Chapter 4
Breast Cancer Risk and Mortality in Women of Latin American Origin

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Introduction

The categories of Hispanic or Latino refer to individuals of diverse national origin (Mexico and all countries in the Caribbean, Central and South America), place of birth (individuals born in the United States whose ancestors were born in Latin America or individuals born in Latin America), and continental ancestral backgrounds (mostly European, Indigenous American (IA), and African, but also including Asian and other minor components). This diversity had not been systematically addressed in cancer epidemiology until recent years, and the lack of extensive datasets with detailed information about subgroups of Latinos has resulted in the placing of a very diverse set of individuals into one category. This is surprising given that Hispanics/Latinos represent the second largest US census racial/ethnic category including ~17% of the US population (50 million individuals) [1].

Breast cancer is the most common cancer in US Latinas [2], but compared to other population groups, incidence is relatively low. Age-adjusted breast cancer incidence rates based on 2010–2014 cases were 127.7 in non-Latina Whites (NLWs), 125.1 in non-Latina Blacks (NLBs), 98.5 in Asians/Pacific Islanders, 93.1 in Latinas,

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and 82.2 in Native Americans/Alaskan Natives [3]. Some studies have shown that despite the lower incidence of breast cancer in Latinas, their mortality risk is higher than NLW women, even after adjustment for tumor characteristics and socioeconomic status [4–8]. However, this observation is not consistent across studies, with several reporting lower risk of breast cancer-specific mortality for Latinas compared to other population groups [9–12]. In addition, Latinas have been reported to have a higher risk of developing aggressive subtypes [13] and of being diagnosed at more advanced stages of the disease [12, 14].

This chapter summarizes works conducted by our group and others on breast cancer risk, characteristics, and survival, in women of Latin American origin, with particular emphasis on observed differences among Latino subgroups.

Breast Cancer Risk in Women of Latin American Origin

The group usually designated by the category of Hispanics/Latinos is not homogeneous, and the risk of developing breast cancer among these women varies by national origin [15], place of birth (US-born vs. foreign-born) [16, 17], and genetic ancestry [18, 19].

A study that was based on cancer registry data from Florida, including diagnosis between the years 1999 and 2001 and ~30,000 Latinas, reported overall age-adjusted incidence rates of 106.4 (100.8–112.3) in this group, 140.4 (137.6–143.2) in NLWs, and 104.9 (98.5–111.7) in NLBs. Incidence rates varied greatly among Latinas by national origin, with Puerto Ricans having the highest rates (116.9; 103.7–131.4), followed by Cubans (108.0; 96.7–120.3) and Mexicans (71.9; 53.1–95.2). The incidence of breast cancer in Caribbean women was markedly higher than that in AAs [15]. The 2000 and 2005 National Health Interview Survey (NHIS) Cancer Control Modules observed a higher 5-year absolute risk in Cubans/Cuban-Americans compared to Mexican/Mexican-Americans and a higher lifetime risk in Dominicans compared to Mexican/Mexican-Americans [20].

Studies have reported that foreign-born Latinas have lower breast cancer incidence than their US-born counterpart [16, 17]. In California, foreign-born Latinas have lower risk of developing breast cancer than US-born [17], with increasing risk with longer US residency [16]. The study based on the Florida Cancer Registry also reported marked differences in incidence between Latinas residing in the United States and those in their countries of origin. Breast cancer incidence rates were reported to be twice or even three times higher in US women of Latin American origin, as in the case of Cubans (31 per 100,000 in Cuba vs. 78 in Florida) [15]. Concordant with these results, a study that compared cancer incidence between Puerto Ricans in the United States and in those residing in the Island found a significantly lower breast cancer incidence among Puerto Rican women who reside in Puerto Rico [21]. Differences in risk of breast cancer by place of birth could be explained by lifestyle changes related to the adoption of a more westernized reproductive behavior (i.e., lower parity, shorter duration of breast-feeding, and later age

at first full-term pregnancy) and dietary or other lifestyle choices (i.e., more fast food, higher alcohol intake, less exercise) [16, 22].

Genetic ancestry also varies among Latinas, and it has been reported that women with high IA ancestry have lower risk of developing breast cancer than those with high European ancestry. This difference was statistically significant after controlling for most established risk factors that are known to differ between Latina and NLW women [18, 19]. The inverse association between IA ancestry and breast cancer risk was partly explained by a genetic variant located near the estrogen receptor 1 gene (ESR1), shown to be of relatively high frequency in women with IA ancestry [23]. In Colombia, patients diagnosed with estrogen receptor-negative breast cancer (HER2-enriched, basal-like, and non-basal triple negative) had the highest African ancestry [24]; however, the role of African ancestry in defining breast cancer risk by Latina national origin has not been fully examined.

Breast Cancer Mortality in Women of Latin American Origin

The described heterogeneity among Latinas not only translates into differences in breast cancer risk but also mortality. Cubans and Puerto Ricans have the highest mortality rates [25], while Mexicans, Central Americans, South Americans, and Dominicans have lower breast cancer mortality rates [25].

Few studies have analyzed differences in cancer mortality by genetic ancestry in women of Latin American origin. In 2013, Fejerman et al. analyzed the association between genetic ancestry and survival in Latina women from the San Francisco Bay area and reported higher mortality hazard in women with more than 50% of IA ancestry compared to women with 50% or less of IA ancestry [26]. Nevertheless, when the association was re-tested in women with uniform access to healthcare, the previously observed disparity in breast cancer-specific mortality was no longer apparent [27].

Ellis et al. showed that stage at diagnosis explained 11% of the survival disparities in Latina women compared to NLW women [28]. Socioeconomic status is an important contributor to health disparities in breast cancer outcomes as reduced screening, diagnostic delays and barriers to comprehensive treatment can lead to later stage at diagnosis [29]. Latina women are less likely to use mammography screening compared to NLW women [29–31]. In addition, delays in the diagnostic biopsy after an abnormal screening study might contribute to the more advanced stages at presentation [29] and delays in treatment initiation [12]. Results of a study based in Chicago showed an inverse association between European genetic ancestry and the risk of late stage at diagnosis (OR 0.70, 95% CI: 0.54–0.92) among Latina patients even after adjusting for multiple social and behavioral risk factors [32].

While breast cancer incidence is relatively low in foreign-born Latinas, they are more likely to be diagnosed with breast cancer at more advanced stages, initiate treatment later, and are less likely to receive guidelines-concordant treatment when compared to US-born Latinas [17]. Some studies have reported that even though

foreign-born Latinas are more likely to be diagnosed with more advanced stages, they have better survival than US-born Latinas [17, 33, 34]. This is a well-known phenomenon called the immigrant paradox that refers to the better health outcomes observed for certain immigrant populations in the United States compared to non-immigrant individuals of similar socioeconomic background [35]. The fact that Latina women experience survival advantages can be related in part to the lifestyles adopted in Latino enclaves, in which they may promote better health attitudes and behaviors such as healthier diets and social support [17, 34, 36]. These enclaves are neighborhoods with dense US-born Latino or Latino immigrant populations that hold certain cultural norms and practices [33, 35]. It is important to mention that the better survival of foreign-born Latinas could be partly an artifact related to the return of these women to their native countries leading to an under-ascertainment of deaths [33, 36].

Breast Tumor Subtypes in Women of Latin American Origin

Breast cancer is a complex and heterogeneous disease that has been classified into four main intrinsic subtypes based on gene expression profiles: luminal A, luminal B, HER2-enriched, and basal-like [37, 38]. Luminal subtypes belong to the estrogen receptor-positive (ER+) group and are characterized by the expression of genes such as the estrogen receptor gene (ESR1) and genes regulated by estrogen such as GATA3 [39]. Although globally, luminal subtypes show the best outcomes, luminal B have a more aggressive phenotype as they express higher levels of proliferation-related genes and growth factor receptors such as HER2 [40, 41]. HER2-enriched and basal-like subtypes are ER-negative (ER−) subtypes. HER2-enriched tumors express ERBB2 and genes in the 17q22.24 locus [39, 42, 43] while basal-like subtype express basement membrane cytokeratins and lack the expression of ESR1 and its co-expressed genes [39]. ER− subtypes have the poorest prognosis when compared to luminal subtypes [44].

The distribution of breast cancer intrinsic subtypes varies among women from different populations, and Latina women have a higher proportion of more aggressive intrinsic subtypes such as ER− tumors than NLW women [13]. This is very important as these subtypes of disease have fewer treatment options and a poorer prognosis than other subtypes [3, 6, 45–48].

This differential distribution of subtypes in Latina compared to NLW women has been shown not only in population-based studies but also in hospital/clinical-based studies in Latin America. In population-based studies from the United States [49–60], the proportion of the triple-negative subtype in Latinas ranged between 10 and 18%, while in NLW women, it ranged between 8 and 15%. On the other hand, HER-enriched tumors ranged between 4 and 24% in Latinas and between 3 and 17% in NLW women. Not only US Latinas, but also Latin American women more generally, have a 20–40% higher risk of developing ER−/PR− and triple-negative breast cancers (TNBC) than NLW women [19, 54, 61–67].

Most studies performed in Latin America are hospital-based [24, 65, 68–73]. The reported proportion of triple-negative subtype in Latin America ranged between 12 and 24% and between 7 and 24% for the HER2-enriched subtype [47] (Fig. 4.1). Countries such as Mexico [47], Peru, and Colombia have higher relative frequency of triple-negative tumors (23%, 21%, and 21%, respectively) compared to other countries in Latin America such as Costa Rica (17%) [69], Brazil (17%) [65], and Puerto Rico (17%) [70]. When comparing hospital-based studies with those performed at national referral centers such as the National Cancer Institutes from each country, differences are also observed. For example, a hospital-based study in Peru reported that the proportion of triple-negative breast cancer was 17% [73] while in the study from The National Cancer Institute from Peru, it was 23% [71]. A similar scenario was observed in Colombia where a hospital-based study reported a proportion of 12% [72], while the Colombian National Cancer Institute reported a proportion of 21% [24] (Fig. 4.1). More studies are needed to decipher the distribution of intrinsic subtypes in a population-based scenario in Latin America and also to analyze the relationship between genetic ancestry tumor subtype.

The heterogeneity in the distribution of breast cancer subtypes in women of Latin American origin can be partly attributed to the differences in the source of

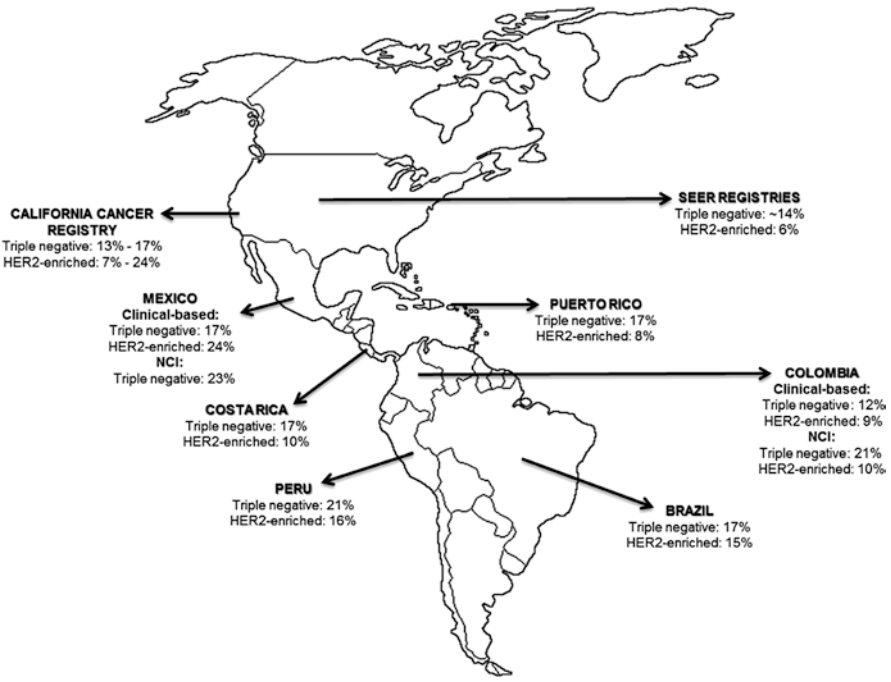

Fig. 4.1 Prevalence of triple-negative and HER2-enriched breast cancers in women of Latin American origin. Differences in the prevalence of these subtypes are noted between the different Latin American countries and also within the same country according to the source used, hospital-based, or reference center

information. National Cancer Institutes in Latin America are usually reference centers that receive patients that could not be adequately served by local hospitals/clinics, likely because of their advanced stage at diagnosis and tumor aggressiveness. Additionally, differences could result from the surrogates used to classify breast cancer into intrinsic subtypes (PAM50 or St. Gallen surrogates), although most studies used the basic classification that includes the evaluation of ER, PR, and HER2 [13].

Recent studies suggested that genetic ancestry could be acting as a modulator of gene expression and a risk modifier for the development of specific subtypes of breast cancer in Latina women [74]. Serrano-Gómez et al. reported that Colombian breast cancer patients with higher IA ancestry showed higher expression of the ERBB2/GRB7/MIEN1 genes in breast tumors of luminal B subtype [74]. These three genes, located in the same region of chromosome 17, have been reported as co-amplified in breast cancer and this event has been associated with poor prognosis [42, 75–77].

Gaps: Do We Have the Right Data to Learn to Predict, Prevent, and Treat Breast Cancer in Women of Latin American Origin?

Genomic technologies have offered new perspectives to expand and improve human health [78]. However, it has been shown that the proportion of samples from minority populations included in large-scale genomic studies remains low [79, 80]. Individuals of Latin American origin only represent 0.54% of the samples included in genome-wide association analyses compared to 81% for those of European ancestry [80]. A similar scenario was observed in The Cancer Genome Atlas (TCGA) where only 3% of the samples are from Latino patients [79]. Increasing the representation of diverse populations in future "omics" research efforts will improve our understanding of the drivers of aggressive tumor biology across different population groups and subgroups [79].

The need for cancer control in Latin America has received significant attention, with specific recommendations to increase investment in cancer registration, given that cancer registration covers approximately 7% of the populations in Latin America, while the equivalent coverage is 83% in North America and 32% in Europe [78, 81].

To assure comprehensive registries, the implementation of population-based cancer registries (PBCR) in Latin America require government support in order to incorporate all sources of information such as data from social security and the private sector [82, 83]. Biorepositories in Latin America hold diverse tissue samples that could enrich our knowledge of the molecular diversity of cancer in Latinos from different regions, but they tend to lack the resources to conduct the research. Therefore, it is through international collaborations, including support from US

institutions and investigators, that we can begin to generate the complex data that we need to better understand cancer risk and outcomes with the consideration of biological, environmental, cultural, and access-related factors in individuals of Latin American origin.

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