Racial Disparity in Quadruple Negative Breast Cancer

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Black/African-American (AA) women, relative to their White/European-American (EA) counterparts, experience disproportionately high breast cancer mortality. Central to this survival disparity, Black/AA women have an unequal burden of aggressive breast cancer subtypes, such as triple-negative breast cancer (ER/PR-, HER2-wild type; TNBC). Quadruple negative breast cancer (QNBC), a subgroup of triple negative breast cancer, has emerged as a highly aggressive breast cancer subtype that disproportionately afflicts and impacts Black/African-American (AA) women.

quadruple negative breast cancer triple-negative breast cancer androgen receptor

1. Introduction

In the United States (US), breast cancer is the leading cancer diagnosis and the second cause of cancer-related death in women [1]. Breast cancer is a heterogeneous disease that can be subdivided into 4 major intrinsic molecular subtypes—either by immunohistochemical (IHC) staining or PAM50 gene expression profiling [2]. The four breast cancer subtypes are: (1) luminal A ($ER^+/PR^+/HER^-$), (2) luminal B ($ER^+/PR^{+/-}/HER2^+$), (3) HER2-enriched ($ER^-/PR^-/HER2^+$), and triple-negative breast cancer ($ER^-/PR^-/HER2^-$, TNBC); these breast cancer subtypes are used to identify targeted therapeutic treatment and potential prevention options.

Breast cancer incidence and mortality rates differ significantly by race/ethnicity in the US. Black/African-American (AA) and White/European-American (EA) experience notably higher incidence and mortality rates of female breast cancer across all ages compared to American Indian/Alaskan Native (AI/AN), Hispanic, and Asian Pacific Islander (API) subpopulations, with rates being the lowest among APIs [3][4]. These racial/ethnic differences have been suggested to be primarily driven by higher rates of luminal A and B molecular subtypes observed among AI/AN, Hispanic, and API women but higher rates of TNBC observed among Black/AA and White/EA women [3]. Furthermore, White/EA and API women display the highest rates of localized breast cancers (64–66%) but lowest rates of regional stage breast cancer (27–30%). Whereas Black/AA and Hispanic women display the lowest rates of localized disease (56–60%) but highest rates of regional disease (35%) [4]. Distant-stage (metastatic) breast cancer contributes to 8% of diagnoses in Black/AA women compared to only 5–6% of diagnoses reported among other racial/ethnicities [4].

Among Black/AA and White/EA women, breast cancer disproportionately impacts Black/AA patients. Although the incidence rates between Black/AA and White/EA women are similar (126.7 vs. 130.8 per 100,000, respectively), Black/AA women experience a 40% higher death rate than White/EA women (28.4 vs. 20.3 per 100,000, respectively). Black/AA women are significantly more likely to present clinically with aggressive breast cancer subtypes such as TNBC, that lack an effective targeted therapy [3][5][6]. Black/AA women are twice as likely to be diagnosed with TNBC than White/EA women (38 vs. 19 per 100,000, respectively). In contrast, White/EA women are more likely to present with the least aggressive breast cancer subtypes, particularly luminal A breast cancer, that is effectively targeted with current therapies [3][4]. Thus, Black/AA women have fewer targeted treatment options compared to White/EA women, which has been suggested to underlie the racially disparate burden in breast cancer. Additionally, among all breast cancer subtypes, Black/AA women have the highest rate of recurrence and the lowest survival [5][6][7]. Within TNBC, even after adjusting for age, stage, grade, and poverty index, Black/AA patients experience significantly shorter survival (HR = 2.1, 95% CI: 1.1–4.0) compared to White/EA patients [8].

Recently a new molecular TNBC subtype has been identified —quadruple-negative breast cancer (QNBC) [9][10][11][12]. Similar to TNBC, QNBC lacks expression of ER/PR and does not overexpress HER2. In addition, QNBC lacks expression of the androgen receptor (AR) [13]. The absence of AR expression in TNBC is linked to more aggressive clinical features upon presentation, younger age at diagnosis, and shorter disease-free survival. QNBC more frequently occurs in Black/AA women (relative to White/EA women) and is emerging as a highly aggressive breast cancer subtype [10][13][14][15][16].

2. TNBC—The Triple Threat

TNBC is frequently referred to as a “triple threat” due to the absence of all three major therapeutic breast cancer targets—ER, PR, and HER2. [17][18]. In addition, TNBC is inherently more clinically aggressive than the other breast cancer subtypes as evidenced by the higher frequency of metastasis and recurrence within 5 years of diagnosis [17][19][20]. Linked with these poor survival statistics, TNBC is characterized by the highest inter-patient and intra-tumoral heterogeneity among the breast cancer subtypes [21][22]. Multiple groups have dissected the heterogeneity of TNBC starting with Lehmann and colleagues, who subdivided TNBC into six distinct molecular subtypes [23][24]. These subtypes include two basal-like subtypes (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem–like (MSL) and luminal androgen receptor (LAR). Liu et al., recently integrated both long coding RNAs and mRNAs to classify TNBCs into 4 distinct subtypes, (1) immunomodulatory (IM)—enriched with immune cell and cytokine signaling; (2) luminal androgen receptor (LAR)—enriched with AR signaling; (3) mesenchymal-like subtype (MES)—enriched with growth factor signaling, and (4) basal-like immunosuppressed (BLIS)—enriched with cell cycle and DNA repair processes and downregulated immune response [25].

TNBC subtypes differ in their aggressive biological potential. The two basal-like subtypes (BL1 and BL2 or BLIS) and immunomodulatory (IM) subtypes carry a worse prognosis, while the AR+ LAR subtype carries a more favorable prognosis. Black/AA women more frequently have aggressive TNBC subtypes (BL1, BL2, and IM) and White/EA women more frequently present with the less aggressive LAR subtype [7][10][26].

3. AR Signaling/Pathway

AR is a type I nuclear receptor that is expressed in multiple tissue types in both sexes, including in the breast [27]. Although widely known to be instrumental in male biology as ER is in female biology, AR also plays a critical role in female biology [28]. AR is indispensable for both female fertility and breast growth [29]. The androgen, testosterone, is synthesized in the ovaries and adrenal glands in women and is converted to dihydrotestosterone (DHT) or 17β-estradiol (E2) in breast tissue. DHT or E2 binds to the AR or ERα to stimulate or inhibit cell proliferation [30][31][32]. When AR is not bound to its ligand, it is located in the cytoplasm, bound to heat shock proteins. Upon ligand binding, AR undergoes a conformational change, disassociates from heat shock proteins, becomes activated, and dimerizes with another activated AR [27]. These AR dimers translocate to the nucleus to bind to androgen-responsive elements (AREs) within target genes to modulate transcription. This AR-mediated gene transcription can result in differentiation, proliferation, apoptosis, or angiogenesis [33]. AR can also be activated independent of its ligand via crosstalk with key signaling pathways such as PI3K/Akt, ERK, mammalian target of rapamycin (mTOR), Wnt/β-catenin or via interaction with FOXA1 [34].

4. AR Pathway as a Therapeutic Target for TNBC

Nuclear AR is expressed in approximately 12–35% of TNBCs and has emerged as a promising therapeutic target [35]. AR inhibitors and antagonists, such as enzalutamide and bicalutamide, have elicited a promising response in vitro and in clinical testing. LAR TNBC cell lines had a higher sensitivity to bicalutamide [23]. In AR-positive TNBC models, both in vitro and in vivo, enzalutamide reduced proliferation, blocked invasion, and increased apoptosis [36][37][38]. In women with metastatic AR-positive TNBC treated with enzalutamide, in a nonrandomized phase II clinical trial, Traina and colleagues observed a clinical response rate of 25% at 24 weeks and a median progression-free survival (PFS) of 14.7 weeks to [39]. Similarly, in AR-positive metastatic TNBC, bicalutamide elicited a clinical benefit rate of 19% at 24 weeks and a median PFS of 12 weeks [40].

Apalutamide is structurally similar to enzalutamide but does not induce AR nuclear translocation or DNA binding [41]. Darolutamide antagonizes AR mutants such as F876 L, W741L, and T877A [42]. Apalutamide and darolutamide are currently under evaluation as promising new-generation AR inhibitors in phase III clinical trials for non-metastatic castration-resistant prostate cancer (NCT01946204 and NCT02200614, respectively) [43]. Thus, these new AR inhibitors may be tested in AR-positive TNBC patients in the future. Agents that target intracrine and adrenal androgen biosynthesis, such as the CYP17 inhibitors, abiraterone acetate and seviteronel, are also promising alternative treatments for AR-positive TNBC. In a phase II multicenter trial with metastatic or inoperable locally advanced AR-positive TNBC patients, abiraterone acetate (in combination with prednisone to offset aldosterone production) elicited a clinical benefit rate (CBR) of 20.0% at 6 months and median PFS at 2.8 months. Preliminary pharmacokinetic data from a phase I/II trial with seviteronel showed a significant reduction in testosterone in AR-positive TNBC patients [44]. Preclinical studies also demonstrate that seviteronel may sensitize AR-positive TNBC patients to radiotherapy [45]. Furthermore, since compensatory pathways often crosstalk with the AR pathway, the future of AR inhibition will likely require the inclusion of targeted therapies that impair these alternative pathways. Cyclin D1 and Rb protein expression is often upregulated in AR-positive TNBCs [46]. Thus,

clinical trials are already underway that combine AR inhibitors with CDK4/6 inhibitors, such as palbociclib and ribociclib [44]. AR-positive TNBC biology is also characterized by PIK3CA mutations and p-AKT [23][47][48]. A multi-institutional phase I/II study (TBCRC032) has commenced to determine the safety and efficacy of combining AR inhibitors such as enzalutamide with the PI3K inhibitor, taselisib, in metastatic AR-positive BC patients [49]. The combination resulted in a significant increase in the CBR among AR-positive TNBC patients.

5. A Double-Edged Sword: Controversial Role of ARs in ER+ Breast Cancer and TNBC

Similar to ERs and PRs, the AR is a member of the nuclear steroid hormone receptor family and transcriptionally regulates target genes. Testosterone and dihydrotestosterone are androgens that directly or indirectly (as prohormones) stimulate AR-signaling [50][51]. Upon binding of androgens to an AR, the receptor translocates into the nucleus and binds to the promoter of target genes to enhance transcriptional activity [51]. AR-signaling plays an important role in both the development of normal breast tissue and in breast tumorigenesis and progression [52][53]. Several studies have defined androgens as potential tumor suppressors in ER-positive breast cancer with anti-proliferative activities. The anti-proliferative activity of ARs in ER-positive breast cancer is thought to be the result of crosstalk between AR and ER signaling pathways [54]. ERs promote proliferation by binding to estrogen response elements (EREs) in cis-regulatory elements of estrogen-regulated genes [51][55]. ARs can competitively bind to EREs to suppress estrogen-mediated tumor proliferation [52][56].

In contrast to ER-positive breast cancer, ARs promote proliferation of ER-/PR-negative breast cancer cell lines [57]. This finding is supported by studies by Garay et al. and Doanne et al. who raised the possibility of therapeutic targeting of the androgen pathway in TNBC [47][58]. Mechanistic studies in TNBC cell lines provide evidence that the AR interacts with AREs and stimulates tumor cell proliferation in an androgen-dependent manner [51].

Despite mechanistic studies in ER-/PR-negative cell lines, the role of AR signaling in TNBC is controversial [59][60][61]. AR expression in TNBC has been reported to range from as low as 7% to as high as 75% [61][62][63][64][65]. Studies investigating the prognostic role of the AR in TNBCs have similarly reported diverse results. Multiple groups have reported that negative AR status confers an aggressive disease course in TNBCs [12][63][64][66][67]. Loss of AR expression has been associated with younger age at presentation, lower stage, grade, mitotic scores, Ki-67, and lymphovascular invasion [60][61][63][68]. Additionally, several groups have reported that lack of AR expression in TNBC is associated with an increased risk of recurrence, distant metastasis, shorter DFS and shorter OS [63][69][70][71][72][73][74]. Paradoxically, some other studies have shown the opposite trend where AR positivity has been associated with younger age at diagnosis, higher nuclear grade, higher tumor stage, greater lymph node metastases and increased mortality [38][61][63][64][68][69][75][76][77].

The controversy over the AR is attributed to multiple factors, including variation in sample preservation (e.g., cold hypoxia time), use of different AR antibodies, staining methods, scoring methods, cut off values, lack of external validation, confounding effects of patient selection, and the existence of 15 different AR splice variants [78]. But perhaps one of the most significant contributors to this controversy is biogeographic ancestry. In a multi-

institutional study, AR in TNBC was found to be a positive prognostic biomarker in US and Nigerian (West African) cohorts but a negative prognostic biomarker in women from Norway and Ireland [9]. This finding suggests that AR expression may confer a poor prognosis in TNBC that occurs in women of European ancestry but a favorable prognosis in women of West African ancestry. Differences in AR signaling networks in women of different genetic ancestry, however, is poorly understood.

6. QNBC—The Quadruple Threat

While some TNBC express AR, approximately 65–88% of TNBC lack AR expression. AR-negative TNBC is called quadruple-negative breast cancer (QNBC: $ER^-/PR^-/HER2^-/AR^-$) and is considered a “quadruple threat”. Accumulating evidence suggests that QNBCs are significantly more aggressive than AR-positive TNBCs. QNBC has also been linked to the clinically aggressive basal-like molecular phenotype; in contrast, AR-positive TNBCs are linked with a less aggressive luminal phenotype [10][13]. Thus, QNBC is increasingly recognized as an aggressive, hard-to-treat breast cancer subtype.

7. A New Racial Disparity in Breast Cancer: Characterization of QNBC Disparity in Women of African versus European Ancestry

Recent studies provide evidence that the AR is differentially expressed in TNBC from women of African- versus European-ancestry. Gasparini et al. showed that the frequency of AR-positive TNBC was greater in White/EA versus Black/AA women (25.5% versus 16.7%, respectively) [12]. In a US cohort, it was revealed that among Black/AA compared to White/EA TNBC patients, the percentage of patients negative for AR expression was significantly higher (80.1% vs. 70.3%, respectively) [9]. Davis et al. corroborated these findings by showing that in multiple publicly available cohorts, AR mRNA expression was lower in TNBCs from Black/AA versus White/EA women, irrespective of ER and PR status [10]. In the same study, 100% of Black/AA women with TNBC were shown to be AR-negative. Several groups have also reported that QNBC is even more prevalent among native West African than Black/AA women. In TNBC from East African and White/EA women, AR expression levels were similar [9][11][79]. These findings suggest that low AR expression in TNBC is strongly associated with West African-ancestry as opposed to East African- or European-ancestry.

Emerging evidence suggests that QNBC is clinically more aggressive in Black/AA versus White/EA women. PAM50 subtyping of AR-negative TNBC in TCGA, showed that Black/AAs have a higher percentage of basal-like tumors than White/EAs (77% versus 70%, respectively) [10]. In addition, subtyping of the same AR-negative tumors, showed that Black/AA women (compared to White/EA) have a higher percentage of aggressive TNBC subtypes such as BL1 (24% versus 16%), BL2 (16% versus 12%), and IM (24% versus 19%) subtypes but a lower percentage of the LAR (0% versus 2%) subtype [10][26]. Furthermore, among women with AR-negative basal-like TNBC, Black/AA women exhibited a significantly shorter time of progression than White/EA women [10].

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