Chapter 10
Molecular Profiles of Breast Cancer in Hispanic/Latina

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Introduction

Breast cancer is the most common cancer in women worldwide and is the second leading cause of cancer death among women in the United States [1]. Although it is the most incident cancer at the global level, its incidence and mortality rates vary among the population groups in the United States [2]. African American (AA) and Hispanic/Latina (H/L) women have a lower incidence of breast cancer (125.5 per 100,000 and 91.9 per 100,000, respectively) compared to non-Hispanic White (NHW) women (128.7 per 100,000) [2]. Mortality rates for breast cancer are higher

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in AA women (29.5 per 100,000) and lower in H/L women (14.2 per 100,000) when compared to NHW women (20.8 per 100,000) [2].

Breast Cancer Intrinsic Subtypes

Breast cancer is a complex and heterogeneous disease in terms of histology, therapeutic response, metastatic patterns, and outcomes [3]. In 2000, Perou et al. published the first classification of breast cancer into intrinsic subtypes based on data from gene expression microarrays [4]. They used complementary DNA (cDNA) microarrays to analyze breast cancer tissue from 65 surgical specimens of human breast tumors from 42 different patients. These samples were collected at Stanford University California, or at the Haukeland University Hospital in Bergen, Norway, so presumably included women of mostly European descent. Gene expression analysis separated intrinsic subtypes of breast cancer into two main groups based on the expression of estrogen receptor (ER). Within these two groups, four intrinsic subtypes were identified: luminal A and luminal B subtypes, which are positive for the ER expression (ER+); and HER2-enriched and basal-like, both ER negative (ER−) [5, 6]. One year later, Sorlie et al. [7] analyzed the clinical implications of this new classification of breast cancer [8] and reported differences in breast cancer outcomes between the intrinsic subtypes [7].

Genetic Ancestry and Breast Cancer Characteristics

Each Latin American country shows variations in the proportions of European, African, and Native American ancestries, and countries such as Mexico, Peru, and Bolivia are predominantly indigenous while Argentina and Uruguay are predominantly European [9]; there are differences not only in genetic ancestry but also in lifestyles and exposures of breast cancer [10].

Increasing evidence shows that breast cancer characteristics differ according to genetic ancestry. European ancestry in H/L women has been associated with an increased risk for breast cancer in women from the San Francisco Bay area [11], and this finding was replicated in women from Mexico [12]. Also, Fejerman et al. [11] did not find any associations between genetic ancestry and tumor characteristics such as hormone receptor status. Al-Alem et al. [13], however, studied the association between genetic ancestry and breast cancer characteristics in a group of 656 women (255 NHW, 277 AA, and 124 H/L) from the "Breast Cancer Care in Chicago" study and found that higher European ancestry was protective for later stage at diagnosis in H/L women (OR 0.70, 95% CI 0.54–0.92) and that Indigenous American ancestry (IAA) was associated with later stage at diagnosis (OR 1.36, 95% CI 1.04–1.79). The lack of concordance between the last two studies can be explained by the

variation in the case populations. The study by Fejerman et al. [12] included women from the San Francisco Bay area, presumably of Mexican origin while the Al-Alem et al. study [13] included a larger proportion of women from the Caribbean. This highlights and reinforces the idea that results found in one Hispanic population cannot be generalized for all Latinos and that there is a need to include genetic ancestry in the studies [13].

Growing evidence suggests that differences in gene expression profiles of breast cancer can be influenced by the genetic architecture of the individual's genome [14–17]. These studies have compared gene expression profiles from NHW and AA women with breast cancer in an effort to explain health disparities in the tumor biology context. Martin et al. [16] compared breast tumors from 18 AA and 17 NHW women, and over the 400 differentially expressed genes, they found two genes that could distinguish between the two population groups, *CRYBB2* and *PSPHL*. Similar findings were reported by Field et al. [14] who analyzed 52 matched patients (26 AA and 26 NHW) and compared the gene expression profile between the two population groups. They found 22 differentially expressed genes, including *CRYBB2* and *PSPHL*. Stewart et al. [17], using data from The Cancer Genome Atlas (TCGA) compared gene expression profiles of 574 NHW and 53 AA patients and found 674 differentially expressed genes. Among those, resistin (*RETN*), a gene associated with obesity and diabetes [18], was the most changed. *CRYBB2* was also found to be overexpressed in AA patients [17]. Grunda et al. [15] analyzed the expression of 84 genes involved in breast cancer prognosis associated with therapy, estrogen signaling, and tumor aggressiveness in 11 AA and 11 NHW patients and identified 20 genes that participate in regulatory processes such as G1/S transition, cell adhesion, and estrogen pathway targets. The results suggest that there may be some differences in the gene expression profile as a consequence of ancestry. None of these studies included H/L women in the analysis. More importantly, ancestry was assessed by self-identification, and genetic ancestry was not analyzed.

There is one study from Chavez-MacGregor et al. [19] that investigated the differences in gene and protein expression within each molecular subtype as a consequence of ancestry. They analyzed a group of 376 women belonging to different racial groups (AA, NHW, H/L, and others) and did not find differences in gene and protein expression between racial/ethnic groups. As they discuss in the paper, to perform a more accurate analysis in an admixed population, it is important to analyze their genetic ancestry, as it could lead to misclassification of the population. Even though the latter work did not find ancestry-modulated genes in breast cancer, more studies are needed to answer that question.

Few studies have explored genetic ancestry to assess gene expression differences. Huo et al. [20] analyzed genetic ancestry in 930 patients with breast cancer who were grouped into the categories genomic black (≥50% African ancestry) or genomic white (≥90% European ancestry). After adjusting for intrinsic subtypes, they found 142 differentially expressed genes, with *LOC90784* and *CRYBB2* being the top two most differentially expressed. This result is consistent with previous studies where genetic ancestry was not analyzed [14, 16, 17]. This finding can be

explained by the fact that the genetic ancestry in patients who self-identify as NHW and AA is more uniform, with dominant ancestries being European and African, respectively [20].

Our recent work identified luminal B as the most prevalent subtype in Colombian women with breast cancer [21]. In the context of genetic ancestry, we analyzed gene expression profiles of 42 Colombian women with breast cancer (21 luminal A and 21 luminal B) based on 80 ancestry-informative markers (AIMs) [22]. The patients were categorized according to luminal subtype and to the proportion of European or Native American ancestry. Differential expression analysis was performed according to intrinsic subtype and by ancestry category. We found five genes potentially modulated by genetic ancestry: *ERBB2*, *GRB7*, *GSDMB*, *MIEN1*, and *ONECUT2*. Further studies are needed to explore the prognostic value of this finding and to replicate it in other Latin-American patients.

Other studies have analyzed gene expression profile in H/L women without determining genetic ancestry. DNA repair capacity (DRC) has been previously described as a breast cancer risk factor [23, 24]. DRC can be measured by the host-cell reactivation (HCR) assay that quantifies the capacity of a lymphocyte to repair exogenous DNA [25, 26]. Ramos et al. [27] reported that a low DRC is a breast cancer risk factor in H/L. They compared the DRC in 33 breast cancer patients and 47 healthy controls from Puerto Rico and found that for every 1% decrease in the DRC, there was a 22% increase in breast cancer risk. Matta et al. in 2012 [28] analyzed the DRC from 824 women (285 breast cancer patients and 539 controls) and also found that the DRC was lower in breast cancer patients. One year later, the same group [29] performed microarrays to analyze the expression level of DNA repair genes in women with breast cancer from Puerto Rico compared to controls to explore how DNA repair was dysregulated in breast cancer. They found 21 genes differentially expressed between breast cancer patients and controls: *CHEK2*, *EME1* (*MMS4L*), *ERCC3* (*XPB*), *FANCM*, *H2AFX* (*H2AX*), *HMGB1*, *HUS1*, *MBD4*, *NEIL3*, *PCNA*, *RAD1*, *RAD23B*, *RAD51*, *RAD54B*, *RDM1* (*RAD52B*), *SHFM1* (*DSS1*), *TP1*, *UBE2N* (*UBC13*), and *XRCC5* (*Ku80*). Moreover, they analyzed DRC using the HCR test and found three genes positively associated with the DRC level, *RAD51*, *FANCB*, and *FANCA*. This study is important because the use of inhibitors of DNA repair pathways can interfere with the ability of the cells to survive DNA damage induced by chemotherapeutic agents [27, 30, 31]. The results in Matta et al. [29] and Ramos et al. [27] provide evidence regarding dysregulation of DNA repair capacity at the gene expression level in H/L women with breast cancer. Similar results have been reported in NHW women [32, 33].

Analysis of gene expression profiling has also been used to develop gene signatures to estimate recurrence risk and to better select patients who will benefit from chemotherapy [34–37]. These signatures have been developed and validated in samples of NHW women and have been used in H/L patients with the assumption that the molecular profile would be similar. Kalinsky et al. [38] compared the proliferation index of ER(+)/HER2(−) early stage tumors based on the Oncotype DX gene expression signature in H/L and NHW women and found that tumors from H/L women showed higher proliferation scores than tumors from NHW women.

Conclusions

Hispanic/Latinas are underrepresented in breast cancer studies and usually are analyzed as a whole group. However, the genetic make-up of H/L women may create a bias in genetic association studies and generate false-positive or false-negative associations. It is thus advisable to properly classify genetic ancestry in admixed populations, like Hispanic/Latinos, to better understand the real contribution of genetics to disease susceptibility and to provide this ethnic group the benefits of recent treatment advances.

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