Targeting risk factors for reducing the racially disparate burden in breast cancer

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1. ABSTRACT

African-American (AA) women are more likely to die from breast cancer (BC), at any age, compared to European-American women. Although breakthroughs in pre-clinical studies have resulted in potentially actionable targets in AA BC, drugs that were rationally designed for these targets have performed poorly in clinical trials. Challenges with interpatient and intratumoral heterogeneity, lack of drug sensitivity and specificity, suboptimal biomarker cut-offs, lack of drug response predictive biomarkers, drug side effects, high costs of drug development, and under-representation of AAs in clinical trials complicate the development of targeted therapies for AA BC patients. Accumulating evidence suggests that racial disparities exist in non-genetic risk factors that can alter genetic and epigenetic programs to promote breast tumorigenesis. Herein, we present a “roadmap” that addresses non-genetic risk factors that are suspected to contribute to the racial disparity in BC mortality. Increased targeting of these non-genetic risk factors may proffer a safer and more economical route to alleviating the racially disparate burden in BC.

2. THE RACIALLY DISPARATE BURDEN IN BREAST CANCER

Breast cancer (BC) is the number one form of invasive cancer among women in the United States and ranks second among the leading causes of death from cancer among women today (1). African-American (AA) women have significantly higher BC incidence rates than European-American (EA) women before the age of 40 (2). However, AA women of all ages are more likely to die from BC than EA women, with death rates among AAs being as much as 60% higher in Louisiana and Mississippi (2, 3). AA women tend to be diagnosed with BC at a much younger age compared to their EA counterparts (2). Furthermore, AAs have lower proportions of localized BC and higher proportions of regional and distant-stage BC than other ethnic groups including EAs (2). More aggressive BC subtypes such as estrogen receptor (ER)-negative, progesterone receptor-negative, and triple negative BC (TNBC) have been reported to be more prevalent among AA compared to EA patients leaving AA patients with a lack of drug targets (2). AA women have also shown evidence of a 40-70% higher risk of developing stage IV disease than EA women across all BC subtypes (4-6).

Researchers suspect that distinctions in inherent tumor biology contribute to the racially disparate burden in BC. Thus, cancer health disparity research has focused largely on identifying pharmacologically-targetable biomarkers strongly associated with African ancestry that can improve risk-prognostication and reduce the disproportionately higher mortality rates observed among AA patients. Unfortunately, while many of the targeted therapeutics rationally designed for these biomarkers performed well in preclinical studies, their efficacies in clinical trials haven’t been particularly impressive (7). A variety of factors, as outlined in Figure 1, such as high interpatient and intratumoral heterogeneity, toxic side effects, challenges in validating detection methods with high specificity and sensitivity, suboptimal cut-offs, lack of robust drug response biomarkers, limited understanding of drug mechanism of action, lack of pharmacokinetic/pharmacodynamic studies, high costs of drug development, variability in tissue fixation and immunohistochemical staining methods, all collude to impair the development of personalized medicine for AA BC patients (7-18). Further compounding these issues are the time consuming, costly, and inefficient preclinical and clinical trial processes. Moreover, less than 10% of cancer patients in clinical trials are AA; this under-representation of AAs limits the generalizability of the trials’ findings and represents a preventable disparity in health care that leaves AA patients with fewer effective treatment options (19).

3. ALTERNATIVE ROUTE: TARGETING NON-GENETIC RISK FACTORS IN BC

Many studies suggest a link between non-genetic and anthropometric factors and an increased risk of acquiring BC (20, 21). Many of these non-genetic factors trigger a switch in the genetic program to promote BC onset and/or progression as illustrated in Figure 2. Racial disparities in these established non-biological and anthropometric BC risk factors have been suggested to play a critical role in the divergence in BC mortality rates between AA and EA patients; however, they have received minimal attention (3). Herein, we present a “roadmap” that comprehensively reviews the role of non-biological and anthropometric risk factors in driving the racial disparity in BC and discuss how these factors reprogram the genetic and epigenetic landscape to foster breast pathogenesis. We also consider how these non-genetic risk factors can be effectively and economically “modified,” to help close the stark gap in clinical outcomes between racially-distinct patients.

4. THE FIRST STOP: MAJOR LIFESTYLE CHANGES

“Let food be thy medicine and medicine be thy food” – Hippocrates

AA women may have lifestyle habits and make choices that contribute to more aggressive tumor biology than EA women. Here, we discuss these lifestyle risk factors and how they may contribute to the racially disparate burden in BC.
4.1. Diet

High fat and cholesterol intake but low dietary fiber and vitamin D consumption levels have been suggested to facilitate breast tumor growth and progression (22-25). A high fat intake has been suggested to facilitate breast tumor growth by promoting the accumulation of adipose tissue, which is a site for the conversion of androstenedione to estrone or estrogen (22). Furthermore, a diet rich in polyunsaturated fatty acids can generate mutagenic free radicals and oxidative stress which can lead to epigenetic alterations (26). However, a single serving of broccoli sprouts was found to inhibit histone deacetylase activity along with concurrent induction of histone H3 and H4 acetylation (26). Moreover, a high fiber intake can increase the excretion of estrogens and inhibit the absorption of estrogens into the gut (23). Increased plasma cholesterol levels in mice mammary tumors have been associated with an increase in cyclin D1 expression and a decrease in expression of proteins that protect against BC (24). On average, AA women have been reported to consume a diet higher in total fat and cholesterol but with less dietary fiber than their EA counterparts (27). In one study, AAs consumed less grains, fruits, and vegetables compared to EA women (27). AAs have also been reported to have a 10-fold higher deficiency...
in vitamin D levels compared to EAs as a result of their darker skin pigmentation, low dietary intake of vitamin D, and high obesity prevalence (28, 29).

4.2. Physical activity

It has been suspected that physical activity may prevent breast tumorigenesis by reducing the levels of insulin and insulin-like growth factor I (IGF-1), boosting the anti-tumoral immune response, and preventing the accumulation of excess body fat (30). Furthermore, physical activity has been linked to increased DNA methylation (28). Gordon-Larsen et al. reported that AAs watched more television each week than EAs (20 vs. 11.9 hours, respectively) and spent more time being inactive (27.6 vs. 16.5 hours/week, respectively), and 18.1% of AA and 25.6% of EA girls were reported to participate in regular moderate

Figure 2. Influence of non-genetic risk factors on tumor biology. Schematic of various lifestyle and environmental factors that alter genetic and epigenetic programs to promote aggressive breast tumor biology. An increase in practicing of these lifestyle behaviors and exposure to these environmental carcinogens can lead to an increase in genetic and epigenetic modifications that underlie faster tumor progression.
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to vigorous exercise activity (31). Sheppard and colleagues observed a 64% reduction in risk of BC among AAs who participated in vigorous exercise in one year compared to AAs who did not (32).

4.3. Alcohol intake

Alcohol can increase levels of endogenous estrogens while byproducts of alcohol metabolism can be toxic and lead to DNA modifications that promote cancer (33). Alcohol consumption levels are similar among premenopausal AA and EA women even after controlling for income, region, and location of residence (city vs. suburb) (27). However, lower amounts of a major antioxidant in fruits and vegetables that may protect against alcohol-associated BC, folate, were consumed by AA compared to EA women (33). Folate has been suggested to reduce the risk of alcohol-associated BC by neutralizing the toxic byproduct of alcohol metabolism, reactive oxygen species (33). Furthermore, folate is required for maintenance of DNA methylation patterns (26). Hence, reduced folate intake among AAs may be playing a role in the racially disparate burden in BC.

4.4 Sleep patterns

Studies have reported, on average, less than 6 hours of sleep per night, poorer sleep efficiency, greater onset latency, waking up after sleep onset, and worse overall sleep quality among AAs compared to EAs (34). This racial disparity in sleep duration and quality is associated with higher tumor grade among AA compared to EA BC patients. Among AA patients, regional and distant-stage breast tumors were found to be more prevalent among those who reported 6 compared to 7-8 hours per night of sleep (35). Poorer sleep quality and shorter sleep duration have been associated with increased risk for ER- and progesterone-negative BC as well as TNBC among AA women (36). Melatonin, a hormone secreted at night, prevents breast tumorigenesis by increasing inhibition of breast cell proliferation and invasion or through suppressing mitotic activity of endogenous hormones such as 17β-estradiol (37). Thus, low melatonin levels have been associated with shortened sleeping hours, disruption of circadian regulation, and thus, increased risk for BC (38). AAs are more likely to engage in non-traditional work hours, particularly night shifts, which can disrupt their circadian rhythm, and increase their appetite for more sweet and salty foods, compared to EAs (39, 40). Altered circadian rhythms can lead to epigenetic reprogramming of circadian genes (26). Night shift work has also been linked to alterations in blood DNA methylation and methylation of inflammatory genes such as IFN and TNF (26). Sleep disturbances can also suppress the immune system and promote an increase in the presence of cancer-stimulatory cytokines (41).

5. WARNING SIGNS: TAKE HEED OF THE SIGNS

"Ignoring the signs is a good way to end up at the wrong destination." – Anonymous

Some AA women harbor reproductive factors and/or behaviors and physical features that increase their exposure to estrogens and possibly progesterone too. Family history of cancer is also a sign of an increased likelihood of being diagnosed with the disease. Herein, we discuss these hormone exposures and familial risk factors among AA women.

5.1. Parity and breastfeeding

Parous women have been shown to exhibit a reduced risk of BC compared to nulliparous women although this primarily applies to ER-positive BC, which is more easily targeted therapeutically (42-44). Pregnancy reduces a woman’s cumulative exposure to endogenous hormones due to a lack of menstrual cycles. However, emerging evidence suggests that parous women have an increased likelihood of developing ER-negative BC, and this risk can be attenuated by breastfeeding (45-50). Some studies suggest that, on average, AA women bear more children than EA women. Being more parous has been associated with increased risk for BC among AA women younger than 45 years and is associated with decreased risk among AA women 45 years and older (51). AA mothers have also been reported to be 2.5 times less likely to breastfeed than EAs; while 60% of EA mothers were reported to breastfeed their infants, only 24% of AA mothers did so (52, 53). Studies have reported that parous AA women who did not breastfeed had a greater risk for ER-negative BC and TNBC than for ER-positive BC as lactation delays the reestablishment of ovulation after a woman gives birth (45,53-54).

5.2. Age at menarche

Women with earlier onset of menstruation are exposed to greater cumulative levels of estrogen and progesterone during their lifetime; thus, age at menarche represents a surrogate marker for the level of exposure to these hormones in women (53-55). AA women have been reported to experience the onset of menarche at a younger age than EA women (almost 2-fold greater risk); however, recent studies suggest that the ages may now be similar among the two racial groups (53, 56-58). Evidence suggests that early age at menarche is associated with increased risk for ER-negative BC among AA women (59). Younger age at onset of menstruation during adolescence has been suggested to be linked to various factors including exposure to endocrine-disrupting chemicals (EDCs) such as, BPA and...
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phthalates, being overweight in childhood, obesity, physical inactivity, increased consumption of animal products, dairy, soft drinks, and a diet low in nutrition, which are characteristics frequently observed among the AA population (60-70).

5.3. Body size

High body mass index (BMI) has consistently been reported to be associated with a heightened risk of BC, particularly among postmenopausal women because they harbor high levels of circulating estrogens due to the conversion of the androgen precursor, androstenedione, to estrone or endogenous estrogens in adipose tissue (53) (71-73). A high BMI was shown to be predictive of a poorer patient prognosis and more often associated with ER-negative BC, high S-phase fraction, high histological grade, high mitotic cell count, and large tumor size than a low BMI (74, 75). Bernstein et al. reported that a BMI of greater than 25 (overweight) and greater than 30 (obese) was more prevalent among AA compared to EA women (53). Another study validated this observation after controlling for age, income, region, and urban dwelling (27).

5.4. Breast density

Some studies have reported a higher mammographic density on average among AA compared to EA women (76, 77). An 11%, 15%, and 30% increase in BC risk with every 10% increase in breast density was observed among AA, EA, and Asian American women, respectively, suggesting mammographic density to be a strong predictor of risk for BC among AAs and other ethnic groups (78). Mammographic density has been associated with various reproductive, lifestyle, and anthropometric BC risk factors including: parity, diet, physical activity, and body size (79, 80). A dense breast microenvironment may foster aberrant mammary gland development, homeostasis, and promote breast tumorigenesis (81). Dense tissue may promote extracellular matrix and tissue stiffness, quantitative, or structural alterations of the stromal collagen such as cross-linking; to also foster breast pathogenesis (82-85).

5.5. Family history

A future inclusive of BC may be foreseeable by tracing familial roots in AA women. Irrespective of testing positive for the BC susceptibility genes, BRCA1 and BRCA2, family history of BC has still been associated with an approximately 4-fold risk of developing BC (86). A first-degree family history of BC has been associated with increased incidence of BC and TNBC among AA women (87). Family history may be linked to BC risk because of inherited gene mutations associated with increased risk for BC, such as BRCA1 and BRCA2, as well as shared lifestyle factors that increase risk for breast pathogenesis.

6. WINDY HILL: SETTING UP AN ENVIRONMENT FOR SUCCESS

“You’re a product of your environment, surround yourself with the best.” – Arthur Peter

Toxic environmental exposures can increase a woman’s cumulative lifetime exposure to estrogen (88). Emerging evidence suggest that AAs may be disproportionately exposed to these carcinogenic risk factors compared to EAs. In the following sections, we discuss racial disparities in exposure to environmental risk factors.

6.1. Oral contraceptives

Modern oral contraceptives prevent conception by mimicking the pregnancy state of a woman through raising the levels of estrogen and progestin (a type of progesterone) in the body. This boost in hormone levels can promote breast tumor growth. Oral contraceptive use has been reported to be less frequent among AAs compared to EAs, however its use, particularly longer duration of use, has been associated with an increased risk for ER-positive BC, ER-negative BC, and TNBC among young AA women (53, 89-93). Oral contraceptive use was more strongly associated with ER- and PR- negative, rather than ER-positive BC among AA women and the risk for ER- and PR-negative BC increased with increasing duration of use (94).

6.2. Endocrine-disrupting chemicals

EDCs such as estrogen, phthalates, and parabens, have been suggested to increase the risk for BC as they mimic the activity of estrogen in the body which may stimulate cancer cell proliferation, and accelerate invasion and migration (95-98). AAs have been reported to be more likely to use hair products containing EDCs or hormonally-active compounds such as hair oil, lotion, leave-in conditioner, root stimulator, and perm than EAs (99). AAs may have been exposed to these carcinogenic products as young as infant, toddler, or in utero stage which has been linked to premature or aberrant sexual development among AA women (88) (100). The use of hair products before the age of 13 and use of hair oil and perm among AAs was also associated with early menarche (101).

6.3. Hormone replacement therapy

To alleviate menopausal symptoms, women are often prescribed hormone replacement therapy (HRT) consisting of estrogen and/or progestins. However, HRT use increases a women’s risk for
developing BC owing to the increased exposure to estrogen (53). AAs are prescribed HRT significantly less than EAs due to the high cost of HRT; lack of prescription coverage, and low incidence of osteoporosis among the AA community (53, 102, 103). Combination HRT (estrogen and progestin) and estrogen replacement therapy (HRT with estrogen alone) has been linked to an increased risk for ER-positive BC among AA women while a reduction in their use has been projected to decrease the incidence of ER-positive BC among AAs (53, 104-106).

7. PIT STOP: REFUELING ON RESOURCES TO REACH OUR DESTINATION

“In this country if you don’t have health insurance you are out of luck. It’s a barrier to prevention, early detection, and receipt of standard-of-care treatment.” - Dr. Ahmedin Jemal.

A higher socioeconomic status (SES) has been linked to an increased incidence of BC among EAs, likely due to an increase in behaviors associated with greater risk of BC such as being less parous, late age at first pregnancy, increased use of exogenous hormones, and other established risk factors for BC (107). AA women are more likely to belong to a lower SES group and thus, more likely to be medically underserved (108). Studies report that the racial disparity in BC mortality diminishes after controlling for SES while others suggest that AA race is an independent predictor of BC mortality (109-111). Nonetheless, in this section, we review the socioeconomic disadvantages faced by the AA community that are contributing to their poorer BC clinical outcomes compared to other ethnic groups.

7.1. Timely diagnosis

Tumors, if left undetected, might metastasize leading to a poor prognosis. AA women have been reported to utilize mammography screening less than EA women; however, recent studies claim that this disparity has diminished due to increased awareness and encouragement among the AA community to seek early detection (112-116). Lack of health insurance was also reported to predict delays in diagnosis among AAs though some studies have observed that racial disparities in timely BC diagnoses still persist among a uniform low-income population (117). AA women with annual household incomes of <$15,000 were less likely to undergo a mammogram screening compared to AA women with higher incomes (118). Moreover, the average time span from diagnosis to treatment was reported to be 29.2 days for AAs, and 22.5 days for EAs (p<0.001) (119). AAs have been reported to experience longer delays in surgery, adjuvant chemotherapy, and radiation than EAs among BC patients (117, 120). A smaller household size, loss of one’s job due to their diagnosis, and lower education level was significantly associated with treatment delay among the AA population (117).

7.2. Quality healthcare

Facilities that predominantly serve women of color are less likely to be academic or private institutions, house digital mammography, or employ dedicated breast imaging specialists that correctly read the films compared to facilities predominantly serving EA women (121). These facilities also had broken mammography equipment and lacked quality in care and reporting results back promptly. AA women with early stage disease were 40% more likely to receive inappropriate treatment that failed to meet the standards of the 2000 National Comprehensive Cancer Network (122). AA patients are also 2.49 times more likely to receive reduced cumulative doses of chemotherapy than their EA counterparts (123). Administration of appropriate adjuvant treatment such as radiotherapy, adjuvant chemotherapy, or endocrine therapy following breast-conserving surgery or resection of hormone receptor-negative tumors, was less prevalent among AA compared to EA BC patients (124). Moreover, AA women were more likely to decline surgery than EA women even after controlling for Medicaid insurance and poverty, and among women who did opt for surgery, AA women were more likely to select breast conserving surgery than EA women (111).

7.3. Health insurance

Jemal and his colleagues recently reported that disparities in healthcare insurance are largely driving the disparities in survival rates between AA and EA BC patients (125). AAs have been reported to be twice as likely as EAs to be uninsured and to depend on public insurance such as Medicaid (126). This disparity in health insurance coverage between the ethnic groups accounts for approximately 37% of the excess mortality among AA women compared to differences in tumor characteristics, comorbidities, and treatment which accounted for only 23%, 11.3%, and 4.8%, respectively, of the racial disparity in BC mortality (125). EA women are now less likely to die from BC compared to AA women because they have benefited more from scientific advances in BC detection and treatment such as high-quality mammograms, follow-up after an abnormal mammogram, and targeted therapies due to their higher healthcare insurance coverage rates. As stated by Dr. Nina Brickell, affiliated with The Mount Sinai Hospital in New York, in reference to Jemal et al.’s findings, “This puts it in black and white, literally, and shows that there are survival differences that are based on insurance and there are racial differences based on insurance, so if you give people insurance and get them the care that’s needed, you can have an impact and reduce this excess risk.”
7.4. Area of residence

Non-adherence to mammography screening guidelines among AA women has been associated with residing in decaying neighborhoods with boarded-up or abandoned housing, or living in households without a car (127). In Detroit, AA women living in three vastly segregated suburbs (Pontiac, Ecorse, Inkster) with high unemployment rates, lower education levels, female-headed households, high crime rates, and poverty levels had poor access to mammography screening facilities and thus, an increased likelihood for delayed BC diagnosis (128). Moreover, segregated metropolitan neighborhoods strongly correlated with higher odds of being diagnosed with distant-staged BC among both AA and EA women (129). Further, unsafe neighborhoods have been suggested to contribute to low vitamin D levels, which is associated with increased BC incidence and mortality rates as well as TNBC, and is more prevalent among AA compared to EA women (130, 131). Low-income and minority neighborhoods often have less access to recreational facilities, yet greater access to fast-food outlets and convenience stores that sell calorie dense, processed foods rather than supermarkets selling whole foods such as fruits and vegetables (132, 133). Residing in disadvantaged neighborhoods with high crime rates, low or limited access to healthy foods, and a high prevalence of ambient noise has been associated with obesity, stress, physiologic dysregulation, psychological distress, and poor sleep quality (34) (134, 135).

7.5. Transportation

AA women residing in high poverty neighborhoods characterized by lower education rates and lower median household incomes compared to more affluent neighborhoods experience longer travel times in automobile and public transportation, which frequently limits their access to primary care providers and radiologists (136). Factors such as commuter intensity, public transportation service, and neighborhood safety surrounding the mammography screening facility were reported to reduce desire among AAs to utilize these services, and therefore led to advanced stage of BC at time of diagnosis. AAs and Hispanics in rural areas have been reported to have less access to medical care, to undergoing a mammogram screening, to be unlikely to have health insurance, and to complete fewer visits to physicians compared to their urban counterparts (137, 138). AAs and Hispanics dwelling in rural areas face unequal social conditions such as fewer resources, higher rates of poverty, and less healthcare supplies compared to urban dwellers (138, 139). AA women residing in rural and metropolitan areas were reported to experience a later stage at diagnosis of BC than AA women residing in urban areas (140).

7.6. Stress

DNA methylation patterns can be influenced by environmental stress exposures from early development and later in life (26). AAs more frequently experience stressors in multiple domains of life, greater clustering of stressors, and potentially greater duration and intensity of stressors than EAs (141). AAs and Hispanics have larger constraints in purchasing goods and services due to higher costs of these items and services in residential environments where they are disproportionately located (142). Overrepresentation of minorities in toxic residential and occupational environments can lead to major hardships including: crime, violence, material deprivation, loss of loved ones, recurrent financial strain, relationship conflicts, unemployment, and underemployment that promote psychological distress (143). Exposure to stressors associated with living in low SES neighborhoods such as lack of safety, lack of neighborhood cohesion, and financial struggles including inability to pay rent on time, utilities being shut off for late or missed payments has been associated with higher rates of chronic stress and mental health issues, which can inflict physiological damage including, but not limited to, cancer development (143, 144). Furthermore, early childhood abuse, neglect, and residing in a chaotic home environment has been reported to be more prevalent among AA children residing in poverty and is associated with elevated levels of inflammatory markers such as interleukin-6 (IL-6). Levels of IL-6 have been reported to be significantly higher in AA compared to EA BC patients (145-148). Hypermethylation of the glucocorticoid receptor gene has been found in suicide victims with a history of an abusive childhood but not in individuals with no history of childhood abuse (26). Stressors can also promote an increase in health-compromising or BC-promoting behaviors including increased fast food consumption, smoking, alcoholism, and physical inactivity, which are often coping mechanisms utilized among the AA community (144).

7.7. Education

AA women residing in public housing have been reported to lack sufficient knowledge on BC, were not aware that they are more susceptible to BC, and did not perceive the disease as fatal (149). AAs with low-incomes were also less likely to be aware that consuming a diet high in fat and low in fruits and vegetables as well as a positive family history of the disease may increase their risk for developing BC (149). Many AA women had not heard of terms such as BC subtypes, genomics, targeted therapy, personalized medicine, basal-like BC, TNBC, and BC microenvironment (150). However, among women who were aware of BC screening tests, compliance
was higher among AA compared to EA women (151). In addition, low education and lack of knowledge on BC have been associated with increased practicing of BC-promoting reproductive behaviors among AA women such as shorter breastfeeding duration and birthing more children (51, 152, 153).

7.8. Marital status

Married BC patients tend to be diagnosed at an early age and in an early stage of the disease as well as display smaller tumor size, node negative disease, reduced risk of death, and are white/other race in comparison to single patients. Female-headed households or single mother homes have been reported to be more prevalent among AA and socioeconomically-deprived communities. Studies have reported that female-headed households or single status in economically distressed neighborhoods were associated with reduced access to mammography facilities and late stage BC among all races and ethnicities (128, 154, 155). Furthermore, single motherhood and residing in socioeconomically-deprived neighborhoods has been associated with an increase in BC-promoting reproductive behaviors such as lack of breastfeeding (153, 156, 157).

8. DETOUR: EMBARKING ON OTHER AVENUES TO GET BACK ON TRACK

“When you come to a roadblock, tack a detour.” – Mary Kay Ash

Although BC has been the primary focus in this review, highlighting the role of co-morbid diseases in the racially disparate burden in BC may be just as pertinent. In this section, we propose addressing co-morbid diseases as an alternative strategy in alleviating the racially disparate burden in BC.

8.1. Obesity

Obesity has been suggested to underlie aggressive tumor biology and TNBC by activating phosphoprotein signaling, insulin signaling, and tissue inflammation (5). Thus, obesity can result in increased circulating insulin and pro-inflammatory cytokines such as IL-6, tumor necrosis factor TNF, leptin, chemokine (C-C motif) ligand 2 and transforming growth factor-β, which activate signaling networks involved in cell proliferation and genomic instability, including PI3K-AKT, signal transducer and activator of transcription 3, nuclear factor-κB, WNT-microRNA–p53, and Aurora A-polo-like kinase. Furthermore, dietary macronutrients can influence DNA methylation patterns of obesity-related genes (i.e. FGF2, PTEN, CCKN1A, and ESR1), adipogenesis-related genes (i.e. SOC1/SOCS3), inflammatory-related genes, and intermediary metabolism and insulin signaling pathway genes (26). Obesity has been linked to many lifestyle and environmental factors that AAs are more frequently exposed to than EAs such as low income, lack of access to grocery stores with fresh fruits and vegetables, unsafe neighborhoods, poor sleep quality, stressors such as racism and discrimination, environmental carcinogens, and physical inactivity (5, 158-161). As previously mentioned, AA BC patients harbor more pro-inflammatory cytokines such as IL-6 than EA BC patients. Furthermore, AAs show increased expression of IGF receptor (IGFR) and vascular endothelial growth factor genes compared to EAs (162). Thus, on average, AAs exhibit higher incidence of obesity than EAs, which has been suggested to underlie their more aggressive tumor biology and higher TNBC incidence rates (5, 163-165).

8.2. Diabetes mellitus

Diabetes mellitus can promote chronic inflammation by increasing levels of pro-inflammatory cytokines (5). Hyperinsulinemia and hyperglycemia are two conditions that are a result of diabetes and promote breast carcinogenesis (166). Hyperinsulinemia leads to an increase in IGF-1 levels by inhibiting the IGF binding protein 1. IGF-1 promotes cell proliferation and tumorigenesis through activating growth signaling pathways (166, 167). Hyperglycemia, or high glucose, can promote cancer cell proliferation through direct and indirect mechanisms (168). Some studies have reported that excess intake of sugary foods and carbohydrates, which metabolize into glucose, may be a plausible explanation underlying the development of the condition, however, recent evidence suggest that high dietary saturated fat may be the culprit of the disease (169-171). Diabetes frequently accompanies obesity (172). Thus, incidence of diabetes is often disproportionately higher among racial and ethnic minority groups compared to non-minorities (173), and type II diabetes has been associated with ER-negative BC among AA women (174).

8.3. Hypertension

High blood pressure, or hypertension, can promote chronic tissue inflammation, block and modify apoptosis, and subsequently breast tumorigenesis. Hypertension often co-occurs simultaneously with obesity and type II diabetes and is highest in the world among AAs, with prevalence of this condition reported over 40% among non-Hispanic AAs residing in the US (175). Lifestyle behaviors such as physical inactivity and high sodium intake have been suggested to be contributors to the onset of hypertension. Increased salt sensitivity, higher BMI, and a higher prevalence of refractory (or uncontrolled) blood pressure have been implicated as underling factors in the large gap in hypertension rates between AAs and other ethnic groups (176). Environmental factors such as unsafe
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neighbhors, lack of access to grocery stores, and stress has been associated with a higher prevalence of hypertension among the AA community (5). Racial disparities in hypertension independently predicted survival disparities between AA and EA BC patients (177).

9. TRAVEL GUIDE: NAVIGATING UNFAMILIAR TERRITORY IN OUR QUEST FOR HEALTH

“All adventures, especially new territory, are scary.” – Sally Ride

Culturally-derived beliefs, religious beliefs, and fatalism can prevent AA women from timely BC detection and receiving proper management and have been significantly associated with increased risk for late-stage BC among AA women (178). Next, we address how these barriers may be contributing to the racially disparate burden in BC.

9.1. Cultural perceptions

AA women have been reported to perceive themselves at a lower risk for developing BC compared to EA women and some view BC as a “White disease” (179-181). This low risk view may translate into a lower perceived need for mammography screening and delays in seeking medical attention (178). Some AA women believe that risk for BC increases with age and that younger age protects women from contracting the disease (150). Specifically, AA women residing in public housing were reported to not view themselves as more susceptible to BC, did not perceive BC as a fatal disease, assumed treatment of cancer to be as traumatic as having untreated cancer, and denied the existence of barriers to BC screening (149) (178). Additionally, a number of AA women have been reported to “expect the worst” regarding BC screening, believing that they will likely have an abnormal result and be diagnosed with late-stage disease prompting them to avoid seeking BC screening all together (182). Sadly, some women in the AA community have been reported to believe that surgery causes cancer to spread and is more harmful than it is helpful (183). Consequently, fatalism has emerged as a common perception of BC among many AA women believing that death is an inevitable outcome of the disease (182).

9.2. Religious beliefs

A number of AA women espouse unconventional spiritual beliefs including: only God can cure BC, only God has the power to decide life and death, and divine intervention or miracles can make the disease go away (184, 185). Prayer has been reported as a primary coping mechanism among older AA women with BC (186). These beliefs and practices may deter some AA women from ever seeking or seeking timely BC screening and treatment services, which can result in advanced-staged diagnosis and/or BC mortality (178, 179). Beliefs and practices that only God can cure BC, God is the only controller over health, leaving it in God’s hands, and only disclosing their BC symptoms to God has also been associated with decreased adherence to clinical breast examinations and mammogram recommendations as well as delays in seeking medical care (182, 187-188).

9.3. Fears

Fear often prevents some AA BC patients from seeking medical care. Fears reported regarding the mammogram process among some AA women include: fear of being disrespected by clinicians, pain and discomfort during the mammogram, embarrassment, lack of privacy, losing significant others, and an abnormal mammogram result or incorrect interpretation of the mammogram by their physician (126, 189). There are AA women who fear that death would inevitably result from a mammogram screening, causing them to avoid seeking the exam (182). Furthermore, many AA women fear physician incompetence, medical errors or unintentional harm, unethical experimentation with intent to harm, and discrimination. In particular, AA women reported fear of being recommended unnecessary mastectomy or “wrongful surgery”, as well as being perceived as unattractive or experiencing rejection from their partner after undergoing a mastectomy.

10. FINAL DESTINATION: ARRIVING AT RACIAL EQUALITY IN BC

“Difficult roads often lead to beautiful destinations.” – Hilary Hinton

The overarching aim of addressing the above outlined modifiable and anthropometric risk factors is the narrowing of the large gap in BC mortality rates between AA and EA women. We assert that it may be more pragmatic to target non-genetic risk factors that alter genetic and epigenetic programs to promote breast pathogenesis as summarized in Table 1. Environmental and lifestyle factors can also influence epigenetic mechanisms, such as DNA methylation, histone modifications, and microRNA expression (26). These genetic mutations and epigenetic alterations emerge as novel biomarkers from biological research studies and have become pharmacological targets in pre-clinical and clinical trials but often result in minimal success. However, these non-genetic risk factors can be easily modified by AA women, the community, and the system, which may prevent genetic alterations that are not easily targeted through clinical intervention as conveyed in Figure 3. We encourage
Table 1. Modifiable risk factors that increase BC risk and poor outcomes in AA women

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Mechanism of breast tumorigenesis/tumor progression</th>
<th>Behavioral modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High fat intake</td>
<td>Promotes the accumulation of adipose tissue, which is a site for the conversion of androstenedione to estrone or estrogen, linked to epigenetic alterations</td>
<td>Consume a low fat or plant-based diet; Avoid processed foods</td>
</tr>
<tr>
<td>• High cholesterol intake</td>
<td>Plasma levels in mice mammary tumors can increase cyclin D1 expression and decrease expression of proteins that protect against BC. Also, prevents modulation of the innate and adaptive immune system. Its insufficiency has been linked to a compromised immune defense system. The soluble hormone is more effective against aggressive breast tumor phenotypes.</td>
<td>Avoid or reduce intake of cholesterol-rich foods such as meat, eggs, and dairy</td>
</tr>
<tr>
<td>• Low dietary fiber intake</td>
<td>Increase the excretion of estrogens to inhibit the absorption of estrogens into the gut.</td>
<td>Consume fiber-rich foods such as fruits, vegetables, legumes, and whole grains</td>
</tr>
<tr>
<td>• Low vitamin D intake</td>
<td>Prevent bioactive form of vitamin D,1,25 (OH)2D, from interacting with VDR to reduce BC cell proliferation, angiogenesis, and metastasis as well as induce apoptosis and cell differentiation. Also, prevents modulation of the innate and adaptive immune system. Its insufficiency has been linked to a compromised immune defense system. The soluble hormone is more effective against aggressive breast tumor phenotypes.</td>
<td>Consume vitamin-D rich foods such as fatty fish, mushrooms, fortified milk, and tofu</td>
</tr>
<tr>
<td>• Lack of physical activity</td>
<td>Physical activity reduces the hormone, insulin, and IGF-1 levels as well as boost the anti-tumoral immune response and the accumulation of excess body fat, and has been linked to increased DNA methylation.</td>
<td>Engage in regular moderate to low intensity exercise</td>
</tr>
<tr>
<td>• Alcohol intake</td>
<td>Increases levels of endogenous estrogens while byproducts of alcohol metabolism can be toxic and lead to DNA modifications that promote cancer.</td>
<td>Reduce or avoid alcoholic beverages</td>
</tr>
<tr>
<td>• Lack of folate intake</td>
<td>Folate reduces the risk of alcohol-associated BC by neutralizing the toxic byproduct of alcohol metabolism, reactive oxygen species; Can interfere with maintenance of DNA methylation patterns.</td>
<td>Consume diet rich in fruits, vegetables, and legumes</td>
</tr>
<tr>
<td>• Poor sleep patterns</td>
<td>Melatonin, released during sleep, increases the inhibition of breast cell proliferation and invasion or through suppressing mitotic activity of endogenous hormones such as 17β-estradiol; Alter circadian rhythms that can reprogram circadian genes; Suppress the immune system and promote an increase in the presence of cancer-stimulatory cytokines.</td>
<td>Increase sleep duration and avoid sleep disturbances and circadian disruption</td>
</tr>
<tr>
<td><strong>Reproductive risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Parity</td>
<td>Induce differentiation of target structures, terminal-end buds, and terminal ducts for carcinogenesis.</td>
<td>Increase awareness among nulliparous women and encourage their participation in regular mammograms and breast self-exams</td>
</tr>
<tr>
<td>• Lack of breastfeeding</td>
<td>Lactation delays the reestablishment of ovulation after a woman gives birth.</td>
<td>Engage in and increase duration of breastfeeding after giving birth</td>
</tr>
<tr>
<td>• Early age at menarche</td>
<td>Exposure to greater cumulative levels of estrogen and progesterone during adolescent years.</td>
<td>Avoid risk factors for early onset of menarche such as poor diet and physical inactivity</td>
</tr>
<tr>
<td>• Oral contraceptives</td>
<td>Mimic the pregnancy state of a woman through raising the levels of estrogen and progesterin (a type of progesterone) in the body.</td>
<td>Use non-hormonal or natural based contraceptive methods</td>
</tr>
<tr>
<td>• Hormone replacement therapy</td>
<td>Increases exposure to estrogen.</td>
<td>Use non-hormonal treatments to alleviate menopausal symptoms</td>
</tr>
<tr>
<td><strong>Anthropometric/family history risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High BMI</td>
<td>Conversion of the androgen precursor, androstenedione, to estrone or endogenous estrogens occurs in adipose tissue.</td>
<td>Consume low fat diet and increase level of physical activity</td>
</tr>
<tr>
<td>• High breast density</td>
<td>Can foster aberrant mammary gland development, disrupt homeostasis in the breast microenvironment, and promote extracellular matrix and tissue stiffness, quantitative, or structural alterations of the stromal collagen such as cross-linking, to also foster breast pathogenesis.</td>
<td>Participate in annual BC screenings</td>
</tr>
<tr>
<td>• Positive family history</td>
<td>Inherited gene mutations associated with increased risk for BC, such as BRCA1 and BRCA2, and shared lifestyle factors that increase risk for breast pathogenesis.</td>
<td>Record and share family history with family members and primary care doctors, participate in annual BC screenings</td>
</tr>
<tr>
<td><strong>Environmental risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Endocrine-disrupting chemicals</td>
<td>Mimic the activity of estrogen in the body which may stimulate cancer cell proliferation, and accelerate cell invasion and migration.</td>
<td>Avoid use of EDC-containing products such as hair products and lotions</td>
</tr>
</tbody>
</table>
## Targeting risk factors in racial disparity in breast cancer

<table>
<thead>
<tr>
<th>Socioeconomic risk factors</th>
<th>Economic impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Late diagnosis</strong></td>
<td>Allows more time for tumors to growth, invade, and metastasize</td>
</tr>
<tr>
<td><strong>Poor access to quality healthcare</strong></td>
<td>Prevent control of tumor progression</td>
</tr>
<tr>
<td><strong>Lack of health insurance</strong></td>
<td>Unable to benefit from scientific advances in BC detection and treatment such as high-quality mammograms, follow-up after an abnormal mammogram, and targeted therapies that can eradicate tumors</td>
</tr>
<tr>
<td><strong>Area of residence</strong></td>
<td>Decrease in access to quality facilities, education, early detection screening, recreational facilities, and supermarkets that sell fruits and vegetables</td>
</tr>
<tr>
<td><strong>Stress</strong></td>
<td>Elevation of inflammatory markers such as IL-6; increase likelihood for consuming high fat and processed foods; increase likelihood for developing mental illness which can inflict physiological damage and promote carcinogenesis; Influence DNA methylation patterns; Can cause hypermethylation of glucocorticoid receptor gene</td>
</tr>
<tr>
<td><strong>Lack of education</strong></td>
<td>Lack of early detection screening and unawareness of engagement in behaviors that promote tumorigenesis</td>
</tr>
<tr>
<td><strong>Single marital status</strong></td>
<td>Less access to early detection screening and quality healthcare and increased engagement in reproductive behaviors that foster breast tumorigenesis</td>
</tr>
</tbody>
</table>

## Co-morbid diseases risk factors

<table>
<thead>
<tr>
<th>Co-morbid diseases risk factors</th>
<th>Economic impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity</strong></td>
<td>Can result in increased circulating insulin and pro-inflammatory cytokines such as IL-6, TNF, leptin, CCL2, and TGF-β, which activate signaling networks involved in cell proliferation and genomic instability, including PI3K-AKT, STAT3, NF-kB, WNT-miR34 –p53, and Aurora A-PLK; Dietary macronutrients can promote alterations in DNA methylation patterns of obesity-, adipogenesis-, inflammatory-, and insulin signaling-related genes</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>Increase levels of proinflammatory cytokines (8), hyperinsulinemia, and hyperglycemia; Hyperinsulinemia leads to an increase in IGF-1 levels by inhibiting the IGF binding protein 1. IGF-1 promote cell proliferation and tumorigenesis through activating growth signaling pathways. Hyperglycemia, or high glucose, can promote cancer cell proliferation through direct and indirect mechanisms</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>Promote chronic tissue inflammation and block and modify apoptosis</td>
</tr>
</tbody>
</table>

## Culturally-derived beliefs risk factors

<table>
<thead>
<tr>
<th>Culturally-derived beliefs risk factors</th>
<th>Economic impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cultural perceptions</strong></td>
<td>Lower perceived need for mammography screening and delays in seeking medical attention which can control tumor progression</td>
</tr>
<tr>
<td><strong>Religious beliefs</strong></td>
<td>Decreased adherence to clinical breast examinations, mammogram recommendations, and seeking medical attention which can prevent tumor progression</td>
</tr>
<tr>
<td><strong>Fears</strong></td>
<td>Avoid seeking medical exam and treatment which can prevent tumor progression</td>
</tr>
</tbody>
</table>

Abbreviations: 1,25-dihydroxyvitamin D (1,25 (OH)2D); C-C motif chemokine ligand 2 (CCL2); Insulin growth factor-1 (IGF-1); Interleukin-6 (IL-6); MicroRNA34 (miR34); Nuclear factor-κB (NF-κB); phosphatidylinositol-3-kinase (PI3K); Polo-like kinase (PLK); protein kinase B (AKT); Signal transducer and activator of transcription 3 (STAT3); Transforming growth factor-β (TGF-β); Tumor necrosis factor (TNF); Vitamin D receptor (VDR).
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strategies such as local, community-based programs, national intervention efforts, and local and national intervention initiatives that increase awareness, impart knowledge, and disseminate resources on BC risk factors, early screening methods, and treatment options while motivating changes in behaviors that promote BC development/progression among the AA community. We also emphasize the necessity of increased epidemiological research further investigating the role of these non-genetic risk factors in the racially disparate burden. Such studies would provide the basis for evidence-based interventions that aim to modify these behaviors that increase risk of developing BC or suffering from worse outcomes following BC. Many of these risk factors are interrelated, and targeting a few of them may eliminate many of them. Hence, increased targeting of non-genetic risk factors among women of African descent may address the root of the racially disparate burden in BC.

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**Key Words:** Modifiable Risk Factors, Anthropometric Risk Factors, African-American, Breast Cancer, Racial Disparity, Review

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