REVIEWS

The Physiological Mechanisms of Triple Negative Breast Cancer in African American Women

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Keywords: triple-negative breast cancer, African-American, women, health disparities

https://doi.org/10.52504/001c.57753

Georgetown Medical Review

Vol. 6, Issue 1, 2022

Breast cancer is one of the leading causes of cancer-related mortality among women. Multiple subtypes exist for tumor biology, but triple-negative breast cancer (TNBC) lacks expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor. TNBC accounts for 20% of breast cancers and is one of the most aggressive subtypes associated with an earlier age susceptibility, racial and ethnic differences, and limited targeted therapies. African American women bear a disproportionate burden in oncology-related health disparities. This population of women is diagnosed at later stages often with regional to distant metastases, high tumor grades, aberrant sequence mutations, treatment delays, and decreased disease-free survival. This review explores the multifactorial nature of this health disparity by addressing the physiological mechanisms, socioeconomic factors, ancestral differences, and challenges associated with diagnosis and treatment methods in the era of precision medicine.

Introduction

Breast cancer represents 30% of cancers affecting women, and recent statistics have shown that in 2022 alone close to 287 850 new cases of breast cancer were detected.[1] The Surveillance, Epidemiology, and End Results Program collects data on the incidence, prevalence, survival, and mortality rate for the cluster of breast cancer subtypes.[2] Data from the 2019 Surveillance, Epidemiology, and End Results Program showed that African American women had the highest rates of triple-negative breast cancer (TNBC) despite a lower lifetime risk compared with White women.[2] The age incidence curves increase with age and occur at an early onset (<45 years), at a rate of 56.3 per 100 000 for African American women aged 50 to 64 years and 72.3 per 100 000 for women aged 65 to 74 years.[3] The mortality rate for this group is much greater compared with other races or ethnicities for Asian, Hispanic, and Native American women in the US.[4] Stage at diagnosis is a predictor factor for survival outcomes and is significantly lower for African American women.[1] The 5-year survival for localized disease is approximately 90% but drops to 12% for distant metastases.[2] This is concerning considering the fact that African American women are typically diagnosed at advanced stages. There are a variety of factors, biological and nonbiological—namely tumor biology, genetic mutations, health care access, comorbidities, and ineffective treatment options—that exacerbate the mortality gap and contribute to the complex nature of TNBC affecting African American women.

Background

Breast development is dependent on the multiple signaling pathways and receptors such as estrogen receptors (ERs), *ERBB2* (formerly known as *HER2*), and Wnt/β-catenin signaling pathways, which control stem cell proliferation, differentiation, motility, and cell death.[4] Proper diagnosis often involves confirmation through histological and immunochemistry profiles that measure ER and progesterone receptor (PR) protein levels in breast cancer cell lines. Differentiation between breast cancer types depends on the cells affected, which are usually classified as carcinomas or sarcomas. The most common cell type, carcinoma, involves the epithelial cells lining lobules and ducts.[4] Subtypes can be further differentiated by a cluster of genes and receptors; these are the ER expressions (the luminal cluster), human epidermal growth factor 2 (HER2) expressions, proliferation, and a unique cluster of genes called the basal cluster.[4]

The ERs α and β have separate roles in signaling the promotion of growth through the cell cycle and interaction with cyclin D checkpoints.[4] In contrast, *BRCA1* acts as a tumor suppressor by repairing DNA damage through homology-directed repair and inhibiting ERα signaling, slowing tumorigenesis.[4] Deletions, mutations, and/or loss of function in the *BRCA* genes lead to decreased DNA repair efficiency and tumor formation. Progesterone functions in the initiation and maintenance of pregnancy.[5] This hormone binds to protein receptor isoforms PR-A and PR-B, which control gene transcription and modulate growth factors.[5] *ERBB2* is a receptor tyrosine kinase with multiple ligand-binding domains that activate downstream signaling pathways (MAPK/PI3K), which affect gene expression and aid cell proliferation.[4] Dysregulation of these pathways altogether contributes to the pathogenesis of TNBC through uncontrolled growth, progression, and invasiveness.

Physiological Mechanisms

PATHOLOGY

TNBC refers to the immunophenotype of breast cancer that is immunologically negative or lacks expression for ER, PR, and *ERBB2* receptors.[6] A recent gene profile analysis by Lehmann et al[7] divided TNBC into 6 subtypes: basal-like 1, basal-like 2, mesenchymal, mesenchymal stem-like, immunomodulatory, and luminal androgen receptor. From a pathology standpoint, the histologic characteristics include solid-pushing borders, areas of necrosis, and dense lymphocytic infiltrate/metastasis.[8] African American women tend to have a large percentage of basal-like breast cancer with morphological variants that are higher tumor grades, mitotic index, central necrosis, and node positivity.[9,10] Lindner et al[11] compared tumor samples from women of different racial and ethnic backgrounds and found that the profiles from African American women had decreased *BRCA1* expression, increased activation of insulin-like growth factor 1 receptor, and increased

expression of vascular endothelial growth factor–activated genes. Tumor vascularization can be attributed to high microvessel area scores and node positivity, which are elevated in African American women with TNBC.[11]

Diverse cell types are present in the tumor microenvironment and play distinct roles in the initiation, progression, and invasive stages that represent the hallmarks of cancer. Once cellular remodeling occurs, it confers resistance against chemotherapy. The heterogeneous nature of the tumor microenvironment can influence disease progression, leading to invasion of the lymph nodes and distant metastasis.[12,13] The presence of nodal involvement in TNBC causes difficulty in determining targeted treatment.

GENETICS

An existing body of literature supports the link between family history and the risk of developing breast cancer in a woman's lifetime. Having a first-degree relative with breast cancer significantly increases the risk for ER-positive, ER-negative/PR-negative/*ERBB2*-positive, and triple-negative subtypes.[14] One in 4 African American women from high-risk families has an increased risk of *BRCA* mutations and 20.4% of African American women with TNBC have a germline mutation of *BRCA1*.[15,16] Breast cancers with ER-negative receptor status typically have severe genetic abnormalities and dysfunctional cell cycle regulators such as p53, *BRCA1*, and oncogenic amplification of *ERBB2*.[8] Germline mutations of *BARD1*, *RAD51C/D*, *PALB2*, and *CHEK2* are examples of genes involved in stabilizing DNA repair.[15] Dysfunction in single-nucleotide polymorphisms rs8170 and rs13074711 inhibit downstream signaling for apoptosis and antitumor responses.[15] Other transcription factors, such as forkhead box O (FOXO) or FOXO3a, were highly expressed in TNBC tumors and resulted in adverse outcomes related to metastasis and mortality.[4] Genes in the functional pathway for Wnt signaling appeared to be upregulated in a cohort of African American women with TNBC, and this dysregulation was also linked to shorter recurrence.[17]

The African American Breast Cancer Epidemiology and Risk (AMBER) Consortium compiles biomarker data from 2 case-control studies (Carolina Breast Cancer Study and Women's Circle of Health Study) and 2 prospective cohort studies (Black Women's Health Study and Multiethnic Cohort Study) to identify breast cancer risks.[18] This is one of the largest studies to collect data on African American women as a method to investigate the unique mechanisms for breast cancer heterogeneity in this high-risk group. A genome analysis by Haddad et al[19] used data from the AMBER Consortium to examine the variation in mutations for African American women with breast cancer. They found that genes *PDE4D* and *FBXL22* served as tumor-promoting factors that aid cancer cell survival.[19] The 2017 study by Ademuyiwa et al[20] analyzed data from the Cancer Genome Atlas to identify mutational characteristics in women diagnosed with TNBC. Their results revealed that African American women had a higher prevalence of *TP53*,

PIK3, and *MLL3* gene mutations compared with White women.[20] Although there is still more to uncover with genome-wide analyses, it is believed that African American women tend to have more sequence variations or mutations of unknown pathogenicity.[15]

Deepak et al[12] and Deshmukh et al[21] completed studies that identified distinct differences in the tumor microenvironment of African American women compared with other racial and ethnic groups with a TNBC diagnosis. There is also heterogeneity in the presence of TNBC among different ethnic groups of Black women, with the highest rates observed in African American (triple negative representing 23.7% of cases) and West African women (24.1%) compared with lower rates observed in East African (11.6%) and Caribbean women (21.2%).[15] Jiagge et al[9] also found distinct differences in the frequency of TNBC among White women at 15.5%, East African (Ethiopian) women at 15.0%, West African women (Ghanian) at 53.2%, and African American women at approximately 30%. Sharing ancestral similarities in part due to the Atlantic slave trade and migration patterns are possible explanations for the genetic admixture and the variance of risk.[9] These factors, coupled with high incidence rates of deleterious *BRCA* mutations in African American women, highlight the need for early genetic testing/counseling.

BODY COMPOSITION

Emerging evidence suggests an association between lifestyle factors contributing to obesity and other comorbidities also implicated in breast cancer. Obesity rates are much higher among African American people due to a variety of reasons associated with low socioeconomic status, food insecurity, lack of green spaces, and other conditions. A study by Prakash et al[22] showed that 29% of African American women with obesity had TNBC compared with 8.6% of African American women without obesity. Chronic inflammation due to visceral obesity can also enhance breast cancer development by creating a hypoxic environment and activating inflammatory markers that make treatment difficult and metastasis more likely.[23] The metabolic syndrome resulting from visceral obesity leads to elevated glucose levels, dyslipidemia, and hyperinsulinemia, which in turn stimulate cancer cell proliferation, angiogenesis, and aid tumor progression.[22]

The effects of obesity on premenopausal and postmenopausal women seem to have opposing trends based on body mass index (BMI) and waist to hip ratio (WHR) measurements.[22] An increase in fat accumulation and free estrogen levels has been shown to increase the risk of breast cancer in postmenopausal women.[23] During menopause, the source of estrogen comes from adipose tissue stores once the ovaries decrease estrogen production, which can elevate the risk of breast cancer.[21] Circulating estrogen can be transformed into oxidative metabolites that induce DNA damage and carcinogenesis or increase cell proliferation by inhibiting apoptosis via the MAPK/PIK3 pathway.[23] Robinson et al[24] investigated the association between changes in body

composition (BMI vs WHR) among premenopausal and postmenopausal African American women and cancer risk. This study determined that higher adult BMI and greater adiposity are associated with reduced risk of breast cancer in premenopausal women and increased risk in postmenopausal women.[24] Age-specific changes also showed a different risk ratio, wherein a greater BMI at age 35 years showed a positive trend with increased cancer risk among premenopausal African American women.[25] Visceral obesity is best measured by waist circumference or WHR as a predictor of metabolic syndrome. Results from the AMBER Consortium and Carolina Breast Cancer Study determined that higher WHR (>0.85) was associated with increased risk of TNBC for both premenopausal and postmenopausal women.[26]

LIFESTYLE

Other lifestyle factors, such as physical activity and diet, can impact breast cancer rates. Balanced diets (low fat, fruits, and vegetables) demonstrate a significant reduction in death from breast cancer.[15] The Women's Health Initiative implemented a dietary modification (low fat, increased grains, and fruit) intervention in women to determine the effects of breast cancer incidence and mortality.[27] The results showed a significantly lower mortality risk for those later diagnosed with breast cancer among postmenopausal women.[27] High-fat diets, in comparison, stimulate fat tissue to release the hormone leptin, which has been implicated in enhancing tumor lethality.[21] Leptin is also secreted by cancer cells and contributes to cellular matrix deposition within the tumor microenvironment and decreases apoptosis.[21,26] This association stresses the importance of diet modification as a preventive measure against breast cancer.

A potential inverse relationship exists between the level of physical activity and breast cancer incidence and recurrence. Engaging in more physical activity led to a decreased incidence of ER-negative/PR-negative breast cancer compared with ER-positive tumors.[15] Dethlefsen et al[28] measured the effect of exercise on breast cancer cell lines and healthy controls. Serum blood samples taken immediately after an exercise session from both patients with breast cancer and healthy women yielded positive results and reduced cancer cell viability in vitro by approximately 10%.[28] Cancer cell lines MCF-7 (luminal A classification) and MDA-MB-231 (triple-negative) were directly stimulated with epinephrine to activate Hippo signaling, which is involved in cell proliferation.[28] Once activated, Hippo signaling reduced breast cancer cell viability and suppressed tumor growth when catecholamines epinephrine and norepinephrine were added to in vivo cultures and tumor-bearing mice.[28] Future studies need to further investigate how exercise regulates signaling pathways involved in carcinogenesis.

HORMONE METABOLISM

This section explores the influence of hormone metabolism and dysregulation pre/post menopause and contraceptive use on TNBC. Pelicano et al[29] studied the metabolic properties of TNBC that promote cell proliferation. This study found that TNBC, compared with ER-positive cancers, is highly anaerobic and dependent on glucose.[29] The Warburg effect applies to TNBC wherein cancer cells use glycolysis as its predominant pathway for energy production with less reliance on mitochondrial respiration even in the presence of oxygen.[29] One study applied glycolytic inhibitors, such as 2-deoxyglucose and 3-bromo-2-oxopropionate-1-propyl ester, to test anticancer activities (cell death) as a possible treatment method.[29] TNBC cell lines treated with 3-bromo-2-oxopropionate-1-propyl ester were highly sensitive to glycolytic inhibition with a substantial decrement in ATP production.[29] Chemotherapeutics that target the metabolic pathways of tumor cells is another focal research topic.

Developmental changes such as the age at menarche, parity, contraceptive use, and the onset of menopause are factors that contribute to TNBC. Androgen activation or expression can be upregulated, leading to tumorigenesis through genomic signaling.[30] The early onset of TNBC that is androgen receptor positive can be associated with higher serum levels of estrogen/androgen in premenopausal women.[30] Estrogen's role, in particular, has significant downstream effects. In oral contraceptive use, it can stimulate angiogenesis, ER binding, and stromal cell recruitment leading to cancer development.[14] Several epidemiological studies have assessed the association between oral contraceptive use and the risk of developing breast cancer based on receptor subtype (ER-positive/ER-negative/TNBC). A cohort study from the Black Women's Health Survey by Rosenberg et al[31] concluded that oral contraceptive use for longer durations (5-15 years) significantly affects the development of ER-negative cancers in African American women.[31] Limitations to note include the formulations of oral contraceptives that change regarding hormone dosage, which could also affect cancer risk. Phipps et al[14] investigated whether reproductive/menstrual history and use of oral contraceptives were associated with the risk of triple-negative and/or ER-positive breast cancers. Their results determined that women with TNBC were younger, had a family history of breast cancer, and had a higher grade and larger tumor size than those with ER-positive breast cancer.[14] Contraceptive use in younger women (<40 years) for more than a year was associated with a more than 4-fold increased risk of TNBC.[14] Researchers should analyze the long-term outcomes of contraceptive use on ER-negative cancers that differ in their hormone metabolism than ER-positive types that are more sensitive to hormone-targeted therapies.

DIAGNOSIS AND TREATMENT

The American Cancer Society recommends beginning screening with mammography for women aged 40 to 44 years with average risk. Women older than 45 years should be screened annually and then biennially between ages 50 and 55 years.[32] Diagnostic criteria for TNBC use magnetic resonance imaging or mammograms to detect microcalcifications, biopsy, and immunochemistry profiles to identify receptor types.[33] Current treatment recommendations for breast cancer involve breast-conserving surgery through lumpectomy combined with radiation, mastectomy, or neoadjuvant chemotherapy to shrink tumors before surgery.[1] The invasiveness of TNBC and its subtype variations make it extremely difficult to treat. The signaling pathways and subtypes involved in TNBC are potential targets for testing pharmaceutical sensitivity, progression, and overall survival. Mechanisms to treat tumorigenesis involve downregulating uncontrolled growth and stimulating pathways that induce apoptosis.

The timing of chemotherapy administration is crucial to prevent recurrence and overall survival and is recommended for any tumor size greater than 0.5 cm.[6] Neoadjuvant refers to chemotherapy given before initial surgery, while adjuvant is administered after surgery.[34] Neoadjuvant therapy aims to slow disease and preserve the breast and is recommended for patients in advanced stages II to III.[35] Adjuvant therapy that is dose-dense or administered in shorter intervals has been linked to better survival outcomes. If residual cancer remains after neoadjuvant dosing, the likelihood of recurrence increases.[34] The pathologic response rate (pCR) is a standard measurement that assesses the absence of residual cancer to monitor treatment progress.[35] TNBC has a lower pCR and often requires neoadjuvant therapy given the advanced tumor grade. This ultimately leads to lower overall rates of pCR without nodal involvement for African American women and is compounded by the delay in receipt of chemotherapy.

Inequities due to low socioeconomic status lead to adverse health outcomes, especially in the case of survival. Although one of the aims of the Affordable Care Act was to increase the amount of Americans insured, disparities are still present in the insurance rates among African American individuals, at around 11.9%, compared with White American individuals, at 8.2%.[36] Access to quality oncology care is limited in impoverished areas.[36] The Southwest Oncology Group, after standardizing patients during chemotherapy treatment, found that African American women had worse overall outcomes.[37] This finding could suggest a difference in chemosensitivity.[37] Researchers have also determined that African American women are more likely to experience inappropriate treatment doses and discontinuation.[1] Inappropriate care consists of breast-conserving surgery without radiotherapy,

mastectomy without lymph node dissection, or dose reductions in chemotherapy. African American women were also less likely to undergo surgery or be treated with radiation.[38]

Treatment guidelines suggest a combination therapy for 4 to 6 cycles using taxanes, anthracyclines, cyclophosphamide, cisplatin, and fluorouracil.[39] Taxanes function to inhibit microtubule polymerization, which prevents mitotic division in the cell cycle.[39] Taxane-targeted therapy can be successful in initiating apoptosis in TNBC.[39] Anthracyclines are derived from antibiotics, are an effective chemotherapeutic drug for multiple cancers, and are suitable for basal-like and M-type TNBC subtypes. Together taxanes and anthracyclines have been associated with resistance and chemotoxicity as first-line therapies. TNBC-targeted therapies, such as poly(ADP-ribose) polymerase (PARP) inhibitors, androgen receptor antagonists, and immunomodulation have been the subjects of new clinical trials.[39]

Patients with *BRCA1/2* mutations and TNBC are more likely to have PARP DNA repair dysregulation or deficiencies.[40] PARP inhibitors (olaparib) combined with PIK3 antagonists (Novartis) are currently being explored as drugs that promote apoptosis and DNA repair.[39] Immune modulation to target cancer cells is an emerging topic for TNBC. Programmed cell death-ligand 1, a checkpoint receptor, can be appropriated by tumor cells, which downregulate/inhibit T-cell proliferation.[39] Immunotherapies that focus on Programmed cell death-ligand 1 and protein receptors, such as CTLA-4, can successfully suppress growth and extend survival.[39] Overall survival for stage I triple-negative cancers was similar to other receptor subtypes, but outcomes worsen with increasing stage.[15] Using platinum-based therapies (carboplatin, cyclophosphamide, gemcitabine), which induce apoptosis via DNA strand breaks have shown mixed results for improving pCR. Clinical trials, such as the Doxorubicin Hydrochloride and Cyclophosphamide Followed by Paclitaxel With or Without Carboplatin in Treating Patients With Triple-Negative Breast Cancer Study (NCT02488967) and Platinum in Treating Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy Study (NCT02445391), are investigating the efficacy of platinum therapies in combination with other standard treatments.[41,42] These trials are working to find appropriate treatment strategies that factor individual tumor biology through precision medicine and address the underlying pathways contributing to cancer cell proliferation. Clinical trials centered around immunotherapy show somewhat promising results for molecular markers of TNBC. However, most trials fail to represent and recruit high-risk African American women with distinct tumor biology into research participation for therapeutic trials.

Conclusions

Given the aggressive nature of TNBC, this subtype warrants extensive research for prevention and treatment methods that effectively promote disease-free survival while decreasing the recurrence rate. Lifestyle factors contributing to body composition influence the metabolic mechanisms that accelerate tumorigenesis through fat metabolites and oxidative damage. *BRCA1/2* mutations in TNBC have damaging effects that promote uncontrolled cell growth due to the dysfunction in tumor suppression. Targeted adjuvant therapies that generally work for ER-positive cancers are unsuitable for the molecular complexities of TNBC.

Future directions should also examine the exact mechanisms predisposing African American women to TNBC. The meta-analysis by Howard et al[15] noted the increased risk of death when controlling for other factors such as delays in follow-up or treatment initiation, stage at diagnosis, comorbidities, and socioeconomic status. Disparities are still evident in the diagnosis (2- to 3-fold risk), treatment, and survival stages. The COVID-19 pandemic likely magnified inequities through screening delays for millions. A recent study by Yacona et al[43] discovered a disproportionate difference in total mammograms, biopsies, and minimal cancer detection between institutions serving predominantly White vs African American populations. Clinical trials lack diverse patient populations that should adequately reflect those most at risk. There is still much to learn about the underlying factors promoting TNBC, whether it relates to deleterious mutations, lifestyle, hormones, or unknown exposures. Researchers must continue to discover appropriate biomarkers to aid detection, test treatment modalities, and prolong disease-free survival for all women.

REFERENCES

1. Giaquinto AN, Sung H, Miller KD, et al. Breast cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(6):524-541. doi:10.3322/caac.21754

2. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 9 Regs Research Data with Delay-Adjustment, Malignant Only, based on the November 2018 submission. *National Cancer Institute, Surveillance Research Program, Surveillance Systems Branch*. Published online 2019.

3. Amirikia KC, Mills P, Bush J, Newman LA. Higher population-based incidence rates of triple-negative breast cancer among young African-American women: implications for breast cancer screening recommendations. *Cancer*. 2011;117(12):2747-2753. doi:10.1002/cncr.25862

4. Feng Y, Spezia M, Huang S, et al. Breast cancer development and progression: risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes Dis*. 2018;5(2):77-106. doi:10.1016/j.gendis.2018.05.001

5. Trabert B, Sherman ME, Kannan N, Stanczyk FZ. Progesterone and breast cancer. *Endocr Rev*. 2020;41(2):320-344. doi:10.1210/endrev/bnz001

6. Ismail-Khan R, Bui MM. A review of triple-negative breast cancer. *Cancer Control*. 2010;17(3):173-176. doi:10.1177/107327481001700305

7. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121(7):2750-2767. doi:10.1172/jci45014

8. Allison KH. Molecular pathology of breast cancer: what a pathologist needs to know. *Am J Clin Pathol*. 2012;138(6):770-780. doi:10.1309/ajcpiv9iq1mrqmoo

9. Jiagge E, Chitale D, Newman LA. Triple-negative breast cancer, stem cells, and African ancestry. *Am J Pathol*. 2018;188(2):271-279. doi:10.1016/j.ajpath.2017.06.020

10. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006;295(21):2492-2502. doi:10.1001/jama.295.21.2492

11. Lindner R, Sullivan C, Offor O, et al. Molecular phenotypes in triple negative breast cancer from African American patients suggest targets for therapy. *PLoS One*. 2013;8(11):e71915. doi:10.1371/journal.pone.0071915

12. Deepak KGK, Vempati R, Nagaraju GP, et al. Tumor microenvironment: challenges and opportunities in targeting metastasis of triple negative breast cancer. *Pharmacol Res*. 2020;153:104683. doi:10.1016/j.phrs.2020.104683

13. Al-Mahmood S, Sapiezynski J, Garbuzenko OB, Minko T. Metastatic and triple-negative breast cancer: challenges and treatment options. *Drug Deliv Transl Res*. 2018;8(5):1483-1507. doi:10.1007/s13346-018-0551-3

14. Phipps AI, Buist DSM, Malone KE, et al. Family history of breast cancer in first-degree relatives and triple-negative breast cancer risk. *Breast Cancer Res Treat*. 2011;126(3):671-678. doi:10.1007/s10549-010-1148-9

15. Howard FM, Olopade OI. Epidemiology of triple-negative breast cancer: a review. *Cancer J*. 2021;27(1):8-16. doi:10.1097/ppo.0000000000000500

16. Dietze EC, Sistrunk C, Miranda-Carboni G, O'Regan R, Seewaldt VL. Triple-negative breast cancer in African-American women: disparities versus biology. *Nat Rev Cancer*. 2015;15(4):248-254. doi:10.1038/nrc3896

17. Siddharth S, Sharma D. Racial disparity and triple-negative breast cancer in African-American women: a multifaceted affair between obesity, biology, and socioeconomic determinants. *Cancers (Basel)*. 2018;10(12):514. doi:10.3390/cancers10120514

18. Allott EH, Geradts J, Cohen SM, et al. Frequency of breast cancer subtypes among African American women in the AMBER consortium. *Breast Cancer Res*. 2018;20(1):12. doi:10.1186/s13058-018-0939-5

19. Haddad SA, Ruiz-Narváez EA, Haiman CA, et al. An exome-wide analysis of low frequency and rare variants in relation to risk of breast cancer in African American Women: the AMBER Consortium. *Carcinogenesis*. 2016;37(9):870-877. doi:10.1093/carcin/bgw067

20. Ademuyiwa FO, Tao Y, Luo J, Weilbaecher K, Ma CX. Differences in the mutational landscape of triple-negative breast cancer in African Americans and Caucasians. *Breast Cancer Res Treat*. 2017;161(3):491-499. doi:10.1007/s10549-016-4062-y

21. Deshmukh SK, Srivastava SK, Tyagi N, et al. Emerging evidence for the role of differential tumor microenvironment in breast cancer racial disparity: a closer look at the surroundings. *Carcinogenesis*. 2017;38(8):757-765. doi:10.1093/carcin/bgx037

22. Prakash O, Hossain F, Danos D, Lassak A, Scribner R, Miele L. Racial disparities in triple negative breast cancer: a review of the role of biologic and non-biologic factors. *Front Public Health*. 2020;8:576964. doi:10.3389/fpubh.2020.576964

23. Iwase T, Wang X, Shrimanker TV, Kolonin MG, Ueno NT. Body composition and breast cancer risk and treatment: mechanisms and impact. *Breast Cancer Res Treat*. 2021;186(2):273-283. doi:10.1007/s10549-020-06092-5

24. Robinson WR, Tse CK, Olshan AF, Troester MA. Body size across the life course and risk of premenopausal and postmenopausal breast cancer in Black women, the Carolina Breast Cancer Study, 1993-2001. *Cancer Causes Control*. 2014;25(9):1101-1117. doi:10.1007/s10552-014-0411-5

25. Schoemaker MJ, Nichols HB, Wright LB, et al. Association of body mass index and age with subsequent breast cancer risk in premenopausal women. *JAMA Oncol*. 2018;4(11):e181771. doi:10.1001/jamaoncol.2018.1771

26. Dietze EC, Chavez TA, Seewaldt VL. Obesity and triple-negative breast cancer: disparities, controversies, and biology. *Am J Pathol*. 2018;188(2):280-290. doi:10.1016/j.ajpath.2017.09.018

27. Chlebowski RT, Aragaki AK, Anderson GL, et al. Dietary modification and breast cancer mortality: long-term follow-up of the Women's Health Initiative randomized trial. *J Clin Oncol*. 2020;38(13):1419-1428. doi:10.1200/jco.19.00435

28. Dethlefsen C, Hansen LS, Lillelund C, et al. Exercise-induced catecholamines activate the hippo tumor suppressor pathway to reduce risks of breast cancer development. *Cancer Res*. 2017;77(18):4894-4904. doi:10.1158/0008-5472.can-16-3125

29. Pelicano H, Zhang W, Liu J, et al. Mitochondrial dysfunction in some triple-negative breast cancer cell lines: role of mTOR pathway and therapeutic potential. *Breast Cancer Res*. 2014;16(5):434. doi:10.1186/s13058-014-0434-6

30. Honma N, Matsuda Y, Mikami T. Carcinogenesis of triple-negative breast cancer and sex steroid hormones. *Cancers (Basel)*. 2021;13(11):2588. doi:10.3390/cancers13112588

31. Rosenberg L, Boggs DA, Wise LA, Adams-Campbell LL, Palmer JR. Oral contraceptive use and estrogen/progesterone receptor-negative breast cancer among African American women. *Cancer Epidemiol Biomarkers Prev*. 2010;19(8):2073-2079. doi:10.1158/1055-9965.EPI-10-0428

32. Oeffinger KC, Fontham ETH, Etzioni R, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA*. 2015;314(15):1599-1614. doi:10.1001/jama.2015.12783

33. Trayes KP, Cokenakes SEH. Breast cancer treatment. *Am Fam Physician*. 2021;104(2):171-178.

34. Marra A, Curigliano G. Adjuvant and neoadjuvant treatment of triple-negative breast cancer with chemotherapy. *Cancer J*. 2021;27(1):41-49. doi:10.1097/ppo.0000000000000498

35. Mahtani R, Kittaneh M, Kalinsky K, et al. Advances in therapeutic approaches for triple-negative breast cancer. *Clin Breast Cancer*. 2021;21(5):383-390. doi:10.1016/j.clbc.2020.12.011

36. Newman LA, Kaljee LM. Health disparities and triple-negative breast cancer in african american women: a review. *JAMA Surg*. 2017;152(5):485-493. doi:10.1001/jamasurg.2017.0005

37. Killelea BK, Yang VQ, Wang SY, et al. Racial differences in the use and outcome of neoadjuvant chemotherapy for breast cancer: results from the National Cancer Data Base. *J Clin Oncol*. 2015;33(36):4267-4276. doi:10.1200/jco.2015.63.7801

38. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. *Arch Intern Med*. 2003;163(1):49-56. doi:10.1001/archinte.163.1.49

39. Yin L, Duan JJ, Bian XW, Yu SC. Triple-negative breast cancer molecular subtyping and treatment progress. *Breast Cancer Res*. 2020;22(1):61. doi:10.1186/s13058-020-01296-5

40. Ge J, Zuo W, Chen Y, Shao Z, Yu K. The advance of adjuvant treatment for triple-negative breast cancer. *Cancer Biol Med*. 2021;19(2):187-201. doi:10.20892/j.issn.2095-3941.2020.0752

41. Konstantinopoulos PA, Barry WT, Birrer M, et al. Olaparib and α-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial. *Lancet Oncol*. 2019;20(4):570-580. doi:10.1016/s1470-2045(18)30905-7

42. Mayer IA, Zhao F, Arteaga CL, et al. Randomized phase III postoperative trial of platinum based chemotherapy versus capecitabine in patients with residual triple-negative breast cancer following neoadjuvant chemotherapy: ECOG-ACRIN EA1131. *J Clin Oncol*. 2021;39(23):2539-2551. doi:10.1200/jco.21.00976

43. Yacona K, Hanna MW, Niyazi S, et al. Can COVID-19 worsen racial disparities in breast cancer screening and diagnosis? *J Clin Imaging Sci*. 2022;12:35. doi:10.25259/jcis_26_2022