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Authors

Lynce, Filipa
Graves, Kristi D
Jandorf, Lina
et al.

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Genomic Disparities in Breast Cancer Among Latinas

Filipa Lynce, MD, **Kristi D. Graves, PhD**, **Lina Jandorf, MA**, **Charité Ricker, MS**, **Eida Castro, PsyD**, **Laura Moreno**, **Bianca Augusto**, **Laura Fejerman, PhD**, and **Susan T. Vadaparampil, PhD**

Georgetown Lombardi Comprehensive Cancer Center (FL, KDG), Washington, District of Columbia, Department of Hematology and Oncology (FL), MedStar Georgetown University Hospital, Washington, District of Columbia, Department of Oncology (KDG), Georgetown University, Washington, District of Columbia, Department of Oncological Science (LJ), Icahn School of Medicine at Mount Sinai, New York, New York, Department of Medicine (CR), University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, Department of Psychiatry (EC), Ponce Health Sciences University, Ponce, Puerto Rico, Department of Health Outcomes and Behavior, H. Lee Moffitt Cancer Center & Research Institute (LM, BA, STV), Tampa, Florida, and the Department of Medicine (LF), University of California, San Francisco, California

Abstract

Background—Breast cancer is the most common cancer diagnosed among Latinas in the United States and the leading cause of cancer-related death among this population. Latinas tend to be diagnosed at a later stage and have worse prognostic features than their non-Hispanic white counterparts. Genetic and genomic factors may contribute to observed breast cancer health disparities in Latinas.

Methods—We provide a landscape of our current understanding and the existing gaps that need to be filled across the cancer prevention and control continuum.

Results—We summarize available data on mutations in high and moderate penetrance genes for inherited risk of breast cancer and the associated literature on disparities in awareness of and uptake of genetic counseling and testing in Latina populations. We also discuss common genetic polymorphisms and risk of breast cancer in Latinas. In the treatment setting, we examine tumor genomics and pharmacogenomics in Latina patients with breast cancer.

Conclusions—As the US population continues to diversify, extending genetic and genomic research into this underserved and understudied population is critical. By understanding the risk of breast cancer among ethnically diverse populations, we will be better positioned to make treatment advancements for earlier stages of cancer, identify more effective and ideally less toxic treatment regimens, and increase rates of survival.

Address correspondence to: Susan T. Vadaparampil, PhD, Department of Health Outcomes and Behavior, Moffitt Cancer Center, 12902 Magnolia Drive, MRC-CANCONT, Tampa, FL 33612. Susan.Vadaparampil@Moffitt.org.

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Keywords

breast cancer; Latinas; Hispanics; genetics; genomics; disparities; treatment; prevention

Introduction

An estimated 55 million individuals living in the United States identify as being Hispanic or Latino.[1] Latinos are a culturally and genetically diverse group with origins in Mexico, the Caribbean, Central American, and South America. In the United States, 64.0% of Latinos are of Mexican background, 9.6% of Puerto Rican background, 3.8% of Salvadoran background, 3.7% of Cuban background, 3.2% of Dominican background, 2.4% of Guatemalan background, and the remainder are of other origins.[2] Although the terms *Hispanic* and *Latino*/*Latina* are often interchangeably used, we selected the term *Latina* for the current manuscript as we feel it extends beyond spoken language to reflect both origin and cultural traditions of women from Latin America.

Breast cancer is the most common cancer diagnosed among Latinas in the United States and is the leading cause of cancer-related death in this population.[10] Although the overall prevalence of breast cancer in Latinas is lower than in non-Hispanic whites, Latinas tend to be diagnosed at a later stage and have worse prognostic features (eg, triple negative disease and HER2–positive disease).[3] A myriad of socioeconomic and cultural factors contribute to health disparities in breast cancer among Latinas,[4–6] but biological factors — particularly genomics — remain an important but understudied consideration.

High and Moderate Penetrance Genes

Approximately 10% to 15% of breast cancer cases are attributed to inherited gene mutations.[7] Although multiple genes confer an inherited risk fir cancer,[8] *BRCA* mutations are the most prevalent and penetrant mutations, accounting for the majority of hereditary types of breast cancer.[9] *BRCA* mutations result in an increased lifetime risk of breast cancer of up to approximately 60% to 70% and a lifetime ovarian cancer risk of up to 40%.[10–12] Among Latinas, breast cancer is often diagnosed at younger ages and with worse prognostic features, including increased rates of triple-negative disease, than their non-Hispanic white counterparts.[13–16] Triple-negative disease and premenopausal breast cancer are both clinical characteristics associated with a higher probability of having a *BRCA1*/*2* mutation.[17,18]

Prevalence of *BRCA*

The prevalence of *BRCA* mutations in the general US population is estimated to be 1 in 400, excluding women of Ashkenazi Jewish descent in whom prevalence is 1 in 40.[19–21] However, less is known about the prevalence among racial and ethnic minority groups, including Latinas as a whole or by subethnicity based on country of origin. A review examined the spectrum of *BRCA1* and *BRCA2* mutations in Latin America and the Caribbean using studies published between the years 1994 and 2015.[22] Six of the 33 studies were conducted among Latina living in the United States, with the vast majority of participants drawn from clinic-based samples of patients of Mexican origin with breast

cancer residing in California, Arizona, and Texas.[22] Prevalence estimates of carrying a *BRCA* mutation for this US Latina group ranged from 0.7% to 42% and varied based on whether cases were selected or unselected for family history or clinical characteristics (eg, affected vs unaffected, age at diagnosis), cancer site (eg, breast, ovarian), and type of testing (eg, inclusion of large rearrangement testing).[22] In the cohorts of unselected patients with breast cancer, the *BRCA* mutation prevalence was 1.2% to 4.9%, which was consistent with expected rates.[22]

BRCA mutations have also been documented in all residents of Latin American countries where these genes have been studied, including Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Mexico, Peru, Puerto Rico, Uruguay, and Venezuela.[23–54] Most studies have focused on the spectrum of *BRCA* mutations.[22,55] In a review of *BRCA1* and *BRCA2* mutations in persons living in Latin America and the Caribbean, 36% of the 33 studies primarily focused on Mexican or Mexican American patients.[22] Of the Mexican study population, the mutation prevalence was between 4.3% and 23.0%.[22] For other Latina subethnic groups, the mutation prevalence estimates of each country studied were: Colombia (1.2%–15.6%; 2 studies), Costa Rica (4.5%; 1 study), Cuba (2.6%; 1 study), Peru (4.9%; 1 study), Uruguay (17%; 1 study), and Venezuela (17.2%; 1 study).[22] These studies provide insight into areas of future research of *BRCA* mutation distribution and frequency based on country of origin, the role of specific founder mutations, the contribution of large genomic rearrangements to the spectrum of mutations across various Latina subethnic groups, and the consideration of other non-*BRCA* genes that increase the risk of breast cancer.

Although recurrent mutations were identified within most studies, the specific mutation varied by study and country.[22] *BRCA1* 185delAG has also been documented in Latinas across Latin America and the United States.[43,45–47,50,56–58] One of the 3 Jewish founder mutations, *BRCA1* 185delAG is estimated to have arisen about 800 years ago or earlier and is believed to have been introduced into Latin America about 650 years ago.[59] When this mutation is identified in Latinos, haplotype analysis supports that this mutation is of the same origin as the Jewish founder mutation, rather than a separate genetic event.[60,61] Pooled mutation estimates performed by Porchia et al[55] found that *BRCA1* 185delAG is the second most prevalent *BRCA1* mutation and its frequency is not significantly different between Mexico and other Latin American countries ($P = .70$). However, it is worth noting that not all Central and South American countries were represented in their analysis.[55]

The most common *BRCA1* mutation in the same meta-analysis was deletion of exons 9 to 12.[55] This mutation is estimated to have originated nearly 1,500 years ago near Puebla Mexico.[48,58] However, to date, it has been reported in Mexicans and Mexican Americans alone.[22,35,55,61,62] The contribution of large genomic rearrangements to *BRCA1* in Latin American patients was evaluated in a study of US Latinas and described the prevalence of rearrangements by racial and ethnic groups.[63] Large rearrangements were significantly more common in individuals who reported Latin American ancestry, and the prevalence of rearrangements was two-fold higher than in the overall population tested.[63] This laboratory-based cohort extracted ethnicity data from genetic testing request forms; therefore, no data about subethnicity was available.[63] However, the 2 most frequent *BRCA1* rearrangements identified in this study were deletion of exons 9 to 12 and deletion of exons 1 and 2, likely

reflecting the underlying US Latino population in whom the majority is of Mexican ancestry.[63] In a Puerto Rican study, *BRCA1* deletion of exons 1 to 2 was seen in nearly 20% of study patients positive for *BRCA1*.[52] Because Puerto Ricans represent the second largest US Latino group after those of Mexican ancestry, these findings support utilizing an assay that includes large rearrangements when testing Latinos.[52] The study results also highlight the importance of understanding more granular aspects of ethnicity, such as country of origin, to ensure that all mutations that contribute significantly are captured.

Dutil et al[22] noted that most Latin American studies they reviewed identified a higher proportion of *BRCA1* than *BRCA2* mutations, a finding similar to reports in other populations. However, studies from 4 different countries (Costa Rica,[40] Cuba,[38] Puerto Rico,[52] Uruguay[64]) reported more *BRCA2* mutations than those in *BRCA1*. While these studies may have been limited by sample size and the mutation-detection strategies and technologies,[38,40,52,64] this finding has been also reported in a single US-based clinical site and may warrant further exploration.[68]

The meta-analysis performed by Porchia et al[55] identified recurrent *BRCA2* mutations across all studies with the following pooled prevalence: H372N (0.88%; 95% confidence interval [CI], 0.24–1.92), E49X (0.38%; 95% CI, 0.13–0.75), and 3492insT (0.32%; 95% CI, 0.24–0.53). *BRCA2* 3492insT has been identified in different regions of Spain with a frequency as high as 2.08%.[65–71] Although it is possible that this mutation was introduced in Latin America by the Spaniards, no haplotype studies of this specific mutation were identified to confirm a shared ancestry rather than a separate mutational event.[52]

BRCA1 and *BRCA2* account for the majority of hereditary breast cancer, but other high- and moderate-risk genes also predispose individuals to breast cancer, including *TP53, PTEN, CDH1, STK11, CHEK2, PALB2, ATM*, and others.[25,29,30,72–80] Limited studies have been performed of non-*BRCA* genes in Latina breast cancer cohorts, leaving much to be learned about the prevalence and spectrum of mutations in these genes among Latinas with breast cancer (Table 1).[25,29,30,72–80]

One exception is the Brazilian founder mutation in *TP53*, R337H. Mutations in *TP53* cause Li-Fraumeni syndrome, which is associated with an elevated risk for a wide spectrum of cancers, including adrenal cortical carcinoma, soft-tissue and bone sarcomas, brain tumors, and breast cancer.[81–83] The overall contribution of *TP53* mutations to breast cancer is estimated to be less than 1%, unless selecting for early-onset breast cancer.[84,85] In studies of women diagnosed with breast cancer at or before the age of 30 or 35 years, 5% to 8% had *TP53* mutations.[86–89]

TP53 R337H was first identified in individuals with childhood adrenal cortical carcinomas living in southern Brazil.[90] This mutation occurs in 2.4% to 8.6% of Brazilian women with breast cancer.[72,73,90,91] In a large study, which included 403 patients with breast cancer diagnosed at 45 years or younger, 12.1% carried the *TP53* R337H mutation. Although the mutation was significantly more frequent in younger patients compared with those diagnosed at or above age 55 years ($P < .001$), 5.1% of the older group carried the mutation.[73] To date, no other populations have been identified in whom *TP53* makes such a

significant contribution to breast cancer. The prevalence of this mutation in southern Brazil has been estimated be approximately 0.3%.[92,93] Additional haplotype analyses support the hypothesis that this recurrent mutation is a founder mutation from a shared ancestor.[73,94]

Historically, the genetic assessment for hereditary breast cancer involved the formation of a differential diagnosis followed by a syndrome-by-syndrome evaluation through the sequential testing of genes. However, the rapid integration of next-generation sequencing has enabled simultaneous testing of multiple inherited cancer genes, thereby expanding the use of multigene panels in clinical testing at a reduced cost.[95] This expansion is reflected in the emerging body of literature on breast cancer focused on multigene panel findings from the research, clinical, and laboratory settings.[96–104]

These literature cohorts are predominantly non-Hispanic whites, with Latinas representing less than 1.0% to 7.4% of study participants[96–99,101–103] — thus highlighting another area where future research is needed. One study of 475 patients undergoing multigene panel testing included 228 Latino patients (47.6% of study population), and it reported that the likelihood of detecting a deleterious mutation was no different among the ethnic and racial groups represented.[102] Of the patients with breast cancer (n = 197), 14.8% (n = 28) carried mutations, and, as expected, *BRCA1* and *BRCA2* were the most commonly mutated genes; however, 16 mutations were identified in other genes (*CDH1* = 4, *CHEK2* = 3, *MUTYH* = 3, *PALB2* = 2, *TP53* = 1, *RAD50* = 1, *RAD51D* = 1, *BARD1* = 1).[102] Of note, the likelihood of identifying more than 1 variant of uncertain significance in Latinos was significantly higher than that of non-Hispanics whites.[105] Thus, a need exists for further research to better classify rare variants, especially given the under-representation of Latinos in laboratory and research databases.

Genetic Counseling and Testing

Patient- and Health Care–Related Factors

An important step toward understanding the role of *BRCA* and other high- and moderate-risk breast cancer genes in Latinas is to increase the number of individuals who receive genetic counseling and subsequently elect to undergo testing. However, growing evidence identifies disparities in awareness of and access to genetic counseling among Latinas compared with non-Hispanic white women. Data from health interview surveys from 2000, 2005, and 2010 show that Latinas had the lowest level of awareness about genetic testing for inherited cancer risk than all of the other US racial ethnic groups.[106–108] Using telephone surveys, Gammon et al[109] studied 63 Latinas and 84 non-Hispanic whites at increased risk for carrying a *BRCA1* or *BRCA2* mutation, examining their awareness, cognitions, and psychosocial needs related to genetic counseling and testing. Among those who had not previously undergone genetic counseling (53 of the 120), Latinas were more unaware than their white counterparts of the availability of testing (56.9% vs 34.8%, respectively).[109] Vadaparampil et al[110] reported on a sample of Latinas with a personal or family history of breast cancer, all of whom reported an awareness of genetic risk for breast cancer (ie, family history). However, none of the Latinas had a clear understanding of what genetic testing was and had not received physician referral for genetic testing.[110] Findings did differ based on country of origin — an important are to consider in future work, given the diversity of

Hispanic populations across the United States.[110] In another report, Kaplan et al[111] reported differences in awareness of genetic testing by race and ethnicity such that 19.4% of Latinas had heard of genetic testing compared with 59.4% of whites, 26.1% of Asian Americans, and 31.0% of black women.

In a study of more than 2,400 patients completing a family cancer history form, Mays et al[112] found that, overall, despite low levels of initial awareness, 65 patients (2.7%) met criteria for cancer risk assessment; of those, 72.3% expressed interest in receiving genetic counseling. Furthermore, no differences in interest in genetic services were reported across all racial and ethnic groups.[112] Among 1,536 women with nonmetastatic breast cancer, Jagsi et al[113] found that Latinas had a greater desire for genetic counseling than other groups (58.8% of Spanish-speaking Latinas; 36.7% of English-speaking Latinas; 27.1% of non-Hispanic whites; and 28.1% of blacks). In addition, Lagos et al[114] examined social, cognitive, and cultural variables among Latinas prior to an appointment for genetic counseling. Fifty low-income, underserved Latinas completed the assessment, and the results demonstrated their readiness (having the necessary skills for the genetic-counseling process), low fatalism, and high rate of self-efficacy, and social support.[114] However, this study was conducted in women who showed up to their genetic counseling appointments, thus representing a unique group of women.[114] Vadaparampil et al[115] studied a group of Puerto Rican women (living in Puerto Rico or central Florida) with a family or personal history of breast cancer and found that the vast majority of participants said they would undergo genetic testing within the next 6 months if it was available. Barriers included the cost of testing and potential pain.

Uptake of Services

Given lower levels of patient awareness, physician recommendations may provide a critical approach to increasing utilization of genetic counseling and testing for hereditary risk of breast cancer. However, available studies[113,116,117] suggest a missed clinical opportunity, because both English- and Spanish-speaking Latina survivors of breast cancer were more likely to have unmet needs for discussion with a health care professional about cancer genetic testing than their non-Hispanic white counterparts. For example, Jagsi et al[113] reports that minority patients were the most likely to express an unmet need for a discussion about genetic testing, although they also showed a strong desire for such testing.

Preliminary studies support the uptake of genetic counseling when services are offered.[118–121] One study of predominantly Latina patients (71.4%) offered genetic counseling at the safety-net hospital found that 88.0% kept their appointments.[118] Another study of women (69.6% were Latinas) seen in the safety-net hospital setting reported that 96.4% of them underwent *BRCA* testing when it was recommended to them.[119] Once Latinas were referred, Olaya et al[120] found that they are equally likely as the general population to complete *BRCA* testing. Overall, 52% completed genetic testing, and no differences by race and ethnicity were observed.[120] Woodson et al[121] reported on the utilization of group pretest genetic counseling in a community clinic made up of mostly Latinas (62.3%) with breast cancer; the majority (86.7%) underwent *BRCA* genetic testing when offered.

Overall, these studies have focused on the delivery of cancer genetics services to majority Latina cohorts, demonstrating that genetic counseling and testing is likely well-received by Latinas with breast cancer; however, these studies were all conducted in safety-net hospitals or in community, low-resource settings and were aimed at the provision of service to low-income, uninsured patients.[118–121] Although Latinas continue to be disproportionally uninsured or underinsured, these study findings might not generalize to other health care settings. Thus, further studies are needed across various clinical settings and in a wider representation of Latinas with breast cancer to better understand the utilization of genetic testing as well as the barriers for referrals.

Common Genetic Polymorphisms and Risk of Breast Cancer

Genome-Wide Association Studies

Progress in the discovery of germline genetic polymorphisms associated with breast cancer risk changed pace when technological advances in genotyping made it possible to characterize genome-wide genetic variation at a relatively low cost.[122] In 2007, the first breast cancer genome-wide association studies were published, and they reported a handful of single nucleotide polymorphisms (SNPs) associated with a modest increase in risk.[123–125] Since then, more than 100 common variants that either increase risk for or are protective against developing breast cancer have been discovered and, including replication efforts, data from more than 120,000 women have been analyzed.[123–146] A small proportion of samples included in these major initiatives are from minority populations in the United States (eg, Latinas, African Americans)[123–146] and the first results of genome-wide association studies of Latinas with breast cancer were published in 2014.[147] This latter study represents important but limited progress, considering that the sample size was one-tenth of that available for genome-wide association studies involving women of European origin.[123–125,147]

Until the first genome-wide association studies of breast cancer in women of European origin were published, the search for risk predisposing genetic variants was focused on finding polymorphisms within genes that, for known or hypothesized involvement in the biology of the disease, were likely to contribute to breast cancer risk.[123–125] These studies in US Latinas or Latin American women typically consisted of the replication of previously associated polymorphisms reported in Europeans, with few of these studies looking for variation in samples of Latinas before further testing specific polymorphisms for associations in larger samples.[148,149]

Compared with the hundreds of genome-wide association studies in non-Hispanic white women, we identified 13 case-control studies or cohorts that include US Latina or Latin American women.[150–163] These studies include populations of women of no more than 100 and up to approximately 5,000 women of Latin American origin; combined, the study populations tally approximately 5,000 Latina women with breast cancer and 11,000 Latina healthy controls.[150–163]

Candidate Gene or Pathway Studies

Multiple breast cancer–association studies of candidate genes or pathways have been reported for US Latina and Latin American women during the last 20 years. Genes or pathways studied have included those related to hormone metabolism, hormone receptors, and hormone coactivators or supressors,[148,164–169] growth factors,[149,170–176] matrix metalloproteinases,[177,178] inflammation and energy balance,[158,179–184] metabolism of xenobiotic compounds and oxidative stress,[159,185–188] DNA repair,[160,161,163,189] and angiogenesis.[190] Results reported in these publications should be interpreted with caution, given that approximately 60% of the candidate gene analyses included in our report did not adjust for genetic ancestry, which is a known confounder in genetic association studies in admixed populations.[191,192] In addition, no associations in candidate gene or pathways studies, nor any of the interactions with risk factors, genetic ancestry, or tumor characteristics, have been replicated in independent samples of Latinas.

Replication of Identified Single Nucleotide Polymorphisms

Few studies have included Latinas and tested the association between SNPs discovered in genome-wide association studies of breast cancer conducted in samples of European or Asian women.[193–198] The first study genotyped previously reported SNPs in the 2q35 region and *FGFR2*, *TOX3*, and *MAP3K1*, reported statistically significant replications for the polymorphisms in *FGFR2* and 2q35.[193] Two different studies published the results of analyses conducted in the same sample of high-risk families from Chile and healthy controls, testing associations between previously reported variants in *FGFR2, MAP3K1,* and *TOX3* and the 2q35 and 8q24 regions and breast cancer risk.[197,198] They replicated the associations for *FGFR2, MAP3K1, TOX3,* and 2q35 but not for 8q24.[197,198] An analysis conducted in a pooled sample of Latina cases and controls from the Four-Corners study, San Francisco Bay Area Breast Cancer Study, and a study in Mexico, investigated the association between 10 identified polymorphisms in genome-wide association studies (in region 2q35 and in or near *RELN, MRPS30, RNF146, FGFR2, TOX3, LSP1, TLR1, MAP3K1, RAD51L1)* and breast cancer risk.[195] They replicated associations for the polymorphisms in *RELN, FGFR2, TOX3,* and *TLR1* and 2q35 and found heterogeneity by ancestry for the *RELN*, 2q35, and *TLR1* SNPs.[195] A follow-up study reported that the heterogeneity by ancestry for the 2q35 polymorphism was likely due to the association between genetic ancestry, use of hormone therapy, and breastfeeding.[194] Another analysis of the *FGFR2* polymorphism in the Mexican study reported an interaction between the *FGFR2* polymorphism and alcohol intake.[196] The first genome-wide association study of breast cancer in US Latinas also replicated previous associations, with most of the SNPs being concordant in terms of direction and magnitude of association with those reported in European or Asian populations.[147] Twenty-three of the 83 variants tested had probably values below .05.[147]

Ancestry

Admixture mapping leverages the demographical history of admixed populations to find genomic regions that may carry trait-associated variants.[199–207] An admixed population results from the combination of 2 or more ancestral groups.[200] The principle of admixture

mapping is to identify genomic regions in which cases share more of the same genetic ancestry than either population-based controls (case-control analysis) or compared with the average ancestry of the rest of the genome among cases (case-only analysis).[202] This approach has identified risk variants or risk regions for multiple complex traits, including obesity, hypertension, and cancer.[199,201,203–207] The incidence of breast cancer varies across different racial and ethnic groups in the United States, and Latinas have lower incidence rates than non-Hispanic whites but higher rates than American Indian women.[208] Genetic ancestry has also been associated with breast cancer risk in US Latinas and Mexican women after adjusting for non-genetic risk factors, suggesting that a genetic component could be responsible for the difference in risk.[158,209,210] An admixture mapping study in Latinas reported a statistically significant association between a region in the long arm of chromosome 6 (6q25) near *ESR1* and risk of breast cancer and a suggestive association on chromosome 11.[211] Higher Indigenous American ancestry at chromosome 6q25 was associated with lower risk of breast cancer.[211] This finding was concordant with the previous reports of lower rates of risk of breast cancer among Latinas with high American Indian ancestry compared with women with high European ancestry after adjusting for possible risk factors such as socioeconomic status, number of full-term pregnancies, and breast feeding.[209–211]

One included a discovery phase and replication in 3 additional studies.[147] The study reported genome-wide results that were statistically significant for 2 linked SNPs 56kb upstream of *ESR1* (rs140068132 and rs147157845).[147] These SNPs have a frequency of between 5% and 23% in Latin American populations and are absent in most all other groups.[147] The minor allele was protective, with an associated odds ratio (OR) of 0.60 (95% CI, 0.53–0.67) per allele and was more protective for estrogen receptor (ER)–negative disease than for ER-positive disease (OR for ER-negative disease 0.34; 95% CI, 0.21–0.54).[147]

Treatment

Tumor Genomics

A growing body of evidence suggests differences in the tumor biology of breast carcinoma across various races and ethnicities. Several studies have evaluated the prevalence of phenotypic subtypes of breast cancer in Latinas compared with other population groups.[212–218] Most data have shown a higher proportion of hormone receptor–negative disease types among Latinas when compared with non-Hispanic whites (Table 2).[3,212–216] However, those results have not always been concordant, and the differences seen across these studies could represent small sample sizes, patient age, or unadjusted rates for genetic ancestry. Although studies based on data from the California Cancer Registry indicated a higher proportion of triple-negative tumors,[217] this finding was not confirmed in a Colorado study.[212] In a retrospective study performed in Brazil, patients in the southern regions with a higher percentage of European ancestry and higher socioeconomic status presented with the highest proportion of luminal tumors, whereas the more aggressive subtypes were seen in the northern parts of Brazil, an area with a higher African ancestral influence.[218]

Approximately 15% of breast cancer types overexpress erb-b2 receptor tyrosine kinase 2 (ERBB2; also referred to as epidermal growth factor receptor 2 [HER2 or HER2/neu]) protein.[219] High levels of *HER2* expression identify those women who benefit from treatment with HER2-targeted agents, which have been shown to increase survival in the adjuvant and metastatic settings.[220,221] Most studies with HER2-targeted therapies have enrolled majority populations of non-Hispanic whites, although consistent evidence demonstrates that a higher proportion of *HER2*-positive tumors exist among Latinas, even after adjusting for other tumor characteristics (eg, grade, stage, ER status) and breast cancer risk factors (eg, number of children, alcohol consumption).[212]

Further tumor characterization has been made possible due to advances in molecular tumor profiling. Oncotype DX (Genomic Health, Redwood City, CA) is a 21-gene breast cancer assay — known as a recurrence score — that provides prognostic and predictive information regarding the benefits of adjuvant chemotherapy in patients with ER-positive tumors. Use of Oncotype DX is part of several guidelines from professional medical organizations, including the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the European Society for Medical Oncology.[222–224] The characteristics of this assay and the impact of its results on treatment decisions among Latinas with breast cancer are lacking in the medical literature. Kalinsky et al[225] studied 74 Latinas and 145 non-Hispanic white women matched for age, disease stage, and nodal status, and they observed no differences in the overall recurrence score, ER or progesterone receptor status, or *HER2* expression by Oncotype DX. However, Latinas had a higher expression of *CCNB1* and *AURKA*, 2 genes that are part of the proliferation score and heavily weighted in the calculation of the recurrence score.

Multiple trials whose study populations were mostly comprised of non-Hispanic white women have shown that use of Oncotype DX affects treatment recommendations and leads to an increase in physician and patient confidence in treatment decisions.[226–229] A small study of 96 patients with breast cancer treated in Mexico showed that use of the Oncotype DX changed treatment decisions for 32% of patients, a finding suggesting that its use has a meaningful impact on recommendations for adjuvant treatment.[230] Results from cost-effectiveness analyses indicated that use of the Oncotype DX assay was projected to improve rates of life expectancy when compared with the current standard of care.[231]

Pharmacogenomics

Several factors cause variations in the individual response to drugs, including age, body mass index, diet, and genetic variation.[232–234] SNPs in genes related to drug-metabolizing enzymes have been recognized as important determinants of variability to drug response.[235] Most studies have not been sufficiently powered to determine whether specific chemotherapy agents used to treat breast cancer have different rates of effectiveness and toxicities based on race or ethnicity.[236] However, differences in the metabolism of endocrine therapies have been well documented according to race and ethnicity.[237–240]

In a study that evaluated clinical data and blood samples from patients with breast cancer undergoing adjuvant tamoxifen therapy, mostly non-Hispanic white women (68%) and Latinas (26%) had significantly higher serum levels of tamoxifen and 4-hydroxytamoxifen,

one of tamoxifen metabolites ($P = .02$ and $P = .007$, respectively).[237] In 2 other studies, genetic polymorphisms in *CYP2D6* associated with lower plasma concentrations of the active metabolites of tamoxifen were described in Mexican, Puerto Rican, and Spanish patients.[238,239] A higher prevalence of this poor metabolizer phenotype has also been observed in non-Hispanic whites.[240] In an attempt to clarify whether CYP2D6 allele status influences outcomes from tamoxifen, investigators assessed data from 2 large prospective trials and found that CYP2D6 allele status did not predict clinical benefit of adjuvant tamoxifen in terms of risk of recurrence.[241,242] Therefore, changes in treatment decisions based on CYP2D6 allele status alone are not recommended. Differences in the incidence of polymorphisms of the aromatase gene among different ethnic groups have also been reported and could potentially lead to different outcomes and toxicities among populations.[243] One trial evaluated the benefit of extended hormonal therapy with an aromatase inhibitor after 5 years of tamoxifen treatment in non-Hispanic whites (n = 4,708) and minority women (n = 352; 1.5% were Latinas).[244] In general, the researchers found that, compared with non-Hispanic whites, minorities had fewer associated toxicities and no definitive survival benefit with aromatase inhibitors.[244] However, these results should be cautiously interpreted, because the minorities participants were less adherent to hormonal therapy and the study was not powered to detect survival benefit in the subgroups.[244]

Conclusions

Several genetic and genomic factors are related to the health disparities of breast cancer in Latinas. Increasing our knowledge about the contribution of high- and moderate-penetrance mutations to the risk of breast cancer among Latinas overall and for subgroups based on country of origin is an important priority. Although genetic counseling and testing for inherited susceptibility to breast cancer has been clinically available for nearly 20 years, disparities in awareness, referral to services, and access persist. Therefore, interventions to address barriers related to low levels of awareness and lacking physician referrals are critical.[106–111]

Even though multiple candidate gene studies have been conducted in this population, only identified variants in genome-wide association studies have been systematically replicated. Much larger sample sizes will be required if we expect to discover similar results in Latinas as would be identified for the European genome in view of their Indigenous American component. We cannot assume that overlapping variants alone between different ancestral genomes will be associated with rate of risk, so our efforts should be focused on reducing research disparities by expanding available resources to include large cohorts and case-control studies of diverse populations in and outside the United States.

Latinas remain systematically underrepresented in pharmacogenomics studies and the current studies were not powered to detect outcome differences. They are also underrepresented in clinical treatment trials and other patient-reported outcomes research. Future research should draw from the few models of success in prior studies that have recruited sufficient numbers of Latinos.[245–248] Lessons can also be learned from successful examples of recruiting other racial and ethnic minority patients who have survived breast cancer.[249] Elements that appear to bolster success include partnership with community-

based organizations that provide services to Latinas and the provision of language-concurrent clinical care.[250–252] The heterogeneity of the US Latina population must also be considered, because different cultural influences, levels of awareness of, and interest in genetic and genomic services appear to vary by country of origin.[110]

An urgent need exists to ensure that existing genomic research considers the unique needs of this Latina population. As the US population continues to diversify with up to one-third identifying as Hispanics by 2060,[1] extending genetic and genomic research into this underserved and understudied population will be critical. By understanding the risk of breast cancer among diverse populations, we will be better positioned to make advancements in the number of women diagnosed at earlier stages, identify more effective and less toxic treatment regimens, and increase rates of survival. Meeting these goals will contribute to reducing the current health disparities in these patients with breast cancer.

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Table 1

Select Non-*BRCA* Genes Observed in Latina Populations

Study	Country	Cohort		Gene	Analysis	Findings
		No. of Patients	Inclusion Criteria			
Assumpção[69]	Brazil	123	Family history of breast cancer Family history of ovarian cancer Sporadic breast cancer	*TP53*	Site-specific analysis of *TP53* R337H	2.4% of cases carried the mutation ($P = .0442$)
Carraro[22]		54	Early-onset breast cancer diagnosis < 30 y	*BRCA1* *BRCA2* *CHEK2* *TP53*	Coding introns/exons of *BRCA1/2*, *TP53*, and site-specific analysis of *CHEK2* (c. 1100delC)	22% carried mutations mostly in *BRCA1/2* 2% (n = 1) had *TP53* mutation
Felix[26]		106	HBOC testing	*BRCA1/2* *CHEK2* *TP53*	PCR of each exon of *BRCA1* Site-specific analyses of *BRCA2* (c.5946_5946delT; c. 156_157insAlu), *CHEK2* (c. 1100delC; c.444+1G>A; p.I157T), and *TP53* (p.R337H)	2.8% carried mutations (*BRCA* = 2, *TP53* = 1)
Giacomazzi[70]		874	Family history of cancer (group 1) Consecutive breast cancer (group 2)	*TP53*	Single-site analysis for p.R337H	p.R337H identified in 3.4% (group 1) and 8.6% (group 2) Higher prevalence when diagnosed ≤ 45 y (12.1%) than ≥ 55 y (5.1%) ($P << .001$)
Silva[27]		120	HBOC testing	*ATM* *BRCA1/2* *BRIP1* *CDH1* *CDKN2A* *CTNNB1CHEK2* *MLH1* *MSH6* *NBN* *PALB2* *PTEN* *RAD50* *RAD51* *TP53*	Coding introns/exons of *BRCA1/2* Site-specific analysis of *CHEK2* (c.1100delC) and *TP53* (p. R337H) Array comparative genomic hybridization for CNVs in other 14 genes	26% (n = 31) mutations (*BRCA1/2* = 27, *CHEK2* = 1, *TP53* = 3)
González-Hormazábal[72]	Chile	137 (*BRCA*$^{-}$ = 126, *BRCA*$^{+}$ = 11)	≥ 2 family members with breast cancer ≥ 2 family members with ovarian cancer Family history of male breast cancer Early-onset breast cancer with no family history	*ATM*	PCR-based analysis of coding sequence and exon/intron boundaries of *ATM* Analysis of *ATM* 5557G>A, IVS38-8T>C, IVS24-9delT	5557G>A, IVS38-8T>C, IVS24-9delT associated with elevated risk of breast cancer if *BRCA*$^{-}$ Identification of composite genotype that confers 3.19-fold risk for breast cancer
Jara[71]		143 (*BRCA*$^{-}$ = 131, *BRCA*$^{+}$ = 12)	≥ 2 family members with breast cancer ≥ 2 family members with ovarian cancer	*RAD51D*	PCR-based analysis of coding sequence and exon-intron boundaries of *RAD51D* Analysis of *RAD51D*, c.135G>C	No mutations detected in *RAD51D*

Study	Country	Cohort		Gene	Analysis	Findings
		No. of Patients	Inclusion Criteria			
			Family history of male breast cancer Early-onset breast cancer with no family history			c.135G>C associated with elevated breast cancer risk if *BRCA*$^{-}$
Leyton[73]		436	*BRCA*$^{+}$ ≥ 2 family members with breast cancer ≥ 2 family members with ovarian cancer Single case of early-onset diagnosed ≤ 50 y	*PALB2*	Full gene sequencing in 100 "high-risk" cases Analysis of identified variants	No pathogenic mutations identified 3 variants identified (c.1676A>G[a], c.2993C>T[a], c.1861C>A)
Calderón-Zúñiga[74]	Mexico	94	Familial breast cancer Early-onset breast cancer	*ATM*	PCR-FLP of 3 specific mutations (IVS24-9delT, IVS38-8T>C, 5557G>A)	5557G>A (13%) IVS24-9delT (21% vs 8% controls; *P* = .0122) IVS38-8T>C (< 1%)
Bell[76]	United States	362[b]	Early-onset breast cancer	*CHEK2*	169 cases diagnosed ≤ 40 y had sequencing of coding region of *CHEK2* Specific analysis of 1100delC, H143Y, and 8 other *CHEK2* variants/mutations	Data not reported by ethnicity, but reported "infrequency" of c.1100delC among Latinas
Bretsky[75]		101 [b]	Personal history of breast cancer	*ATM*	20 specific *ATM* missense mutations or polymorphisms	L546V had modest but not significant predictor of risk; almost exclusive to African American women (found in n = 2 Latinas)
Damiola[77]		158 [b]	Breast cancer diagnosed ≤ 45 y	*MRE11, RAD50, NBN*	PCR-based analysis of coding sequence and exon/intron boundaries of *MRE11, RAD50, NBN*	Data not reported by ethnicity *MRE11, RAD50, NBN* are intermediate-risk genes

[a]These variants play a role in risk of breast cancer.

[b]Latinas were part of a larger multiethnic cohort.

CNV = copy number variation, FLP = fragment length polymorphism, HBOC = hereditary breast and ovarian carcinoma, PCR = polymerase chain reaction.

Table 2

Comparison of ER and *HER2* Status in Hispanic, Black, and White Women

Study	No. of Patients	Hispanic	White	Black
Chlebowski[205]	N = 3,800 n = 103 Latinas	ER$^+$: 83.0%	ER$^+$: 87.0%	ER$^+$: 71.0%
Dunnwald[206]	N = 209,276 n = 5,585 Latinas	ER$^+$: 70.2%	ER$^+$: 78.4%	ER$^+$: 60.5%
Hausauer[207]	N = 243,906 n = 15,355 Latinas	ER$^+$: 53.2% (unknown ER status: 29.4%)	ER$^+$: 63.5% (unknown ER status: 22.3%)	ER$^+$: 46.4% (unknown ER status: 29.4%)
Hines[203]	N = 285 n = 69 Latinas	ER$^+$: 63.8% HER2: 31.9% TNBC: 17.4%	ER$^+$: 77.3% HER2: 14.3% TNBC: 15.1%	—
Li[204]	N = 124,934 n = 7,219 Latinas	ER$^+$: 68.7%	ER$^+$: 78%	ER$^+$: 53.4%
Parise[3]	N = 143,184 n = 24,078 Latinas	ER$^+$: 74.6 % *HER2*: 22.2% TNBC: 15.9%	ER$^+$: 82.7% *HER2*: 17.2% TNBC: 11.2%	ER$^+$: 66.5% *HER2*: 20.1% TNBC: 24.5%

ER = estrogen receptor, TNBC = triple-negative breast cancer.