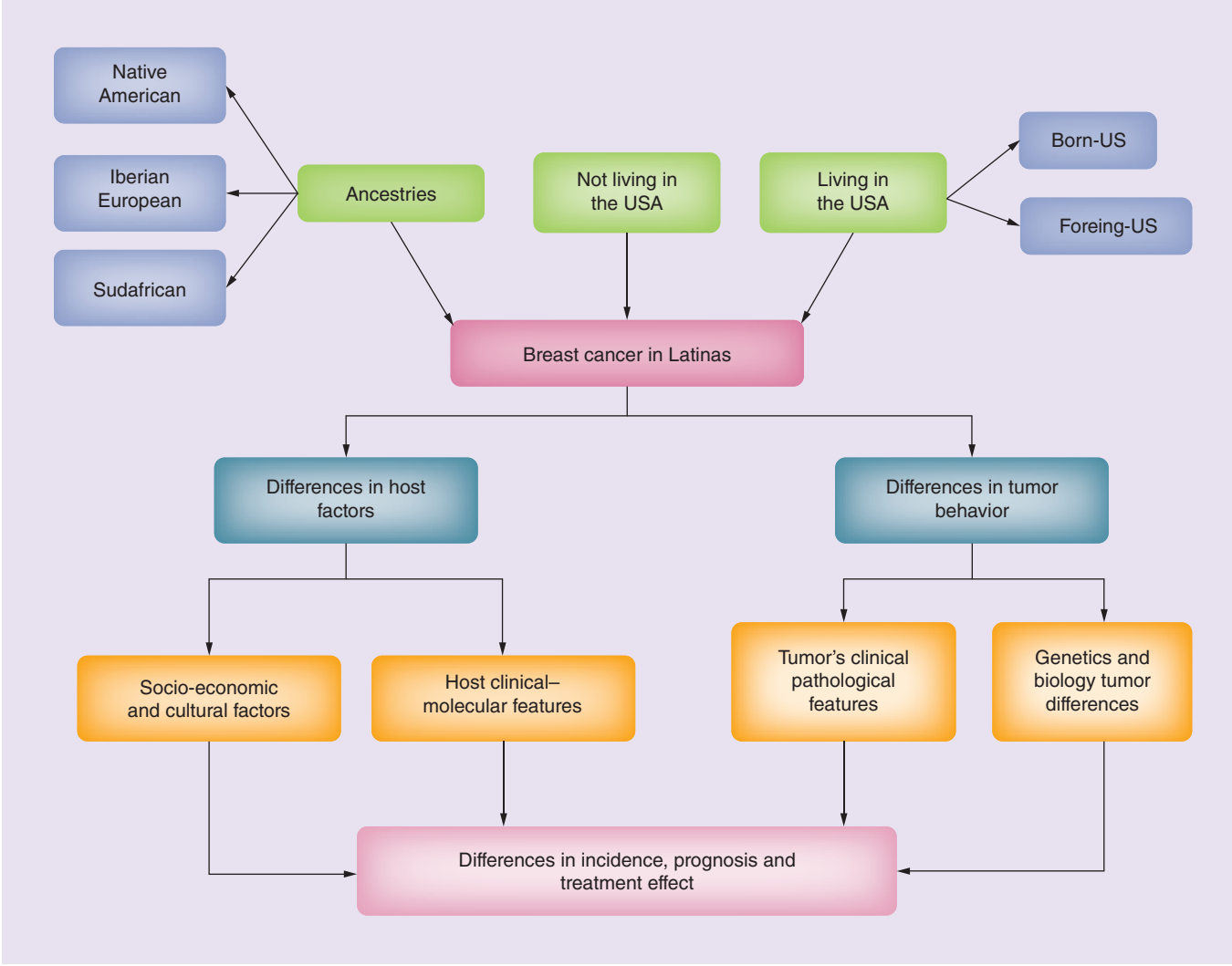

Figure 1. Breast cancer in Latin American population. Latinas is an ethnic group with different proportion of Native-American, Iberian-European and African ancestries. Information is available from Latinas living in or outside the USA, and informs differences in breast cancer prevalence and survival regarding other ethnicities. These differences can be related to host factors including low health coverage and deficit in nutritional status, or related to tumor behavior including higher rates of triple-negative breast cancer.

African components are found in individuals from the northeast region of Brazil, while the European component exceeds 70% in the south and southeast of Brazil [5]. Latinos in the USA have Mexican background in 64.0%, Puerto Rican in 9.6%, Salvadoran in 3.8%, Cuban in 3.7% and the remainder have other origins. Unfortunately, the categorization of Latino origin in patients living in non-Latin American countries carry some bias as a large percentage of this population does not self-identify as Latino [6,7] (Figure 1).

BC incidence in Latinas is lower compared with the US white women (91.9 cases vs 128.1 per 100,000), although it is increasing [8]. Women living in Florida state with Puerto-Rican and Cuban background have higher rates of BC than with Mexican and from other Latin American countries' background. It has been reported higher risk of BC among in-born US Latinas, longer time of US residency, residence in higher socioeconomic area and non-Hispanic neighborhood [9]. Latinas living in the USA are associated with shorter survival. Foreign-born Latinas had marginally better survival than US-born Latinas [10,11].

Fejerman *et al.* evaluated the influence of the proportion of European ancestry (evaluated through 106 gene markers) over 846 Mexican women with BC and 1035 unaffected controls residing in Mexico, and found an increase in BC risk for every 25% increase of European ancestry ($p = 0.019$) [12]. A posterior evaluation of Fejerman *et al.*

found that women with higher proportion of NA ancestry had increased risk of specific BC mortality (p = 0.019) among 899 Hispanic women from the San Francisco Bay area with BC [13].

The epidemiologic findings of lower BC incidence and shorter survival in Latinas were also reported for those living in Latin American countries [14–19]. However, the incidence appears to be higher in the southern countries of Latin America (Uruguay, Argentina, Chile). BC mortality represents the 14% of all cancer deaths in Latin America and is higher than those described in developed countries, and the highest rates have been described in Argentina (20 per 100,000) and Uruguay (24 per 100,000) [20].

Socioeconomic and cultural factors are one of the reasons for these differences, however, several studies have described specific gene and biology properties in breast tumor of Latinas that could contribute with these findings. Differences in host hormonal levels and immune response between Latinas and whites could also influence survival differences.

The aim of the present review is to review published articles and understand the reasons that produce mentioned differences in prevalence and mortality in BC happening in Latinas.

Materials & methods

To conduct this review, a literature search was performed using MEDLINE and Scielo database from 1994 to 2017. The aim was to select original studies in terms of information for BC in Latinas: incidence and mortality in Latinas with BC; differences in host factors: socioeconomic and cultural factors, and clinical-molecular features of host; differences in tumor clinicopathological features; differences in response and tolerance to treatment: chemotherapy and target treatment. The search was performed, initially by using the terms 'Latinas', 'Hispanic' and 'BC'. Subheadings were searched with 'name of every Caribbean, Central and South American Country'. Full text articles were retrieved; the methods were analyzed and reviewed for the selected titles and abstracts with particular attention to contemporary results. Duplicate articles were removed, followed by screening titles and abstracts as per the criteria previously outlined. A total of 1146 articles were identified following removal of duplicates and application of initial filters, with 173 articles nominated, and their methods were assessed in greater detail. That resulted in a further exclusion of 92 articles and, therefore, 81 articles were included in this review for the final qualitative synthesis. These studies form the basis for the following analysis we performed about BC in Latinas.

Results

Differences in host factors

Socioeconomic & cultural factors

Low socioeconomic status is associated with higher BC prevalence and shorter survival, regardless of ethnic origin [21]. In women living in the USA, Latinas are more likely to be uninsured, have lower educational achievements and have higher poverty rates than white women. Health system, education level and economic income in developing countries of Latin America is expected to be poor if we take in count that less than 6% of their gross domestic product is spent on healthcare (vs 10% spent in developed countries) [20]. Availability of clinical examination and mammography for BC screening is low in Latin America countries as described by the Pan-American Health Organization [22]. Additionally, Latinas also appear to be less likely to look for accurate screening or to be compliant with treatment because of social and cultural factors [7].

Known risk factors account for fewer BCs among Hispanic women, suggesting that there are other unidentified involved factors. The number of risk factors is inversely related to the proportion of NA ancestry in BC patients [12–13,23].

High BMI and high breast density are large determinants of endogenous sex steroid hormone level among postmenopausal women and is a speculated causal mechanism for the associated higher BC risk. Overweight and obesity as well as high breast density are risk factors for BC that are culturally acceptable in Latinas. Obesity is also related to Latinas neighborhood which is frequently associated with higher traffic density, higher commuting by car and bad nutritional habits [24]. Different studies have evaluated the influence of BMI over BC in Hispanic population but they have found conflicting results. Recently, Hines *et al.* evaluated the association between risk factors and NA ancestry evaluated by genotyping in 2326 Hispanic and 1854 white postmenopausal women from the USA and Mexico. They found an association between high proportion of NA ancestry and high BMI, but they did not find association between BC risk and BMI in patients with high NA ancestries (p = 0.51) [25]. Food and nutritional habits including high intake of carbohydrates, high glycemic load, low intake of folate and vitamin B12 have been suggested to increase the risk of BC, in particular for postmenopausal women in a Mexican study [26].

Early menarche, late first full-term pregnancy (after 30 years of age), nulliparity and absence of breastfeeding have also been associated with higher BC risk in Latinas [18,19]. However, their risk impact appears to be lower in Hispanics than non-Hispanics in the US population as 4-Corners Breast Cancer Study found [23]. Multiparous (more than five children) is associated with a 30% decreased risk of BC. Latinas have been traditionally described as multiparous and European ancestry tend to be associated with fewer children [19,27]. Furthermore, some series indicate that favorable effect of multiparous is observed in luminal but the opposite effect is observed in triple-negative BC (TNBC; estrogen receptors [ERs] and progesterone receptors [PRs]-negative, HER-2-negative) [28]. Romieu *et al.* reported that parous women who had ever breastfed had a reduction in BC risk (OR: 0.39; 95% CI: 0.25–0.62) compared with parous women who had never breastfed in a Mexican study including 349 BC cases and 1005 controls [29].

The use of contraceptives and use of hormonal replacement therapy, especially combined estrogen and progestin therapies, may increase BC risk [19]. And although their use is lowest in Latinas, especially those with high NA ancestry, they have also been associated with higher BC risk in recent users and for ER negative tumors in Hispanics [27,30].

Clinicomolecular features of host

Approximately 10–15% of BC cases are attributed to inherited gene mutations and *BRCA* mutations are the most prevalent and penetrant mutations of hereditary types of BC. Large studies evaluating the prevalence of *BRCA* mutations in the Hispanic population living in the USA. Hall *et al.* evaluated 46,276 women from Myriad database who underwent DNA full-sequence analysis of the *BRCA* genes, and found that Latin American (14.8%) and African (15.6%) ancestries had higher rates of *BRCA* mutations than western-European ancestry (12.1%), primarily because of an increased prevalence of *BRCA1* mutations [31]. Latin American women had recurrent mutations in 36.6% of all detected mutations and highest rates of uncertain significance mutation variants [31].

John *et al.* evaluated 1727 BC cases enrolled in the Northern California Breast Cancer Family Registry (most were categorized as likely to be hereditary), including 393 Hispanics, and found again that Hispanics had higher *BRCA1* mutations prevalence (3.5%) than white patients (2.2%). The most common mutations in Hispanics was *BRCA* c.68_69delAG (five of 21 carriers) [32].

Weitzel *et al.* evaluated 746 self-reported Hispanics (mostly from Mexico and Central America) with personal or family history of breast or ovarian cancer who underwent *BRCA* testing in the City of Hope Clinical Cancer Genetics Community Research Network (southwestern United States) [33]. Deleterious *BRCA* mutations were detected in 189 (25%; 124 *BRCA1* and 65 *BRCA2*) and 21 (11%) of them were large rearrangement (*BRCA1* ex9-12del in 13 cases). Nine recurrent mutations represented 53% of the total, *BRCA1* c.68_69delAG mutation was found in 18 cases (15% of *BRCA1* carriers), *BRCA1* ex9-12del mutation in 13, *BRCA1* c.211A>G R71G in nine and *BRCA2* c3264dupT 349insT mutation was found in ten. A panel (HISPANEL) of recurrent 114 *BRCA* mutations that is estimated to include 68–77% of *BRCA* mutations in Hispanics was developed [33].

Several recent studies have evaluated *BRCA* mutation in Latin American countries, and some of them have documented prevalence studies in high-risk population and in unselected invasive BC cases in Mexico (six total studies, 6.3–23.0% in high risk, 4.3% in unselected) [34–36], Brazil (eight studies, 3.4–22.5%, 2.3%) [37–38], Argentina (two studies, 16.2–58.3%, unknown) [33,39], Colombia (five studies, 14.3–24.5%, 1.2–4.5%) [40–41], Chile (two studies, 7.1–20.4%, unknown) [42], Costa Rica (one study, 4.5%, unknown) [43], Cuba (one study, 2.6%, unknown) [44], Peru (one study, 4.9%, unknown) [45], Uruguay (one study, 17%, unknown) [46], Venezuela (one study,17.2%, unknown) [47], Trinidad and Tobago (one study, unknown, 10.4%) [48] and The Bahamas (one study, 27.1%, unknown) [49]. Most Latin American studies identified a higher rate of BRCA1 than BRCA2 mutations [37], however studies from Costa Rica [43], Cuba [50], Puerto Rico [51] and Uruguay [46] reported the opposite finding. However, prevalence information could be underestimated due to methodology procedures.

Dutil *et al.* performed a review of publications between 1994 and 2015 about BRCA evaluation in Hispanics and describe that only 8.02% (n = 13) of the reported pathogenic variants were present in two or more Latin American countries [52]. Only 10.4% of BRCA mutations (n = 17) were shared between the US Hispanics and Latin America, and BRCA2 c.5946delT variant is one of the most frequently observed in Latin America (except for Mexico) but has still not been described in the US Hispanics. BRCA1 c.5123C>A is among the ten most frequent pathogenic variants in Latin America and has been reported in four countries of the region, despite it is not one of the most worldwide frequent *BRCA1* variant [52]. They found that c.68_69delAG, c.5266dupC and c.4327C>T variants

are frequent in Latin America and are among the 20 most frequent *BRCA1* variants reported by the Breast Cancer Information Core (BIC) database.

Similar to Weitzel *et al.* publication [33], some Latin American reports find that some *BRCA* mutations are repetitive in some countries of the region (Table 2). Villarreal-Garza *et al.* found that 14 (15%) mutation cases including founder *BRCA1* ex9–12del large rearrangement accounted for 29%, higher prevalence of other large rearrangement and HISPANEL panel accounted for 77% of all the *BRCA* mutations in 96 unselected Mexican women (Mexico DF) with BC [53], and in a later study Villarreal-Garza *et al.* reported that seven mutations and *BRCA1* ex9–12del accounted for 89 and 41% of a total of 44 *BRCA* mutations in 190 <50 years Mexican women (Mexico DF) with TNBC [54]. Three studies performed in Colombian (Bogotá city) in high risk for breast or ovarian cancer women described five recurrent founder mutations: *BRCA1* c.3331_3334delCAAG (the most frequent), *BRCA1* c.5123C>A, *BRCA2* c.2808_2811del4, *BRCA2* 6076 delGTTA and *BRCA2* c.6275_6276delTT [40–41,55]. Two of these mutation (*BRCA1* c.3331_3334delCAAG and *BRCA1* c.5123C>A; along with *BRCA2* c.5616_5620delAGTAA) was found in a screening of 244 unselected Colombian (Medellin) women with BC [56]. Three studies have evaluated more than 1000 Brazilians and describe recurrent *BRCA* mutations [37–38,57]. Esteves *et al.* found *BRCA1* ins6Kb (seven cases), c.5266dupC (four cases), 3261delGinsCC (three cases) in a total of 21 *BRCA* mutation in 612 medium and high risk for breast or ovarian cancer women [38]. Gomes *et al.* found BRCA c.5266dupC (five cases) in a total of nine *BRCA* mutations from 402 BC women unselected for family background (9) [57]. Fernandes *et al.* found *BRCA1* c.5266dupC (18 cases), *BRCA1* c.3331_3334delCAAG (eight cases) and *BRCA2* c.2808_2811delACAA (three cases) in a total of 75 *BRCA* mutations from 349 high-risk breast and ovarian cancer cases [37]. Most ancestry proportion was European (70.6%), African (14.5%), NA (8.0%) and east Asian (6.8%), but no association was found between genetic ancestry and mutational status [37]. Finally, results of Alemar *et al.* suggest that the hypothesis of evaluating only recurrent BRCA mutations is not acceptable for some Latin American countries [58]. They screened *BRCA* mutations through HISPANEL panel (including 15 recurrent mutations previously described in Brazilian patients) in 232 Brazilian patients (southern) at risk for hereditary breast and ovarian cancer, and found a low *BRCA* mutation rate (eight cases; 3.5%) and the presence of the recurrent mutation c.5266dupC in *BRCA1* (five cases). They screened BRCA mutations in a similar Brazilian population (n = 193), but through gene sequencing, and found higher *BRCA* mutation rates (44 cases; 22.8%) and higher rate of recurrent mutations: *BRCA1* c.5266dupC (four cases), c.5177_5180delGAAA (three cases) and *BRCA2* c.2808_2811del (three cases) [58].

Reports from other South-American countries also find similar prevalence of *BRCA* mutations but smaller rates of recurrent mutations [45,50]. Solano *et al.* evaluated *BRCA* gene sequences and large rearrangements in 940 Argentinian women with familial and/or personal history of breast/ovary cancer (including 230 patients without personal but with family history of cancer) and found that recurrent mutations represented only 15.08% of the total 179 mutations [39]. Most frequent were *BRCA1* c.211A>G (n = 11; 1.17%) and *BRCA1* c.181T>G (n = 6; 0.64%), *BRCA2* c.2808_2811delACAA (n = 6; 0.64%) and *BRCA2* c.6037A>T (n = 4; 0.42%). They did not find the highest frequency of large rearrangements (0.54 vs 11%) nor the Mexican founder *BRCA1* ex9–12del previously described [33,39]. A previous study by Solano *et al.* reported results of *BRCA* analysis (analyzed for the three Ashkenazi mutations: *BRCA1* c.66_67delAG, *BRCA1* c.5263insC and *BRCA2* c.5946delT) in 40 Ashkenazi group with affected relatives (17 cases, 42.5%) [69].

Ethnic origin of some *BRCA* mutation described in Latin American countries has been confirmed as Jewish (c.68_69delAG) [70], Spanish (*BRCA1* c.211A>G and *BRCA2* c.2808_2811del4), Portuguese (*BRCA2* c.156_157insAlu), Irish (*BRCA2* c.5946delT), Baltic-zone origin (*BRCA1* c.5266dupC) [21], French (*BRCA1*, c.4327C>T and *BRCA1* 4945_4947delAGAinsTTTT) [71], Sudafrican and African–American (c.5324T>G and c.824_825insAGCCATGTGG in *BRCA1*, and c.1310_1313delAAGA and c.3365_3366delCA in *BRCA2*) [72].

Differences in tumor clinicopathological features

Large American series have compared features of breast tumor of Hispanics and of other ethnic groups. Parise *et al.* evaluated 69,358 BC cases from the California Cancer Registry, including 9855 Hispanic cases and they found younger age and higher rates of TNBC phenotype (especially among youngest) when compared with whites [73]. Banegas *et al.* evaluated 16,380 Hispanic women with BC from the California Cancer Registry and found that hormone receptor (HR)+ HER- subtype was the most common (63%), followed by TNBC (16%) and HR+ HER2+ (14%). Women in lower socioeconomic status neighborhoods had greater risk of TNBC and HR-HER2+ subtypes ($p < 0.05$) [74]. Shavers *et al.* analyzed data from 3978 <36-year-old BC women (including 666 Hispanics) registered in the Surveillance, Epidemiology and End Results (SEER) Program and found higher

Table 1. Comparison of age at diagnosis and estrogen receptor status in Hispanic, black and white women.

Hispanic			Black			White			Year	Ref.
Number of patients	Age	ER negative (%)	Number of patients	Age	ER negative (%)	Number of patients	Age	ER negative (%)		
777	35–50 (33%)	29.9	1016	35–50 (31%)	37.9	4885	35–50 (21%)	22.1	1994	[59]
410	35–49 (31%)	30	1114	35–49 (32%)	42	11,715	35–49% (21%)	26	1996	[60]
9860	NA	21.1	7896	NA	26.4	96,272	NA	17.3	2001	[61]
7219	56 (median)	31.3	10,560	57 (median)	39.2	97,999	62 (median)	22	2003	[62]
6388	60	17[†]	14,170	61	29[‡]	129,037	63	13[§]	2005	[63]
5585	NA	29.8	5724	NA	39.5	78,805	NA	21.6	2007	[64]
15,355	NA	17.3	19,105	NA	24.2	193,513	NA	14.2	2007	[65]
1198	50 (median)	40.4	–	–	–	–	–	–	2010	[66]
2074	50 (median)	43.5	–	–	–	–	–	–	2011	[19]
1122	52 (median)	25.2	1345	53 (median)	38.9	14,268	55 (median)	22.9	2015	[67]
24,078	55 (median)	25.4	8718	57 (median)	33.5	93,325	61 (median)	17.4	2015	[11]
9944	20–49 (33%)	19.7	10,874	20–49 (26.9%)	28.3	72,623	20–49 (17.6%)	14.6	2015	[68]
34,928	56 (median)	24	38,751	57 (median)	33.7	268,675	61 (median)	17.9	2015	[8]

[†]Percentage of a subpopulation (n = 103).
[‡]Percentage of a subpopulation (n = 242).
[§]Percentage of a subpopulation (n = 3455).
ER: Estrogen receptor; NA: Not available.

Table 2. Recurrent BRCA mutations in Latin- American studies.

BRCA mutation	Country	Population	
		High-risk BC (cases with mutation/total)	Unselected BC (cases with mutation/total)
BRCA1			
c.68_69delAG	Brazil	2/612	
	Chile	2/326	
	Peru		7/266
c.181T>G	Argentina	11/940	
c.211A>G	Argentina	11/940	
c.3331_3334delCAAG	Chile	3/326	
	Colombia	5/53	12/766
c.4327>T	Mexico		2/810
c.5123C>A	Colombia	3/53	10/766
	Mexico		4/810
c.5266upC	Brazil	4/612	5/402
BRCA2			
c.2808_2811delACAA	Argentina	6/940	
	Brazil	2/53	10/766
c.4740_4741insTG	Peru		2/266
	Chile	2/326	

BC: Breast cancer.

rates of high histologic grade, high S-phase fractions, aneuploid and ER-negative tumors and more advanced disease stage BC in the Hispanic group [75].

Hines *et al.* found that Hispanic women with a family history of BC have an increased risk to develop HR-BC but not among non-Hispanic whites in the case-control 4-Corners Breast Study performed in south-west USA with 2492 non-Hispanic white and 1347 Hispanic south-western US women (including 36% with BC) [76]. However, Risendal *et al.* found that having a family history of BC was associated with a greater risk for BC in <50-year-old women among non-Hispanics (OR: 2.34; 95% CI: 1.64–3.35) than Hispanics (OR: 1.32; 95% CI: 0.82–2.19) using data collected from the 4-Corners Breast Cancer Study [77]. Li *et al.* found higher risk for positive family history in <50-year-old BC women than older women in 712 BC women (332 Hispanics) and 844 controls (388 Hispanics) included in the New Mexico Women's Health Study; Hispanic women had a trend to have a positive family history (OR: 17; 95% CI 1.1–2.5) than white women (OR: 1.4; 95% CI 1.0–2.0) [78].

Recent studies evaluating BC in Latinas living in Latin America region have been presented [19,79–66]. The first one was performed by our group at the National Cancer Institute in Peru, where Vallejos *et al.* evaluated 1198 women with BC and found a very young appearance age (median age of 50 years old), 31.1% of stage III and 5.2% of stage IV, histologic grade 3 in 41.5% and high prevalence of TNBC (21.3%) [66]. An updated analysis of these data (n = 2226) in comparison to a Spanish series (n = 1539) found higher rates of grade I tumors, large tumor size, lymph node involvement and TNBC subtype and lower rates of lobular histology (12.5 vs 6%). They also found differences in metastases patterns, being the highest rate of brain metastases in Peruvian population (10.4 vs 5.3%). Contralateral BC was more frequent among Spanish patients (12.2 vs 2.8%). TNBC subtype was more likely to develop bone metastases among Spanish patients (25.4 vs 18.5%) [80]. Balko *et al.* evaluated 111 Peruvian TNBC who received chemotherapy and did not achieve pathologic complete response (pCR), and found that 57% belonged to basal-like, 18% to HER2-enriched, 5% to luminal A, 5% to luminal B and 4% to normal-like [81].

Lara-Medina *et al.* evaluated 2074 women with BC treated at the National Cancer Institute in Mexico; and found a very young appearance age (median age of 50 years), higher rates of clinical stage III (44%) and IV (11.7%), higher rates of histological grade III (50.8%) and high prevalence of TNBC (23%) [19]. A pathologic complete response was achieved in 32.8% of all patients (41% of HER2 cases, 29% of TNBC cases and 9% of ER-positive cases). They also found a mean number of child births of 3.1 (0–15 births), and 24.4% of patients had history of hormone contraceptive use. TNBC was associated with younger age, premenopausal status, increase parity, hormone contraceptive use, high histologic grade and advanced disease stage in the univariate

analysis. Premenopausal status, number of child births, high histologic grade and advanced stage keep significantly associated to TNBC in multivariate analysis. TNBC was not associated with overweight or obesity (Table 1) [19].

Some studies report differences in tumor gene expression of some particular molecular pathways and not differences to white race for others. Nagai *et al.* evaluated *TP53* mutations in 242 white and 52 African–Brazilian BC cases [82]. They found that although total *TP53* mutation rate of 17% are among other regions range (12–60%), African predominance was associated with higher frequency of *TP53* mutations (32.7 vs 13.6%) and with differences in both exon-position and nucleotide transversion. It suggests that Latinas gene differences depends on their particular ancestry [82]. Liedtke *et al.* evaluated *PIK3CA* mutations in 140 stage II–III BC cases, including 50 from Hispanic (most from Peru and Mexico); they found mutations in ten (six in exon 9 and four in exon 20) from 50 Hispanic, ten (six in exon 9 and four in exon 20) from 74 Caucasian and two (only in exon 20) from 13 black patients [83]. Dean-Colomb *et al.* evaluated the expression of 421 genes in 98 TNBC tumors from a single-institution candidate for neoadjuvant treatment of different ethnic groups: 19 black, 23 Hispanic and 56 white women. They did not find differences in gene clustering or gene expression among racial groups [84].

Thus, a need exists for further research to better classify molecular variants, especially given the under-representation of Latinos in laboratory and research databases.

Differences in response & tolerance to treatment

Chemotherapy

Racial disparities in BC treatment have been well documented in regard to the use of and response to neoadjuvant chemotherapy.

Chavez-Mac Gregor *et al.* evaluated 2074 BC patients who received anthracycline and taxane-based neoadjuvant chemotherapy at MD-Anderson in TX, USA, including 15.2% Hispanic and found a pCR rate of 14.2% in Hispanics with no differences in pCR rates to other ethnic groups. They also found improved outcomes in Hispanics when compared with whites (contrary to expected worse prognosis) [85].

Killelea *et al.* retrospectively evaluated 127,417 patients with known ethnic group information from the American National Cancer Database who received chemotherapy, including 27,300 in the neoadjuvant setting [86]. Chemotherapy was given more frequently to black, Hispanic and Asian women than to white women ($p > 0.001$), an association probably related to higher rates of advanced stages, high grade as well as TNBC and HER2 + tumors in these women. Black patients had a lower pCR rate for TNBC and HER2 + tumors than white [86]. Recently, Warner *et al.* evaluated the impact of ethnic group and BMI on achievement of pCR after neoadjuvant chemotherapy in 1797 women with BC, including black (14.1%), Hispanic (11.1%), overweight (28.9%) and obese (41.4%) – blacks and Hispanics were more likely to be obese than whites, however, ethnicity was not a significant predictor of pCR (Hispanic vs non-Hispanic: OR: 1.30; 95% CI: 0.67–2.53) [67].

In terms of toxicity, Han *et al.* evaluated toxicities according to four ethnicity groups (103 Caucasian, 30 African–American, 164 Asian and 34 Hispanic patients) in an early stage BC treated with neoadjuvant or adjuvant chemotherapy [87]. Asians had a significantly higher rate of grade 3 hematologic toxicity than Caucasians, African–Americans or Hispanic women (32, 16, 10 and 15%, respectively; $p < 0.05$) [87].

Friese *et al.* evaluated toxicities in 1945 women with early stage BC residing in Los Angeles County and Georgia. Severe toxicity was reported in 866 (45%) cases and was associated with Latina versus white ethnicity (OR: 1.3; 95% CI: 1.1–1.5) [88].

In Latin America-living women, some clinical trials have been fully performed, despite difficulties to compare responses (due to differences in evaluation of response methodology) to Caucasian bibliography; toxicity can be compared because studies share using common Toxicity Criteria. Gomez *et al.* published two clinical trials evaluating pemetrexed at 500 mg/m^2 in 61 Peruvian locally advanced BC without previous treatment and found a toxicity profile that differs in hematologic and liver toxicity to those described in Spanish publications [89,90].

Hormonotherapy & anti-HER2 therapy

Previous studies of ethnic minority women have had larger survival disparities in ER+ than ER- disease, suggesting some aspect of ER pathway could mediate ethnic differences in outcomes. A study evaluating 301 women (including 25% Hispanics) with adjuvant tamoxifen found higher serum levels of tamoxifen ($p = 0.02$) and its metabolite 4-hydroxytamoxifen ($p = 0.007$) among Hispanics than whites [91]. A fact that could be related to a different activity of enzymes in charge of tamoxifen metabolism as cytochrome P450 or *SULT1A1*. *CYP2D6* polymorphism, a P450

gene, is differently expressed in the Hispanic population [92] and *SULTIA1*2**, a *SULT1A1* gene, tended to have a different frequency of a variant genotype in Hispanics than whites [93].

Land *et al.* evaluated tamoxifen symptoms in 973 high-risk women involving 71 non-white patients enrolled in the Breast Cancer Prevention trial STAR and found a slightly stronger leg cramps among white women than non-white (including Hispanic patients; $p = 0.01$) [94].

Moy *et al.* evaluated the effect of extensive adjuvant letrozole in 4708 Caucasian versus 351 non-Caucasian women (included 77 Hispanics) with early BC included in the MA.17 trial [95]. They found no differences in disease-free survival among ethnicity (91.6 vs 92.4% at 4 years) but letrozole after tamoxifen was not associated with an improvement in non-Caucasian ($p = 0.53$). They also found significant lower incidence of hot flashes (49 vs 58%), fatigue (29 vs 39%) and arthritis (2 vs 7%) among non-Caucasian [95].

Crew *et al.* evaluated joint symptoms in 200 postmenopausal women taking aromatase inhibitors: anastrozole, letrozole and exemestane for early stage BC, involving 54 (27%) Hispanic patients, and found no differences by ethnicity [96].

Villarreal-Garza *et al.* reported the outcomes of neoadjuvant trastuzumab in Mexican women with HER2+ disease [97]. A total of 109 (48.8%) patients achieved pCR. Survival was better in patients with ypT0-is and ypN0 than in those with residual invasive disease ($p < 0.01$). Response rates to trastuzumab-based neoadjuvant chemotherapy in Hispanics mimic that of other ethnic groups [97].

A collaborative clinical trial performed in Peru, Brazil and Argentina evaluated lapatinib-based chemotherapy combinations as first- or second-line treatment in 142 HER2+-amplified metastatic BC progressing after taxanes (48% had been previously treated with trastuzumab). The overall response rate (ORR) went from 41 to 56% in the capecitabine, vinorelbine or gemcitabine arm [98] which compares with an ORR on previously published data of 11.1–59.3% [99]. The median progression-free survival went from 7 to 9 months. The most common grade 3 and 4 adverse events were hand-foot syndrome (18%), diarrhea (6–9%) and increased alanine aminotransferase/aspartate aminotransferase (4–13%) and neutropenia (36–47%). Progression-free survival and toxicity also matched with those from other studies of lapatinib–capecitabine and lapatinib–vinorelbine in similar populations [98].

Conclusion & future perspective

Latinas are heterogeneous population underrepresented in pharmacogenomics and clinical trials. Latinas have socioeconomic, cultural, genetic and biologic differences than other ethnias, some of them that increase the risk of BC. Lower prevalence and higher mortality rates of BC in Latinas need to be taken in public policies in the USA where Latinas is the highest growing ethnic group as well as in Latin American countries. It is probably that Latina genes related to molecular differences like higher rates of younger patients and TNBC phenotype need to be added to future BC platforms. We expect that further studies and interventions among this population will allow elucidating the pathogenesis of these differences and lead to new genetic or biologic discoveries that could personalize prevention, diagnosis and treatment in order to improve survival and be beneficial for our health system.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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