Review

Racial Disparity and Triple-Negative Breast Cancer in African-American Women: A Multifaceted Affair between Obesity, Biology, and Socioeconomic Determinants

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Abstract: Triple negative breast cancer (TNBC) is a molecularly heterogeneous disease whose incidence is disproportionately higher in African American (AA) women compared to European American (EA) women. Earlier onset, more advanced stage at diagnosis, and aggressive tumor phenotype are some of the characteristic features of TNBC in women with African ethnicity in comparison to EA women, denoting one of the most significant examples of racial disparity in oncology. It is still contentious whether health disparities result in aggressive behavior of TNBC in AA women or it is indeed a molecularly distinct disease. Given the “gaps-in-knowledge” surrounding racial disparity in TNBC, this review discusses various socioeconomic factors and the genetic predispositions contributing to poor prognosis of TNBC in AA women. While socioeconomic factors may contribute to poorer survival, multiple preclinical and clinical studies suggest inherent genetic risk factors and aberrant activation of oncogenic pathways in AA TNBC. Additionally, AA women are more likely to be obese and obesity is known to drive a molecular circuitry resulting in aggressive tumor progression indicating a potential obesity-TNBC axis at work in AA women. Given the multifactorial nature of AA TNBC, a transdisciplinary approach may help bridge the disparity that exists between AA and EA TNBC.

Keywords: triple negative breast cancer; racial disparity; African-American; risk factors; obesity

1. Introduction

Breast cancer is the second-most common cancer and a leading cause of cancer-related mortality for women in United States [1]. Approximately 266,120 new invasive breast cancer cases are estimated in 2018 according to American Cancer Society. Currently, there are more than 3.1 million breast cancer survivors in United States [2]. Breast cancer has been historically sub-classified on the basis of three molecular markers; estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (EGFR2/Her2), whose presence/absence guide the prognosis and therapeutic interventions. ER/PR positive breast cancer are candidates for endocrine therapy regimens and Her2 positive breast cancer can be targeted with anti-Her2 therapies whereas ER/PR/Her2 negative or triple-negative breast cancer (TNBC) lack any targeted therapies [3]. Owing to technical advances, breast cancer is now classified on the basis of immunohistochemical markers and complementary DNA microarrays [4,5] into six different subtypes, namely, luminal A (ER+ and/or PR+ and HER2−), luminal B (ER+ and/or PR+ and HER2+), HER2 overexpressing (ER−, PR− and HER2+), normal-like, claudin-low and basal-like/TNBC (ER/PR/HER2 negative, cytokeratin 5/6+ and/or epidermal growth factor receptor+) (Figure 1) [3,5,6]. This classification varies in prognosis and therapeutic
Triple negative breast cancer (TNBC) represents a class of heterogeneous cancer cells that exhibit different biological features, clinical presentations, therapeutic response and outcomes. TNBC encompasses 15% to 20% of all breast cancers [9]. TNBC are associated with worse prognosis, early relapse after standard chemotherapy, a high frequency of metastasis to lung, liver and brain and a low overall survival compared to other breast cancer subtypes [10]. To date most clinical trials utilize overall survival (OS) and progression-free survival (PFS) as the endpoints to evaluate the efficacy of therapeutic interventions but variability in postprogression survival (PPS) negatively impacts the correlation between OS and PFS and confounds the conclusions. A recent study including 472 patients evaluated the suitability of OS, PFS, and PPS as different measures of outcomes and concluded that clinical trials should adopt different endpoints based on the tumor characteristics to evaluate the benefits of new drugs. Importantly, OS can be a better endpoint for TNBC patients where PPS is low in contrast to luminal A/B and Her2+ tumors where the PPS is generally longer than a year [11]. Based on molecular profiling, Lehmann and colleagues showed that TNBC can be subdivided into 6 subgroups: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal-like (M), mesenchymal stem-like (MSL), and luminal androgen-receptor (LAR) expressing; and have differential sensitivity to therapeutic agents (Figure 1) [12]. BL1 and BL2 are most...
sensitive to cisplatin, mesenchymal subgroup responds to dasatinib (SRC inhibitor) and NVP-BEZ235 (PI3K/mTOR inhibitor) while LAR are amenable to bicalutamide (an antiandrogen) and alvespimycin (an HSP90 inhibitor) therapy [12]. Basal-like breast cancer, characterized by the presence of genes normally found in basal or myoepithelial cells of the normal breast [5] came into existence owing to the microarray-based expression profiling studies [5]. While TNBC and basal-like breast cancers (BLBC) have multiple overlapping features and these terms are often used interchangeably, both have some important unique features thus have to be acknowledged as distinct subtypes of TNBC [13]. Basal-like tumors possess higher TP53 mutations (44% versus 15%, \( p = 0.001 \)), complex mitotic index (odds ratio = 11.0; 95% confidence interval 5.6–21.7), greater nuclear pleomorphism (odds ratio = 9.7; 95% confidence interval 5.3–18.0) and higher combined grade (odds ratio = 8.3; 95% confidence interval 4.4–15.6). TNBC also encompass other breast cancer subtypes like claudin-low tumors which contain cells with stem cell properties and epithelial to mesenchymal transition potential, interferon rich subgroup encompassing tumors with a significantly better prognosis over other TNBCs [14,15]. Epidemiological studies have reported that TNBC are more common in women of African ancestry in comparison to other ethnic groups [16,17] and TNBC in African American (AA) women is associated with worse clinical outcomes compared to TNBC in European American (EA) women [10]. The age adjusted cumulative incidence rate of all subtypes of breast cancer is slightly lower in AA women in comparison to EA women with 124.3/100,000 cases in AA versus 128.1/100,000 cases in EA in United States; but AA women exhibit a 42% higher mortality rate than EA women [18]. Epidemiological, clinical and preclinical evidence reveal that the contributory factors for such a disparity encompass both biological and socio-economic causes (Figure 2) [19]. A study comparing breast cancer among AA, EA and Hispanic women reported that AA tumors were more likely to be associated with worse pathological characteristics such as larger tumors with less differentiated cancer cells [19].

Figure 2. Overview of various socioeconomic and biological factors contributing to disparity in TNBC progression in African American (AA) versus European American (EA) women. Various socioeconomic factors such as low income and poor access to health care can aid in high prevalence of obesity. Obese state can modify various signaling pathways and directly impact various tumor-promoting biological process including growth, invasion, and migration. These socioeconomic and biological factors contribute to TNBC progression in AA women directly or indirectly.
3. Triple Negative Breast Cancer—Higher Prevalence in African American Women

Surveillance, Epidemiology, and End Results (SEER) data of women diagnosed with breast cancer revealed that TNBC incidences were higher in AA women than any other ethnic or racial group of all ages \((p < 0.05)\) \([20]\) irrespective of the fact that TNBC frequency itself varied across regional population of women of African ancestry \([21]\). TNBC is the most predominant cancer in sub-Saharan Africa (Figure 3) including 22 countries of Americas and the Caribbean \([6,17,22,23]\). The study by Huo and colleagues evaluating the distribution of molecular subtypes of invasive breast tumors in women (mean age 44.8 years) from various geographical areas of Nigeria and Senegal (507 women) found that basal-like TNBC was the most predominant cancer in this region \([24]\). Similarly, 46% of tumors were found to be triple negative in Bamako University Hospital in Mali where mean age of patients was 46 years \([25]\). Another case study of 1216 breast cancer patients from Soweto, South Africa revealed that 90% of women with breast cancer were black and showed 20% prevalence of TNBC which was consistent with the reported frequency of TNBC in AA women \([26]\).

![Figure 3. Prevalence of triple negative breast cancer (TNBC) is shown among European American (EA), African American (AA) and women with African ancestry.](image)

Bowen and colleagues interrogated a UK based breast cancer cohort and found that 22% of black women had TNBC in comparison to 15% of white women \([27]\). In a population-based study of North Carolina Breast Cancer Cohort of 878 AA women and 187 EA women breast cancer cases, it was observed that premenopausal AA women had higher basal breast cancer rate (39%) than postmenopausal AA (14%) or white women of similar age group (16%) \([17]\). Using the data available on tumor grade, stage, ER/PR/HER2 status, patient age and BMI index along with self-identified racial group, Stead and colleagues concluded that the probability of TNBC incidence in AA women was 3 fold higher in comparison to EA women irrespective of age (31% before 50 years versus 29% after 50 years) and obesity (29% obese versus 31% non-obese) \([28]\). To investigate the potential differences between TNBCs and other breast cancer sub-types pertaining to age, race, grade, diagnosis stage, socioeconomic status, and relative survival, Bauer et al. followed women diagnosed with TNBC from 1999 to 2003 using the population-based California Cancer Registry data. This study compared a total of 6370 TNBC cases to 44,704 cases diagnosed with other breast cancers and reported that the non-Hispanic black or black women under the age of 40 were more likely to have TNBC \([16]\). Examining 375,761 invasive breast cancers (including 276,938 non-Hispanic white and 21,681 non-Hispanic black) \([29]\), Amirikia and colleagues found that both Hispanic (median age 54) and non-Hispanic (median age 57) black women were younger than non-Hispanic white women (median age 64) at the time of cancer incidence and had higher TNBC incidences in all age categories. Also, non-Hispanic black women younger than 44 years had the highest lifetime TNBC incidence rates and higher incidence rates of stage III and IV disease \([29]\). Examining data from the Yale TNBC cohort (50 AA and 86 EA tumors), Lindner et al,
showed that basal subtype is more common in AA women [30]. Similar conclusions were put forth by Keenan et al. after analyzing TNBC cases from The Cancer Genome Atlas (TCGA) [31]. Evaluation of TCGA data also showed that TNBC (33.3% vs. 14.9%) and basal (34.8% vs. 16.1%) subtype is more prevalent in AA women in comparison to EA women [32]. The available epidemiological data indicates that although TNBC is not restricted to a specific age or ethnic group, its frequency is higher in women of African ancestry and is associated with survival disadvantage. Overall and recurrence-free survival varies greatly according to the breast cancer subtype with shortest survival associated with basal-like sub-type and HER2/ER negative breast cancer [17]. Since basal like/TNBC incidence is greater in AA women, it seems intuitive that AA women exhibit overall poor prognosis. Indeed, the poorest survival was observed in the non-Hispanic black women with only 14% 5-year relative survival [16]. These disparities suggest the presence/absence of oncogenes/tumor suppressor genes, mutations and altered signaling pathways that might predispose premenopausal AA women to TNBC. Along with molecular alterations, socioeconomic factors may also contribute to overall poor prognosis.

4. Triple Negative Breast Cancer Disparity in African American Women—Biology and Environment

4.1. Genetic Risk Factors

Compared to TNBC in EA women, TNBC in AA women show enhanced p53, BRCA1, Aurora A, Aurora B and polo like signaling networks [33]. BRCA1 mutant breast cancers are typically TNBC [34] and though TNBC incidences are higher in AA women compared to other ethnic groups, incidence of germline BRCA1 mutation is higher in European women. A study focusing on 155 high-risk families at University of Chicago, Illinois, USA, showed that AA women had lower pathogenic variant BRCA1 than non-Hispanic and non-Jewish Caucasians but had higher rate of sequence variations [35]. More importantly, these sequence variations that block BRCA1 function occur in AA women at a lower rate than in European women [36]. Enhancer of zeste homologue 2 (EZH2), a member of Polycomb group family, blocks BRCA1 function by inducing protein kinase B (PKB or AKT) dependent genomic instability [37]. Recent studies have linked EZH2 and aggressive TNBC in AA women. Overexpression of nuclear EZH2 significantly associated with basal-like TNBC in women of African descent in a joint study by Kleer and Newman including 100 invasive breast cancer cases in Ghanaian women [38]. A similar study encompassing 295 breast cancer patients from Netherlands also indicated a high EZH2 expression in basal-like TNBC. Interestingly, some epidemiological studies indicate a prominent role of EZH2 irrespective of ethnic origins [39]. Stewart et al. performed a broad differential gene expression analysis containing sub-type and stage-specific analysis of the breast cancer data from TCGA and found an almost 2 fold elevated expression of Aurora B [33]. There are multiple founder mutations in BRCA genes and genetic variations in other genes associated with breast cancer but their functional significance in TNBC incidence and progression in AA women is currently unclear.

4.2. Socioeconomic Factors

Multiple socioeconomic factors influence the access to standard care, novel treatments and inclusion in clinical trials and contribute to overall prognosis. AA women with breast cancer do not usually avail or have access to appropriate guideline-concordant therapeutic regimens including locoregional treatment, adjuvant radiotherapy, adjuvant systemic therapy and breast reconstruction. Lack of timely screening might result in delayed diagnosis and bigger tumor burden at diagnosis. In addition, limited access to standard treatment modalities might lead to increased tumor progression and poor overall survival. Another layer of complexity is that AA women with breast cancer generally have lower participation in clinical trials investigating novel drug combinations than their EA counterparts [40], which might result in lack of race-specific data for evaluating the efficacy of new drugs and unavailability of new treatment regimens. Owens et al., conducted an interesting study to assess the “awareness” and “confidence in clinical studies” among African-American people and evaluated their impact on overall participation in clinical trials pertaining to cancer research.
They found that AA men and women not only had insufficient knowledge regarding clinical trials and informed consent process, they also lack confidence and trust in cancer research [41]. The findings of this study also state that AA men correlate clinical trials to the term “guinea pigs” and recognized clinical trials as experiments. Two factors—fear and mistrust, appeared as the most important obstacles for AA people to participate in clinical trials. Fear was usually associated with the harms caused during the clinical trial procedure and mistrust arose due to multiple historic unethical research studies for example, Tuskegee Syphilis Study conducted on AA people. Together, fear and mistrust regarding scientific community leads to non-participation of AA people in clinical trials resulting in lack of sufficient race-specific data [41]. A similar study was conducted by Haynes-Maslow et al. for the better understanding of the barriers responsible for low enrollment of African-American women in clinical trials. This study quotes an African-American woman stating, “It is important because we as a race are automatically standoffish and so afraid from past things. We all know about the Tuskegee and we just don’t feel comfortable participating in things, and it’s for lack of knowledge” [42].

Some other major contributors to treatment-related disparities include higher probability that AA breast cancer patients access under-resourced hospitals and have imperfect communication with health care providers as well as biased practices in the health care system. Meta-analysis of socioeconomic status adjusted breast cancer survival in >14,000 AA patients compared to >76,000 EA patients demonstrated a ~30% higher mortality hazard among AA patients [43]. Comorbidities such as diabetes and hypertension are also prominent factors responsible for survival differences among AA and EA breast cancer patients [44]. According to Hershman et al., insufficient delivery of adjuvant breast cancer chemotherapy leads to neutropenia in AA patients [45]. Interestingly, the Southwest Oncology group adjuvant therapy trial’s pooled analyses revealed persistent survival disadvantage for AA patients having breast and prostate cancer (hormonally driven cancers), otherwise equal treatment leads to equal result [46]. Contrasting with the above-mentioned socioeconomic drivers of TNBC disparity among AA and EA women, the 2015 population based study from the SEER program revealed that the incidence and progression of hormone negative or triple negative breast cancer (TNBC) are independent of socioeconomic status [47]. A major caveat associated with population wide studies investigating racial disparity in AA and EA women is smaller sample sizes owing to lower participation rates and the fact that AA community is a minority (~12% of US population).

5. Molecular Pathways as Therapeutic Targets in Triple Negative Breast Cancer

Vascular endothelial growth factor (VEGF), androgen receptor (AR), mammalian target of rapamycin (mTOR), poly (ADP-ribose) polymerase (PARP), epidermal growth factor receptor (EGFR), histone deacetylase (HDAC), and Src oncogenic pathway are some of the major molecular pathways that are currently being targeted in TNBCs. The notion that VEGF inhibitors would prove to be effective against TNBC is based on the fact that TNBCs may require enhanced neoangiogenesis owing to their highly proliferative nature but no studies so far have found any TNBC specific effect of antiangiogenic agents [48]. Anti-VEGF monoclonal antibody, Bevacizumab’s clinical efficacy is currently being evaluated for metastatic TNBC. PARP inhibitors are under development as therapeutic agents for cancers with DNA repair defects like BRCA1/2 mutant TNBCs [49]. US Food and Drug Administration approved Olaparib, a PARP inhibitor, as a solitary-agent in December 2014 for advanced ovarian cancer patients with deleterious or suspected deleterious germ-line BRCA mutation who have had three earlier lines of chemotherapy. Many phase I and II trials have demonstrated antitumor activity of Olaparib in BRCA-mutated breast cancer patients [50–53]. To evaluate the efficacy and safety of Olaparib at two doses (one as maximum tolerated dose while the other as a lower pharmacodynamically active dose), a multi-center proof-of-concept phase II study was designed for BRCA1 and BRCA2 mutant advanced breast cancer [54]. Interestingly, 41% overall response rate (ORR) was noted in patients who were given 400 mg of Olaparib twice daily and 22% ORR was noted in patients who were administered with 100 mg of Olaparib twice daily. However, ORR was 54% and 25%, respectively, in triple negative breast cancer patients who were administered higher and lower doses of Olaparib, respectively.
The OlympiAD trial had approximately 49% TNBC patients and the results demonstrated a significantly longer progression-free-survival (PFS) in the Olaparib group compared to standard therapy [55]. The safety, tolerability, and efficacy of Olaparib were evaluated in combination with paclitaxel in metastatic TNBC patients with ≤1 prior cytotoxic regimen and 37% of patients demonstrated partial response [56]. The combinational effects of veliparib and carboplatin in the neoadjuvant settings was investigated by Rugo et al. in two arms (paclitaxel monotherapy or paclitaxel-veliparib-carboplatin combinational therapy) of breast cancer patients [57]. The calculated PCR was observed to be 51% in paclitaxel-veliparib-carboplatin versus 26% in the control group [57]. The results from a phase II study of metastatic TNBC patients, O'Shaughnessy et al. showed that the inclusion of iniparib to gemcitabine and carboplatin enhanced the clinical benefit rate to 56% from 34% (p = 0.01) as well as the overall response rate to 52% from 32% (p = 0.02). Apart from this, iniparib inclusion also prolonged the median PFS from 3.6 months to 5.9 months with a median overall survival from 7.7 months to 12.3 months [58]. PARP inhibition seems to be a promising approach against TNBC (Table 1) but none of these trials focus on racial disparity. No race-specific information is available about the participants of these trials. The efficacy of these agents needs to be explored in multicenter clinical trials including AA as well as EA breast cancer patients [57].

Table 1. Ongoing trials investigating poly (ADP-ribose) polymerase (PARP) inhibitors in TNBC.

| Phase | Clinical Trial | Treatment | ClinicalTrials.gov Identifier |
|-------|----------------|-----------|------------------------------|
| Phase 1 | A pilot study of Olaparib and Durvalumab in patients with metastatic triple negative breast cancer (TNBC) | Olaparib Durvalumab | NCT03544125 |
| Phase 1 | A phase I of Olaparib with Radiation Therapy in patients with inflammatory, loco-regional advanced or metastatic TNBC | Olaparib Radiation Therapy | NCT03109080 |
| Phase 1 | An open, non-randomized, multi-center Phase I study to access the safety and efficacy of Fluzoparib given in combination with Apatinib | Fluzoparib Apatinib | NCT03075462 |
| Phase 1 | A phase I study of PARP inhibitor Olaparib and HSP90 inhibitor AT13387 | Olaparib Onalespib | NCT02898207 |
| Phase 2 | A phase II open-label, randomized study of PARP inhibition either alone or in combination with anti-PD-L1 Therapy | Atezolizumab Olaparib | NCT02849496 |
| Phase 1 | Phase 1/2 clinical study of Niraparib in combination with Pembrolizumab (MK-3475) | Niraparib Pembrolizumab | NCT02657889 |
| Phase 2 | A phase II clinical trial of the PARP inhibitor Talazoparib | Talazoparib Tosylate | NCT02401347 |

Though the androgen receptor (AR) is present in normal as well as malignant breast tissue, its expression level varies according to the breast cancer subtype. AR is expressed in 10–15% of TNBCs [59,60]. Similarities exist between LAR and apocrine subtype and reports show that LAR subtype comprises breast cancer with apocrine histology [61,62]. Doane et al. identified a cell line exhibiting the molecular profile of LAR subtype [63], used it in preclinical models, validated its androgen reliant growth in estrogen free manner and successful inhibition using flutamide (AR antagonist). This study served as the first proof-of-principle study supporting androgen deprivation as a targeted therapy for LAR-TNBC [61,63]. Gucalp et al. conducted a multicenter Phase II study of bicalutamide at a dose of 150 mg per day in AR positive (12% of patients), and ER and PR negative metastatic breast cancer involving 26 patients (many of them were HER2 negative). A clinical benefit rate (CBR) of 19% for bicalutamide was revealed by this study with a median progression free survival (PFS) of 12 weeks [64]. Minor side effects included fatigue, hot flashes, limb edema, and transaminase elevation were observed [64]. Another multicenter phase II trial assessed the activity of next-generation anti-androgen enzalutamide in advanced AR positive TNBCs in two stages. In the first stage, 26 patients were given an oral dose of 160 mg per day of enzalutamide; assessed for the primary end point of the CBR at 16 weeks. The result demonstrated 42% CBR (95% confidence interval 24–62%) with one...
In the second stage, 165 patients were screened (75 patients had AR IHC ≤ 10% with more than one post baseline evaluation). Data revealed a CBR of 35% with a median progression free survival (PFS) of 14.7 weeks [66]. It would be worthwhile to mention an isolated clinical case of a heavily pretreated woman with TNBC and AR positivity who achieved a complete clinical response after 4 months of bicalutamide treatment [67]. An overview of main ongoing trials investigating AR targeting drugs is provided (Table 2) and it is interesting to note that none of these trials considered race-specific issues. With promising results, these new targeted therapies may also prove to be beneficial for AA TNBC but certainly requires careful assessment. Moving forward clinical studies focusing on the racial disparity in treatment response need to be conducted.

Table 2. Studies investigating androgen receptor (AR) inhibitors in TNBC.

| Phase  | Clinical Trial                                                                 | Treatment             | ClinicalTrials.gov Identifier |
|--------|-------------------------------------------------------------------------------|-----------------------|-------------------------------|
| Phase 1 | A phase I/II, single arm, non-randomized study of Ribociclib (LEE011), a CDK 4/6 inhibitor, in combination with Bicalutamide, an androgen receptor (AR) inhibitor | Ribociclib            | NCT03090165                  |
| Phase 2 | A phase Ib/II trial of Taselisib (GDC-0032), a PI3K inhibitor, in combination with Enzalutamide in patient with AR+ve TNBC | Enzalutamide Taselisib | NCT02457910                  |
|        | A phase 2 open-label study to evaluate the efficacy and safety of VT-464, previous treatment with Enzalutamide | VT-464                | NCT02130700                  |

The fact that a large fraction of TNBC tumors overexpress EGFR puts forth EGFR as an attractive therapeutic target in TNBC. The combination of Cetuximab (monoclonal antibody) with Carboplatin revealed impressive effects on TNBC patients with a response rate of 17% [68]. In a randomized phase II trial, 173 metastatic TNBC patients pre-treated with only one previous line of chemotherapy for metastatic disease were given cisplatin either alone or in combination with cetuximab. Improvement in activity was noted in the combinational group with overall response rate (ORR) of 20% versus 10% with a progression free survival (PFS) of 3.7 versus 1.5 months [69]. Overexpression of Src tyrosine kinase is commonly observed in TNBC and has been associated with metastatic disease progression [70]. Preclinical evidence showed that dasatinib, an oral inhibitor of Src, c-kit and platelet derived growth factor receptor-β inhibits growth of TNBC cells. Moreover, the combination of dasatinib and cisplatin imparts synergistic effects in dasatinib-sensitive cells [70,71]. In a single arm phase I trial, dasatinib (70 mg twice daily) was given to metastatic TNBC patients pre-treated with anthracycline and a taxane showed a disease control rate of 9.3% with a 4.3% confirmed partial response rate along with a PFS of 8.3 weeks [72]. AKT and phosphatase and tensin homolog (PTEN) regulate PI3K signaling and mTOR is an effector node of PI3K cascade. PTEN loss is commonly observed in TNBC which leads to mTOR activation [73]. Presently, mTOR inhibitors are being assessed in TNBC or HER2 negative breast cancer patients [74]. The oral dose of 10 mg/day everolimus showed an overall response rate (ORR) of 12% in a phase II trial of first- or second-line treatment of metastatic breast cancer patients [74]. Aberrant Rb pathway is a significant feature of TNBC [75] and many druggable targets are present in this setting like Aurora kinase, polo-like kinase and Hsp90. In the TCGA data set, MYC is amplified in approximately 30% of basal-like breast cancers [75] which suggest CDK inhibition as a plausible targeting strategy in MYC amplified basal-like breast cancer [76]. Similarly, basal-like breast cancers are also driven by FOXM1 which also indicates that growth inducing cascades can be targeted for basal-like breast cancer [75]. TNBC exhibit resistance to taxanes and elevated MAPK/ERK pathway has been attributed to taxane resistance [77]. Hence, efficacy of MEK (a component of the MAPK/ERK pathway)
inhibitor, cobimetinib, was tested in a randomized, phase II, double-blind, multicenter clinical trial in combination with paclitaxel in advanced TNBC patients [78]. Combination of cobimetinib and paclitaxel showed increased progression free survival. Several MEK inhibitors are being tested in clinical trials in combination with other targeted and chemotherapies (Table 3).

Table 3. Studies investigating mitogen-activated protein kinase kinase (MEK) inhibitors in TNBC.

| Phase 1 | Clinical Trial | Treatment | ClinicalTrials.gov Identifier |
|---------|----------------|-----------|--------------------------------|
| Phase 2 | Neoadjuvant chemotherapy Docetaxel with or without Selumetinib in patients with TNBC | Selumetinib, Doxorubicin, Cyclophosphamide, Docetaxel | NCT02685657 |
| Early phase 1 | Defining the TNBC kinome response to GSK1120212, MEK inhibitor | GSK1120212 | NCT01467310 |
| Phase 2 | A single arm, phase II study of single agent Trametinib followed by Trametinib in combination with GSK21411795 | Trametinib, GSK21411795 | NCT01964924 |
| Phase 1 | Safety, pharmacokinetics (PK) of AKT and MEK combination | GSK1120212, GSK21411795 | NCT0138085 |
| Phase 1 | A study to investigate safety, pharmacokinetics and pharmacodynamics of BKM120 plus GSK1120212 | BKM120, GSK1121212 | NCT01155453 |
| Phase 1 | Safety, pharmacokinetics and pharmacodynamics of BKM120 plus MEK162 | BEZ235, MEK162 | NCT01337765 |
| Phase 1 | A phase Ib, Open-label, Multi-center, Dose-escalation, and Expansion Study of an Orally Administered Combination of BKM120 Plus MEK162 | BKM120, MEK162 | NCT01363232 |

Platinum agents such as carboplatin, oxaliplatin and cisplatin function as DNA damaging compounds that cause DNA strand breaks resulting in apoptotic cell death hence they can be particularly effective in BRCA1/2 mutant TNBCs. Many studies have been investigating the effectiveness of platinum-based neoadjuvant chemotherapy in TNBC patients [79]. Meta-analysis of 2109 TNBC patients receiving either platinum-based (n = 1046) or platinum-free chemotherapy (n = 1063) observed a significant increase in pCR rate (15.1%) with platinum-based chemotherapy in the neoadjuvant setting [80]. Various immunotherapy strategies are being examined in TNBC including immune checkpoint blockade (Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibition, programmed death ligand-1/programmed cell death-1 PD-L1/PD-1 inhibition, CD47 checkpoint blockade), vaccines (DR5 DNA vaccination, dendritic cells (DC)-based vaccines etc.) and others with variable efficacy [81]. Combination therapy approaches encompassing standard therapy with immunotherapy are showing promise against TNBC. Evaluating a combination approach with Atezolizumab (targeting PD-L1) and Nanoparticle albumin-bound (nab)-paclitaxel, Schmid et al. observed prolonged progression-free survival [82]. Though it is still early to draw conclusive inferences with regard to immunotherapy in TNBC, completion of multiple ongoing clinical trials will provide evidence supporting the efficacy of combination regimens involving immunotherapy and standard chemotherapy.

Multiple new combinational or sequential therapies are currently under investigation in well-designed prospective clinical trials to counter TNBC based on their unique biology in this era of precision medicine. Even with considerable advancement in understanding the unique biology of TNBC in AA women owing to epidemiological, clinical and preclinical studies, very few clinical trials have undertaken the task to directly compare the efficacy of therapeutic agents in AA vs. EA TNBC patients; only one such trial is currently active (Table 4).
6. Cancer Stem Cells, Triple Negative Breast Cancer, and African-American Ancestry

Cancer stem cells (CSC), a rare population of cancer cells harboring the potential for self-renewal and differentiation, have been shown to exist in breast cancer. Some major characteristics of cancer stem cells are heterogeneity, asymmetric cell division, quiescence, and drug resistance enabling them to lead to cancer progression and relapse [83]. CSCs in breast cancer are generally characterized with a \(CD44^+ / CD24^-\) and/or \(ALDH1^+\) (ALDH1A1+) population [84]. Nalwoga et al., observed that 48% breast cancer with African origin overexpressed \(ALDH1^+\) population [85] while only 19% and 30% breast tumors from non-African women in Michigan and France overexpressed \(ALDH1^+\) population [86]. Wnt signaling leads to progenitor cell renewal and is involved in embryologic development. A number of studies suggest the activation of Wnt signaling pathway in TNBC [87,88]. Microarray analysis demonstrated that \(FZD7\) (a major component of the Wnt signaling pathway) is upregulated in TNBC cell lines and tumor samples [89]. Increased LDL receptor related protein 6 (LRP6) upregulates Wnt signaling and leads to increased stemness in TNBC cells [90]. A study conducted by Getz et al., revealed that Wnt signaling pathway represents a major functional pathway in AA TNBC cohort [91] and genes associated with Wnt signaling like \(TNC, Car1, FOXO3A\) and \(TCF4\) are significantly induced in AA TNBC [91]. Examination of \(WNT10B\) and its target gene, \(HMGA2\), in TNBC cohorts showed that both \(WNT10B\) and \(HMGA2\) were upregulated in TNBCs-\(WNT10B\) (88% in AA and 73% in EA) and \(HMGA2\) (88% in AA and 80% in EA) [92]. Co-activation of Wnt and Hedgehog signaling in TNBC samples correlated with shorter recurrence and poor survival [93]. SMO, a major node of Hedgehog pathway directly activates \(MYCN\) which induces the expression of Cyclin-D1 and \(FOXM1\) and \(FOXM1\) is a transcription factor related to growth and progression of TNBC [94]. Nakshatri et al., studied the distribution of mammary stem cell phenotype in the healthy breast tissue samples from AA and EA women from the Susan G Komen Tissue Bank (Indianapolis, IN) and found that \(CD44^+ / CD24^-\) and endothelial protein C-receptor (EPCR or APC receptor) +/epithelial cell adhesion molecule (EpCAM) − multipotent stem cells were significantly overexpressed in AA in comparison to EA [95]. Although the notion that an abundance of CSCs can potentially explain the inherently aggressive biology of TNBCs in AA women is gaining traction and is supported by multiple studies, additional population based studies are required to prove this concept.

7. Obesity, a Coconspirator in TNBC Disparity

According to the Center for Disease Control and Prevention (CDC), obesity is defined as a body mass index (BMI) \(\geq 30\) kg/m\(^2\) and these individuals are considered as metabolically unhealthy [96]. Waist/hip ratio (WHR) is also used to measure the abdominal obesity. According to the World Health Organization, a WHR of \(\geq 0.85\) is considered to be an increased risk for metabolic disorders [97]. A significant increase in prevalence of obesity (35.3% to 40.4%) was noted in United States between 2005 to 2014 and the incidence of severe obesity also increased from 7.4% to 9.9% [98,99]. The Carolina Breast Cancer Study advocates that high body mass index and high waist/hip ratio enhances the probability of basal-like TNBC in premenopausal AA women [17]. A retrospective study of 620 white patients with invasive breast cancer in West Virginia (one of the states where obesity rates are higher in the United States) showed higher occurrence of TNBC in younger patients (45%) compared to other breast cancer subtypes (27%) [100]. More women with TNBC were obese (50%) in comparison to women harboring...
other subtypes of breast cancer (36%) [100]. Stage 3 of the Carolina Breast Cancer Study included women from 44 North Carolina counties from 2008 to 2014. Here, the WHR was estimated across the highest and lowest groups ($\geq 0.84$ to $<0.77$) relative to TNBC basal-type subset. Among all, women with higher WHR had increased risk for developing basal-type subset of TNBC [101]. Both premenopausal and postmenopausal women with increased WHR had higher probability of developing basal-like TNBC subset in comparison to the women with lower WHR [101]. Importantly, premenopausal AA women revealed maximum prevalence of basal-like TNBC as well as the basal-like TNBC risk factors [101]. A case-control study examining the link between BMI and risk of breast cancer in AA and non-Hispanic EA, The Women’s Contraceptive and Reproductive Experiences (CARE), reported that premenopausal ER−/PR− breast cancer is inversely associated with the BMI of a woman at 18 years of age while the current BMI exhibits positive association with postmenopausal ER+/PR+ breast cancer [102]. To decipher the potential risk factors for early aggressive breast cancer among AA and non-Hispanic EA women, The Women’s Circle of Health Study was constituted as a multisite case-control study in New Jersey and New York. This study observed a significant reverse relation of high BMI with ER−/PR− breast cancer among postmenopausal women and an enhanced risk of premenopausal breast cancer was associated with increased WHR [103,104]. A collaboration of the four studies: the Carolina Breast Cancer Study [101], the Women’s Circle of Health Study [102], the Black Women’s Health Study [105], and the Multiethnic Cohort Study [106] constitute the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium [107]. Overall goal of the AMBER Consortium was to examine the discrepancies among results observed within the individual studies regarding obesity (measured either by BMI and/or WHR) and TNBC connection. Focusing on both premenopausal and postmenopausal AA women, AMBER Consortium examined how obesity (both general and central obesity) might associate with breast cancer subtypes [107,108]. According to the AMBER Consortium, AA women are impacted by general and central obesity depending on their menopausal status and hormone receptor subtype [107]. Different studies showed varied trends associating obesity and breast cancer in AA women depending on the use of BMI or WHR. Higher recent BMI correlated with increased risk for ER+ breast cancer and decreased risk for TNBC in postmenopausal women. However, elevated BMI was linked to lower frequency of premenopausal ER+ cancer as well as all subtypes of postmenopausal cancer [107] in premenopausal women. Interestingly, studies using WHR as a measure of obesity showed that high WHR in postmenopausal women associated with all breast cancer subtypes whereas in premenopausal women high WHR was associated with an increased probability of premenopausal ER+ tumors but not others [107]. AMBER concludes that there may be multiple mechanisms associating obesity with TNBC and other subtypes of breast cancer in AA women [107].

While most studies examining connection between obesity and disease prevalence use BMI, WHR or waist circumference, Capers et al., explored the importance of body shape in EA and AA women to predict disease associations [109]. In this study, 552 AA and EA women were recruited and body shapes, body fat distribution and body composition were recorded using digital photography, android-gynoid ratio (AGR) and dual-energy X-ray absorptiometry respectively. Interestingly, this study noted striking differences based on the race/ethnicity with AA women having higher mean BMI, mean AGR, mean total body fat, mean trunk fat, and mean leg fat in comparison to EA women. Also, apple body shape was more prevalent among AA women compared to EA women [109]. Obese AA and EA women also exhibit differences in distribution of adipose tissue, insulin resistance, and lipoprotein subclasses in intervention studies and interestingly only EA women showed decreased fasting insulin levels [110]. These clinical studies indicate that obesity in AA women might be different from obesity in EA women and may influence disease progression in a differential manner. Multiple studies have shown the negative impact of obesity on breast cancer progression including TNBC progression however no clinical trial has directly evaluated TNBC progression in obese AA and EA women. Obese people have increased circulating levels of insulin and inflammatory cytokines (IL-6, IL-8, TNF, and leptin) which can potentially induce STAT3, NFKB and EZH2 signaling [111] and may contribute to poor prognosis
of AA TNBC (Figure 4). As obesity is common among AA women, obese state has been proposed as a major driver of aggressive TNBC biology in AA women.

Figure 4. Adipocytes in obese state secrete proinflammatory cytokines in the tumor microenvironment and induce the major hallmarks of cancer development (proliferation, survival, migration, invasion, and angiogenesis).

8. Conclusions

Despite significant improvements in breast cancer diagnosis and therapeutics, TNBC remains a challenge owing to aggressive progression and lack of targeted therapies. In recent years, it has become evident that younger AA women are disproportionately affected by TNBC. Although many epidemiological and clinical studies have shown a higher prevalence of TNBC in women of African descent and put forth various genetic and environmental factors that may influence aggressive progression of TNBC in AA women, we still lack bigger studies focusing entirely on racial disparity in TNBC with emphasis on underprivileged AA women. Owing to the robust molecular classification, we now appreciate that TNBC subtype of breast cancer is heterogeneous in nature comprising of multiple sub-subtypes. In this era of personalized medicine, much effort has been dedicated to developing personalized therapeutic regimens based on molecular profile of breast cancer. To provide benefits of all the advancement in “personalized medicine” to AA TNBC patients in future, we need better understanding of the TNBC tumors arising in AA women. There are many unanswered queries such as deciphering the impact of genes vs. means in AA TNBC development; the molecular classification of AA TNBC tumors; understanding the prevalence of various TNBC subtypes in AA women, and elucidating the key molecular signaling pathway (Figure 5). It will be important to study various cancer stem cell signaling pathways (Wnt, Hedgehog and Notch) in AA TNBC as aberrant activation of cancer stem cells pathways may be the key node underlying the aggressive phenotype of AA TNBC and may explain disparities in AA TNBC progression. Obesity is known to disproportionately affect AA women and obese state has been associated with increased breast cancer incidence and progression hence a vital need exists to examine the role of obesity in driving TNBC in AA women. Higher TNBC incidence and an aggressive biology compounded with poor income, lower education, poor access to screening and standard treatment results in poor overall survival outcomes of TNBC in AA women. TNBC disparity in AA and EA women stems from a complex interaction of socioeconomic factors and biology. In conclusion, improving survival in AA TNBC cohort would require a transdisciplinary approach involving a cohesive interplay encompassing biology, genetics, socioeconomic factors, culture, and environment.
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References

1. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer Statistics, 2017. *CA Cancer J. Clin.* 2017, 67, 7–30. [CrossRef] [PubMed]
2. DeSantis, C.E.; Lin, C.C.; Mariotto, A.B.; Siegel, R.L.; Kramer, J.L.; Altekruse, S.F.; Ward, E.M.; Jemal, A. Cancer treatment and survivorship statistics, 2014. *CA Cancer J. Clin.* 2014, 64, 252–271. [CrossRef] [PubMed]
3. Engebraaten, O.; Vollan, H.K.M.; Borresen-Dale, A.L. Triple-negative breast cancer and the need for new therapeutic targets. *Am. J. Pathol.* 2013, 183, 1064–1074. [CrossRef] [PubMed]
4. Nielsen, T.O.; Hsu, F.D.; Jensen, K.; Cheang, M.; Karaca, G.; Hu, Z.; Hernandez-Boussard, T.; Livasy, C.; Cowan, D.; Dressler, L.; et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin. Cancer Res.* 2004, 10, 5367–5374. [CrossRef] [PubMed]
5. Perou, C.M.; Sorlie, T.; Eisen, M.B.; van de Rijn, M.; Jeffrey, S.S.; Rees, C.A.; Pollack, J.R.; Ross, D.T.; Johnsen, H.; Akslen, L.A.; et al. Molecular portraits of human breast tumours. *Nature* 2000, 406, 747–752. [CrossRef] [PubMed]
6. Sorlie, T.; Perou, C.M.; Tibshirani, R.; Aas, T.; Geisler, S.; Johnsen, H.; Hastie, T.; Eisen, M.B.; van de Rijn, M.; Jeffrey, S.S.; et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc. Natl. Acad. Sci. USA* 2001, 98, 10869–10874. [CrossRef] [PubMed]
7. Van de Rijn, M.; Perou, C.M.; Tibshirani, R.; Haas, P.; Kallioniemi, O.; Kononen, J.; Torhorst, J.; Sauter, G.; Zuber, M.; Kochli, O.R.; et al. Expression of cytokeratins 17 and 5 identifies a group of breast carcinomas with poor clinical outcome. *Am. J. Pathol.* 2002, 161, 1991–1996. [CrossRef]
8. Rakha, E.A.; Putti, T.C.; Abd El-Rehim, D.M.; Paish, C.; Green, A.R.; Powe, D.G.; Lee, A.H.; Robertson, J.F.; Ellis, I.O. Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation. *J. Pathol.* 2006, 208, 495–506. [CrossRef] [PubMed]
9. Rakha, E.A.; El-Sayed, M.E.; Green, A.R.; Lee, A.H.; Robertson, J.F.; Ellis, I.O. Prognostic markers in triple-negative breast cancer. *Cancer* 2007, 109, 25–32. [CrossRef] [PubMed]
10. Dietze, E.C.; Sistrunk, C.; Miranda-Carboni, G.; O’Regan, R.; Seewaldt, V.L. Triple-negative breast cancer in African-American women: Disparities versus biology. Nat. Rev. Cancer 2015, 15, 248–254. [CrossRef] [PubMed]

11. Bonotto, M.; Gerratana, L.; Poletto, E.; Driol, P.; Giangreco, M.; Russo, S.; Minisini, A.M.; Andreetta, C.; Mansutti, M.; Pisa, F.E.; et al. Measures of outcome in metastatic breast cancer: Insights from a real-world scenario. Oncologist 2014, 19, 608–615. [CrossRef] [PubMed]

12. Lehmann, B.D.; Bauer, J.A.; Chen, X.; Sanders, M.E.; Chakravarthy, A.B.; Shyr, Y.; Pietenpol, J.A. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J. Clin. Investig. 2011, 121, 2750–2767. [CrossRef] [PubMed]

13. Rakha, E.A.; Reis-Filho, J.S.; Ellis, I.O. Basal-like breast cancer: A critical review. J. Clin. Oncol. 2008, 26, 2568–2581. [CrossRef] [PubMed]

14. Weigelt, B.; Baehner, F.L.; Reis-Filho, J.S. The contribution of gene expression profiling to breast cancer classification, prognostication and prediction: A retrospective of the last decade. J. Pathol. 2010, 220, 263–280. [CrossRef] [PubMed]

15. Sotiriou, C.; Pusztai, L. Gene-expression signatures in breast cancer. N. Engl. J. Med. 2009, 360, 790–800. [CrossRef] [PubMed]

16. Bauer, K.R.; Brown, M.; Cress, R.D.; Parise, C.A.; Caggiano, V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California cancer Registry. Cancer 2007, 109, 1721–1728. [CrossRef] [PubMed]

17. Carey, L.A.; Perou, C.M.; Livasy, C.A.; Dressler, L.G.; Cowan, D.; Conway, K.; Karaca, G.; Troester, M.A.; Tse, C.K.; Edmiston, S.; et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006, 295, 2492–2502. [CrossRef] [PubMed]

18. DeSantis, C.; Siegel, R.; Jemal, A. Breast Cancer Facts & Figures 2015–2016. Available online: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2015-2016.pdf (accessed on 13 December 2018).

19. Danforth, D.N., Jr. Disparities in breast cancer outcomes between Caucasian and African American women: A model for describing the relationship of biological and nonbiological factors. Breast Cancer Res. 2013, 15, e208. [CrossRef] [PubMed]

20. Clarke, C.A.; Keegan, T.H.; Yang, J.; Press, D.J.; Kurian, A.W.; Patel, A.H.; Lacey, J.V., Jr. Age-specific incidence of breast cancer subtypes: Understanding the black-white crossover. J. Natl. Cancer Inst. 2012, 104, 1094–1101. [CrossRef] [PubMed]

21. Brewster, A.M.; Chavez-MacGregor, M.; Brown, P. Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. Lancet. Oncol. 2014, 15, 625–634. [CrossRef]

22. Kohler, B.A.; Sherman, R.L.; Howlader, N.; Jemal, A.; Ryerson, A.B.; Henry, K.A.; Boscoe, F.P.; Cronin, K.A.; Lake, A.; Noon, A.M.; et al. Annual Report to the Nation on the Status of Cancer, 1975–2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. J. Natl. Cancer Inst. 2015, 107, e048. [CrossRef] [PubMed]

23. Jiagge, E.; Jibril, A.S.; Chitale, D.; Bensenhaver, J.M.; Awuah, B.; Hoenerhoff, M.; Adjai, E.; Bekele, M.; Abebe, E.; Nathanson, S.D.; et al. Comparative Analysis of Breast Cancer Phenotypes in African American, White American, and West Versus East African patients: Correlation Between African Ancestry and Triple-Negative Breast Cancer. Ann. Surg. Oncol. 2016, 23, 3843–3849. [CrossRef] [PubMed]

24. Huo, D.; Ikpat, F.; Khramtsov, A.; Dangou, J.M.; Nanda, R.; Dignam, J.; Zhang, B.; Grushko, T.; Zhang, C.; Oluwasola, O.; et al. Population differences in breast cancer: Survey in indigenous African women reveals over-representation of triple-negative breast cancer. J. Clin. Oncol. 2009, 27, 4515–4521. [CrossRef] [PubMed]

25. Ly, M.; Antoine, M.; Dembele, A.K.; Levy, P.; Rodenas, A.; Toure, B.A.; Badiaga, Y.; Dembele, B.K.; Bagayogo, D.C.; Diallo, Y.L.; et al. High incidence of triple-negative tumors in sub-saharan Africa: A prospective study of breast cancer characteristics and risk factors in Malian women seen in a Bamako university hospital. Oncology 2012, 83, 257–263. [CrossRef] [PubMed]

26. McCormack, V.A.; Joffe, M.; van den Berg, E.; Broeze, N.; Silva Idos, S.; Romieu, I.; Jacobson, J.S.; Neugut, A.I.; Schuz, J.; Cubasch, H. Breast cancer receptor status and stage at diagnosis in over 1200 consecutive public hospital patients in Soweto, South Africa: A case series. Breast Cancer Res. 2013, 15, e84. [CrossRef] [PubMed]
27. Bowen, R.L.; Duffy, S.W.; Ryan, D.A.; Hart, I.R.; Jones, J.L. Early onset of breast cancer in a group of British black women. *Br. J. Cancer* 2008, 98, 277–281. [CrossRef] [PubMed]

28. Stead, L.A.; Lash, T.L.; Sobieraj, J.E.; Chi, D.D.; Westrup, J.L.; Charlot, M.; Blanchard, R.A.; Lee, J.C.; King, T.C.; Rosenberg, C.L. Triple-negative breast cancers are increased in black women regardless of age or body mass index. *Breast Cancer Res. Treat.* 2009, 11, e25. [CrossRef] [PubMed]

29. Amirikia, K.C.; Mills, P.; Bush, J.; Newman, L.A. Higher population-based incidence rates of triple-negative breast cancer among young African-American women: Implications for breast cancer screening recommendations. *Cancer* 2011, 117, 2747–2753. [CrossRef] [PubMed]

30. Lindner, R.; Sullivan, C.; Ofor, O.; Lezon-Geyda, K.; Halligan, K.; Fischbach, N.; Shah, M.; Bossuyt, V.; Schulz, V.; Tuck, D.P.; et al. Molecular phenotypes in triple negative breast cancer from African American patients suggest targets for therapy. *PLoS ONE* 2013, 8, e71915. [CrossRef] [PubMed]

31. Keenan, T.; Moy, B.; Mroz, E.A.; Ross, K.; Niemierko, A.; Rocco, J.W.; Isakoff, S.; Ellisen, L.W.; Bardia, A. Comparison of the Genomic Landscape Between Primary Breast Cancer in African American Versus White Women and the Association of Racial Differences with Tumor Recurrence. *J. Clin. Oncol.* 2015, 33, 3621–3627. [CrossRef] [PubMed]

32. Ademuyiwa, F.O.; Tao, Y.; Luo, J.; Weilbaecher, K.; Ma, C.X. Differences in the mutational landscape of triple-negative breast cancer in African Americans and Caucasians. *Breast Cancer Res. Treat.* 2017, 161, 491–499. [CrossRef] [PubMed]

33. Stewart, P.A.; Luks, J.; Roycik, M.D.; Sang, Q.X.; Zhang, J. Differentially expressed transcripts and dysregulated signaling pathways and networks in African American breast cancer. *PLoS ONE* 2013, 8, e82460. [CrossRef] [PubMed]

34. Mavaddat, N.; Barrowdale, D.; Andruulis, I.L.; Domchek, S.M.; Eccles, D.; Nevanlinna, H.; Ramus, S.J.; Spurdle, A.; Robson, M.; Sherman, M.; et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: Results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol. Biomark. Prev.* 2012, 21, 134–147. [CrossRef] [PubMed]

35. Nanda, R.; Schummm, L.P.; Cummings, S.; Fackenthal, J.D.; Sveen, L.; Ademuyiwa, F.; Cobleigh, M.; Esserman, L.; Lindor, N.M.; Neuhausen, S.L.; et al. Genetic testing in an ethnically diverse cohort of high-risk women: A comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *JAMA* 2005, 294, 1925–1933. [CrossRef] [PubMed]

36. Szabo, C.I.; King, M.C. Population genetics of BRCA1 and BRCA2. *Am. J. Hum. Genet.* 1997, 60, 1013–1020.

37. Gonzalez, M.E.; DuPrie, M.L.; Krueger, H.; Merajver, S.D.; Ventura, A.C.; Toy, K.A.; Kleer, C.G. Histone methyltransferase EZH2 induces Akt-dependent genomic instability and BRCA1 inhibition in breast cancer. *Cancer Res.* 2008, 11, 2360–2370. [CrossRef] [PubMed]

38. Pang, J.; Toy, K.A.; Griffith, K.A.; Awuah, B.; Quayson, S.; Newman, L.A.; Kleer, C.G. Invasive breast carcinomas in Ghana: High frequency of high grade, basal-like histology and high EZH2 expression. *Breast Cancer Res. Treat.* 2012, 135, 59–66. [CrossRef] [PubMed]

39. Pietersen, A.M.; Horlings, H.M.; Hauptmann, M.; Langerod, A.; Ajouaou, A.; Cornelissen-Steiijger, P.; Wessels, L.F.; Jonkers, J.; van de Vijver, M.J.; van Lohuizen, M. EZH2 and BMI1 inversely correlate with prognosis and TP53 mutation in breast cancer. *Breast Cancer Res. Treat.* 2008, 10, e19. [CrossRef] [PubMed]

40. Shavers, V.L.; Brown, M.L. Racial and ethnic disparities in the receipt of cancer treatment. *J. Natl. Cancer Inst.* 2002, 94, 334–357. [CrossRef]

41. Owens, O.L.; Jackson, D.D.; Thomas, T.L.; Friedman, D.B.; Hebert, J.R. African American men’s and women’s perceptions of clinical trials research: Focusing on prostate cancer among a high-risk population in the South. *J. Health Care Poor Underserved* 2013, 24, 1784–1800. [CrossRef] [PubMed]

42. Haynes-Maslow, L.; Godley, P.; Dimartino, L.; White, B.; Odom, J.; Richmond, A.; Carpenter, W. African American women’s perceptions of cancer clinical trials. *Cancer Med.* 2014, 3, 1430–1439. [CrossRef] [PubMed]

43. Newman, L.A.; Griffith, K.A.; Jatoi, I.; Simon, M.S.; Crowe, J.P.; Colditz, G.A. Meta-analysis of survival in African American and white American patients with breast cancer: Ethnicity compared with socioeconomic status. *J. Clin. Oncol.* 2006, 24, 1342–1349. [CrossRef] [PubMed]

44. Tammemagi, C.M.; Neren, D.; Neslund-Dudas, C.; Feldkamp, C.; Nathanson, D. Comorbidity and survival disparities among black and white patients with breast cancer. *JAMA* 2005, 294, 1765–1772. [CrossRef] [PubMed]
45. Hershman, D.; Weinberg, M.; Rosner, Z.; Alexis, K.; Tiersten, A.; Grann, V.R.; Troxel, A.; Neugut, A.I. Ethnic neutropenia and treatment delay in African American women undergoing chemotherapy for early-stage breast cancer. *J. Natl. Cancer Inst.* **2003**, *95*, 1545–1548. [CrossRef]

46. Albain, K.S.; Unger, J.M.; Crowley, J.J.; Coltman, C.A., Jr.; Hershman, D.L. Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology Group. *J. Natl. Cancer Inst.* **2009**, *101*, 984–992. [CrossRef] [PubMed]

47. Akinyemiju, T.F.; Pisu, M.; Waterbor, J.W.; Altekruse, S.F. Socioeconomic status and incidence of breast cancer by hormone receptor subtype. *Springerplus* **2015**, *4*, 015–1282. [CrossRef] [PubMed]

48. O'Shaughnessy, J.; Dieras, V.; Glaspy, J.; Brufulsky, A.; Miller, K.; Miles, D.; Koralewski, P.; Phan, S.; Bhattacharya, S. Comparison of Subgroup Analyses of PFS from Three Phase III Studies of Bevacizumab in Combination with Chemotherapy in Patients with HER2-Negative Metastatic Breast Cancer (MBC). *Cancer Res.* **2009**, *69*, 207. [CrossRef]

49. Turner, N.; Tutt, A.; Ashworth, A. Hallmarks of “BRCAness” in sporadic cancers. *Nat. Rev. Cancer.* **2004**, *4*, 814–819. [CrossRef] [PubMed]

50. Fong, P.C.; Boss, D.S.; Yap, T.A.; Tutt, A.; Wu, P.; Mergui-Roelvink, M.; Mortimer, P.; Swaisland, H.; Lau, A.; O’Connor, M.J.; et al. Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N. Engl. J. Med.* **2009**, *361*, 123–134. [CrossRef] [PubMed]

51. Tutt, A.; Robson, M.; Garber, J.E.; Domchek, S.M.; Audeh, M.W.; Weitzel, J.N.; Friedlander, M.; Arun, B.; Loman, N.; Schmutzler, R.K.; et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial. *Lancet* **2010**, *376*, 235–244. [CrossRef] [PubMed]

52. Kaufman, B.; Shapira-Frommer, R.; Schmutzler, R.K.; Audeh, M.W.; Friedlander, M.; Balmana, J.; Mitchell, G.; Fried, G.; Stemmer, S.M.; Hubert, A.; et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J. Clin. Oncol.* **2015**, *33*, 244–250. [CrossRef] [PubMed]

53. Gelmon, K.A.; Tischkowitz, M.; Mackay, H.; Swenerton, K.; Robidoux, A.; Tonkin, K.; Hirte, H.; Huntsman, D.; Clemons, M.; Gilks, B.; et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: A phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol.* **2011**, *12*, 852–861. [CrossRef] [PubMed]

54. Brown, J.S.; O’Carrigan, B.; Jackson, S.P.; Yap, T.A. Targeting DNA Repair in Cancer: Beyond PARP Inhibitors. *Cancer Discov.* **2017**, *7*, 20–37. [CrossRef] [PubMed]

55. Robson, M.; Im, S.A.; Senkus, E.; Xu, B.; Domchek, S.M.; Masuda, N.; Delaloge, S.; Li, W.; Tung, N.; Armstrong, A.; et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N. Engl. J. Med.* **2017**, *377*, 523–533. [CrossRef] [PubMed]

56. Dent, R.A.; Lindeman, G.J.; Clemons, M.; Wildiers, H.; Chan, A.; McCarthy, N.; Singer, C.F.; Lowe, E.S.; Watkins, C.L.; Carmichael, J. Phase I trial of the oral PARP inhibitor olaparib in combination with paclitaxel for first- or second-line treatment of patients with metastatic triple-negative breast cancer. *Breast Cancer Res.* **2013**, *15*, e88. [CrossRef] [PubMed]

57. Rugo, H.S.; Olopade, O.I.; DeMichele, A.; Yau, C.; van’t Veer, L.J.; Buxton, M.B.; Hogarth, M.; Hylton, N.M.; Paoloni, M.; Perlmutter, J.; et al. Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer. *N. Engl. J. Med.* **2016**, *375*, 23–34. [CrossRef] [PubMed]

58. O’Shaughnessy, J.; Osborne, C.; Pippen, J.E.; Yoffe, M.; Patt, D.; Rocha, C.; Koo, I.C.; Sherman, B.M.; Bradley, C. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N. Engl. J. Med.* **2011**, *364*, 205–214. [CrossRef] [PubMed]

59. Niemeier, L.A.; Dabbs, D.J.; Beriwal, S.; Striebel, J.M.; Bhargava, R. Androgen receptor in breast cancer: Expression in estrogen receptor-positive tumors and in estrogen receptor-negative tumors with apocrine differentiation. *Mod. Pathol.* **2010**, *23*, 205–212. [CrossRef] [PubMed]

60. Barton, V.N.; D’Amato, N.C.; Gordon, M.A.; Christenson, J.L.; Elias, A.; Richer, J.K. Androgen Receptor Biology in Triple Negative Breast Cancer: A Case for Classification as AR+ or Quadrapule Negative Disease. *Horm. Cancer* **2015**, *6*, 206–213. [CrossRef] [PubMed]

61. Proverbs-Singh, T.; Feldman, J.L.; Morris, M.J.; Autio, K.A.; Traina, T.A. Targeting the androgen receptor in prostate and breast cancer: Several new agents in development. *Endocr. Relat. Cancer* **2015**, *22*, 87–106. [CrossRef] [PubMed]
Cancers 2018, 10, 514

62. Farmer, P.; Bonnefoi, H.; Becette, V.; Tubiana-Hulin, M.; Fumoleau, P.; Larsimont, D.; Macgrogan, G.; Bergh, J.; Cameron, D.; Goldstein, D.; et al. Identification of molecular apocrine breast tumours by microarray analysis. Oncogene 2005, 24, 4660–4671. [CrossRef] [PubMed]

63. Doane, A.S.; Danso, M.; Lal, P.; Donaton, M.; Zhang, L.; Hudis, C.; Gerald, W.L. An estrogen receptor-negative breast cancer subset characterized by a hormonally regulated transcriptional program and response to androgen. Oncogene 2006, 25, 3994–4008. [CrossRef] [PubMed]

64. Guca, A.; Tolaney, S.; Isakoff, S.J.; Ingle, J.N.; Liu, M.C.; Carey, L.A.; Blackwell, K.; Rugo, H.; Nabell, L.; Forero, A.; et al. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic Breast Cancer. Clin. Cancer Res. 2013, 19, 5505–5512. [CrossRef] [PubMed]

65. A Traina, T.; O’Shaughnessy, J.; Nanda, R.; Schwartzberg, L.; Abramson, V.; Cortes, J.; Peterson, A.; Tudor, I.; Blaney, M.; L. Steinberg, J.; et al. Abstract P5-19-09: Preliminary results from a phase 2 single-arm study of enzalutamide, an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC). Cancer Res. 2015, 75, 5–19. [CrossRef]

66. Traina, T.A.; Miller, K.; Yardley, D.A.; O’Shaughnessy, J.; Cortes, J.; Awada, A.; Kelly, C.M.; Trudeau, M.E.; Schmid, P.; Gianni, L.; et al. Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC). J. Clin. Oncol. 2015, 33, 1003.

67. Arce-Salinas, C.; Riesco-Martinez, M.C.; Hanna, W.; Bedard, P.; Warner, E. Complete Response of Metastatic Androgen Receptor-Positive Breast Cancer to Bicalutamide: Case Report and Review of the Literature. J. Clin. Oncol. 2016, 34, e2. [CrossRef] [PubMed]

68. Carey, L.A.; Rugo, H.S.; Marcom, P.K.; Mayer, E.L.; Esteva, F.J.; Ma, C.X.; Liu, M.C.; Stormiolo, A.M.; Rimawi, M.F.; Forero-Torres, A.; et al. TBCRC 001: Randomized phase II study of the combination of carboplatin in stage IV triple-negative breast cancer. J. Clin. Oncol. 2012, 30, 2615–2623. [CrossRef] [PubMed]

69. Baselga, J.; Gomez, P.; Greil, R.; Braga, S.; Climent, M.A.; Wardley, A.M.; Kaufman, B.; Stemmer, S.M.; Pego, A.; Chan, A.; et al. Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. J. Clin. Oncol. 2013, 31, 2586–2592. [CrossRef] [PubMed]

70. Finn, R.S.; Dering, J.; Ginther, C.; Wilson, C.A.; Glaspy, P.; Tchekmedyian, N.; Slamon, D.J. Dasatinib, an orally active small molecule inhibitor of both the src and abl kinases, selectively inhibits growth of basal-type /"triple-negative" breast cancer cell lines growing in vitro. Breast Cancer Res. Treat. 2007, 105, 319–326. [CrossRef] [PubMed]

71. Tryfonopoulos, D.; Walsh, S.; Collins, D.M.; Flanagan, L.; Quinn, C.; Corkery, B.; McDermott, E.W.; Evoy, D.; Pierce, A.; O’Donovan, N.; et al. Src: A potential target for the treatment of triple-negative breast cancer. Ann. Oncol. 2011, 22, 2234–2240. [CrossRef] [PubMed]

72. Fornier, M.N.; Morris, P.G.; Abbuzzi, A.; D’Andrea, G.; Gilewski, T.; Bromberg, J.; Dang, C.; Dickler, M.; Modi, S.; Seidman, A.D.; et al. A phase I study of dasatinib and weekly paclitaxel for metastatic breast cancer. Ann. Oncol. 2011, 22, 2575–2581. [CrossRef] [PubMed]

73. Saal, L.H.; Holm, K.; Maurer, M.; Memeo, L.; Su, T.; Wang, X.; Yu, J.S.; Mansukhani, M.; Enoksson, J.; et al. PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. Cancer Res. 2005, 65, 2554–2559. [CrossRef] [PubMed]

74. Ellard, S.L.; Clemons, M.; Gelmon, K.A.; Norris, B.; Kennecke, H.; Chia, S.; Pritchard, K.; Eisen, A.; Vandenberg, T.; Taylor, M.; et al. Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163. J. Clin. Oncol. 2009, 27, 4536–4541. [CrossRef] [PubMed]

75. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012, 490, 61–70. [CrossRef] [PubMed]

76. Horiiuchi, D.; Kusdara, L.; Huskey, N.E.; Chandriani, S.; Lenburg, M.E.; Gonzalez-Angulo, A.M.; Creasman, K.J.; Bazarov, A.V.; Smyth, J.W.; Davis, S.E.; et al. MYC pathway activation in triple-negative breast cancer is synthetic lethal with CDK inhibition. J. Exp. Med. 2012, 209, 679–696. [CrossRef] [PubMed]

77. Cargnello, M.; Roux, P.P. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol. Mol. Biol. Rev. 2011, 75, 50–83. [CrossRef] [PubMed]
78. Brufsky, A.; Kim, S.B.; Velu, T.; Garcia-Saenz, J.A.; Tan-Chiu, E.; Sohn, J.H.; Dirix, L.; Borms, M.V.; Liu, M.C.; Moezi, M.M.; et al. Cobimetinib (C) combined with paclitaxel (P) as a first-line treatment in patients (pts) with advanced triple-negative breast cancer (COLET study): Updated clinical and biomarker results. Cancer Res. 2017, 77, 4–22. [CrossRef]

79. Gerratana, L.; Fanotto, V.; Polizzari, G.; Agostinnetto, E.; Puglisi, F. Do platinum salts fit all triple negative breast cancers? Cancer Treat. Rev. 2016, 48, 34–41. [CrossRef] [PubMed]

80. Poggio, F.; Bruzzone, M.; Ceppi, M.; Ponde, N.F.; La Valle, G.; Del Mastro, L.; de Azambuja, E.; Lambertini, M. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: A systematic review and meta-analysis. Ann. Oncol. 2018, 29, 1497–1508. [CrossRef] [PubMed]

81. Wang, X.; Qi, Y.; Kong, X.; Zhai, J.; Li, Y.; Song, Y.; Wang, J.; Feng, X.; Fang, Y. Recent Advances in the Research of Immunotherapy for Triple-Negative Breast Cancer. Cancer Lett. 2018, 442, 409–428. [CrossRef] [PubMed]

82. Schmid, P.; Adams, S.; Rugo, H.S.; Schneeweiss, A.; Barrios, C.H.; Iwata, H.; Dieras, V.; Hegg, R.; Im, S.A.; Shaw Wright, G.; et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N. Engl. J. Med. 2018, 379, 2108–2121. [CrossRef] [PubMed]

83. Li, L.; Neaves, W.B. Normal stem cells and cancer stem cells: The niche matters. Cancer Res. 2006, 66, 4553–4557. [CrossRef] [PubMed]

84. Al-Hajj, M.; Wicha, M.S.; Benito-Hernandez, A.; Morrison, S.J.; Clarke, M.F. Prospective identification of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell 2007, 1, 555–567. [CrossRef] [PubMed]

85. Nalwoga, H.; Arnes, J.B.; Wabinga, H.; Akslen, L.A. Expression of aldehyde dehydrogenase 1 (ALDH1) is associated with basal-like markers and features of aggressive tumours in African breast cancer. Br. J. Cancer 2010, 102, 369–375. [CrossRef] [PubMed]

86. Ginestier, C.; Hur, M.H.; Charafe-Jauffret, E.; Monville, F.; Dutcher, J.; Brown, M.; Jacquemier, J.; Viens, P.; Kleer, C.G.; Liu, S.; et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a critical role in cell proliferation in triple negative breast cancer. Oncogene 2011, 30, 4437–4446. [CrossRef] [PubMed]

87. Barker, N.; Clevers, H. Mining the Wnt pathway for cancer therapeutics. Nat. Rev. Drug. Discov. 2006, 5, 997–1014. [CrossRef] [PubMed]

88. Bayet-Robert, M.; Kwiatkowski, F.; Leheurteur, M.; Gachon, F.; Planchat, E.; Abrial, C.; Mouret-Reynier, M.A.; Ulasov, I.; Lesniak, M.S.; et al. Abstract A74: Differential Wnt signaling in African American and Caucasian women with advanced and metastatic breast cancer. Cancer Biol. Ther. 2010, 9, 8–14. [CrossRef] [PubMed]

89. Yang, L.; Wu, X.; Wang, Y.; Zhang, K.; Wu, J.; Yuan, Y.C.; Deng, X.; Chen, L.; Kim, C.C.; Lau, S.; et al. FZD7 has a critical role in cell proliferation in triple negative breast cancer. Oncogene 2011, 30, 4437–4446. [CrossRef] [PubMed]

90. Ibrahim, S.A.; Hassan, H.; Vilardo, L.; Kumar, S.K.; Kumar, A.V.; Kelsch, R.; Schneider, C.; Kiesel, L.; Eich, H.T.; Zucchi, I.; et al. Syndecan-1 (CD138) modulates triple-negative breast cancer stem cell properties via regulation of LRP-6 and IL-6-mediated STAT3 signaling. PLoS ONE 2013, 8, e85737. [CrossRef] [PubMed]

91. Getz, J.E.; Teoh, D.B.; Nasser, S.; Waibhav, T.; Christophe, L.R.; Yellapantula, V.; Ahearn, M.E.; Gomez, C.R.; Jorda, M.; Pegram, M.D.; et al. Abstract A74: Differential Wnt signaling in African American and Caucasian women with triple-negative breast cancer. Cancer Epidemiol. Biomark. Prev. 2015, 24, e74. [CrossRef]

92. Wend, P.; Runke, S.; Wend, K.; Anchondo, B.; Yesayan, M.; Jardim, M.; Hardie, N.; Loddenkemper, C.; Ulasov, I.; Lesniak, M.S.; et al. WNT10B/beta-catenin signalling induces HMG2A2 and proliferation in metastatic triple-negative breast cancer. EMBO J. 2013, 5, 264–279. [CrossRef] [PubMed]

93. Arnold, K.M.; Pohlig, R.T.; Sims-Mourtada, J. Co-activation of Hedgehog and Wnt signaling pathways is associated with poor outcomes in triple negative breast cancer. Oncol. Lett. 2017, 14, 5285–5292. [CrossRef] [PubMed]

94. Polkinghorn, W.R.; Tarbell, N.J. Medulloblastoma: Tumorigenesis, current clinical paradigm, and efforts to improve risk stratification. Nat. Clin. Pract. Oncol. 2007, 4, 295–304. [CrossRef] [PubMed]

95. Nakshatri, H.; Anjanappa, M.; Bhat-Nakshatri, P. Ethnicity-Dependent and -Independent Heterogeneity in Healthy Normal Breast Hierarchy Impacts Tumor Characterization. Sci. Rep. 2015, 5, e13526. [CrossRef] [PubMed]

96. CDC. Available online: https://www.cdc.gov/obesity/adult/defining.html (accessed on 25 September 2018).
97. World Health Organization. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. Available online: http://apps.who.int/iris/bitstream/handle/10665/44583/?sequence=1 (accessed on 14 December 2018).

98. Flegal, K.M.; Kruszon-Moran, D.; Carroll, M.D.; Fryar, C.D.; Ogden, C.L. Trends in Obesity Among Adults in the United States, 2005 to 2014. *JAMA* 2016, 315, 2284–2291. [CrossRef] [PubMed]

99. Seidell, J.C.; Halberstadt, J. Obesity: The obesity epidemic in the USA-no end in sight? *Nat. Rev. Endocrinol.* 2016, 12, 499–500. [CrossRef] [PubMed]

100. Vona-Davis, L.; Rose, D.P.; Hazard, H.; Howard-McNatt, M.; Adkins, F.; Partin, J.; Hobbs, G. Triple-negative breast cancer and obesity in a rural Appalachian population. *Cancer Epidemiol. Biomark. Prev.* 2008, 17, 3319–3324. [CrossRef] [PubMed]

101. Millikan, R.C.; Newman, B.; Tse, C.K.; Moorman, P.G.; Conway, K.; Dressler, L.G.; Smith, L.V.; Labbok, M.H.; Geradts, J.; Bensen, J.T.; et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res. Treat.* 2008, 109, 123–139. [CrossRef] [PubMed]

102. Berstad, P.; Coates, R.J.; Bernstein, L.; Folger, S.G.; Malone, K.E.; Marchbanks, P.A.; Weiss, L.K.; Liff, J.M.; McDonald, J.A.; Strom, B.L.; et al. A case-control study of body mass index and breast cancer risk in white and African-American women. *Cancer Epidemiol. Biomark. Prev.* 2010, 19, 1532–1544. [CrossRef] [PubMed]

103. McGee, S.A.; Durham, D.D.; Tse, C.K.; Millikan, R.C. Determinants of breast cancer treatment delay differ for African American and White women. *Cancer Epidemiol. Biomark. Prev.* 2013, 22, 1227–1238. [CrossRef] [PubMed]

104. Ambrosone, C.B.; Ciupak, G.L.; Bandera, E.V.; Jandorf, L.; Bovbjerg, D.H.; Zirpoli, G.; Pawlish, K.; Godbold, J.; Furberg, H.; Fatone, A.; et al. Conducting Molecular Epidemiological Research in the Age of HIPAA: A Multi-Institutional Case-Control Study of Breast Cancer in African-American and European-American Women. *J. Oncol.* 2009, 871250, e25. [CrossRef] [PubMed]

105. Rosenberg, L.; Adams-Campbell, L.; Palmer, J.R. The Black Women’s Health Study: A follow-up study for causes and prevention of illness. *J. Am. Med. Womens Assoc.* 1972, 50, 56–58.

106. Kolonel, L.N.; Henderson, B.E.; Hankin, J.H.; Nomura, A.M.; Wilkens, L.R.; Pike, M.C.; Stram, D.O.; Monroe, K.R.; Earle, M.E.; Nagamine, F.S. A multiethnic cohort in Hawaii and Los Angeles: Baseline characteristics. *Am. J. Epidemiol.* 2000, 151, 346–357. [CrossRef] [PubMed]

107. Bandera, E.V.; Chandran, U.; Hong, C.C.; Troester, M.A.; Bethea, T.N.; Adams-Campbell, L.L.; Haiman, C.A.; Park, S.Y.; Olshan, A.F.; Ambrosone, C.B.; et al. Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. *Breast Cancer Res. Treat.* 2015, 150, 655–666. [CrossRef] [PubMed]

108. Palmer, J.R.; Ambrosone, C.B.; Olshan, A.F. A collaborative study of the etiology of breast cancer subtypes in African American women: The AMBER consortium. *Cancer Causes Control* 2014, 25, 309–319. [CrossRef] [PubMed]

109. Capers, P.L.; Kinsey, A.W.; Miskell, E.L.; Aftuso, O. Visual Representation of Body Shape in African-American and European American Women: Clinical Considerations. *Clin. Med. Insights Womens Health* 2016, 9, 63–70. [CrossRef] [PubMed]

110. Niswender, K.D.; Fazio, S.; Gower, B.A.; Silver, H.J. Balanced high fat diet reduces cardiovascular risk in obese women although changes in adipose tissue, lipoproteins, and insulin resistance differ by race. *Metabolism* 2018, 82, 125–134. [CrossRef] [PubMed]

111. Sharma, D.; Davidson, N.E. Obesity and breast cancer: A multipartite connection. *J. Mammary Gland Biol. Neoplasia* 2013, 18, 253–255. [CrossRef] [PubMed]