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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 FACTOS 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.

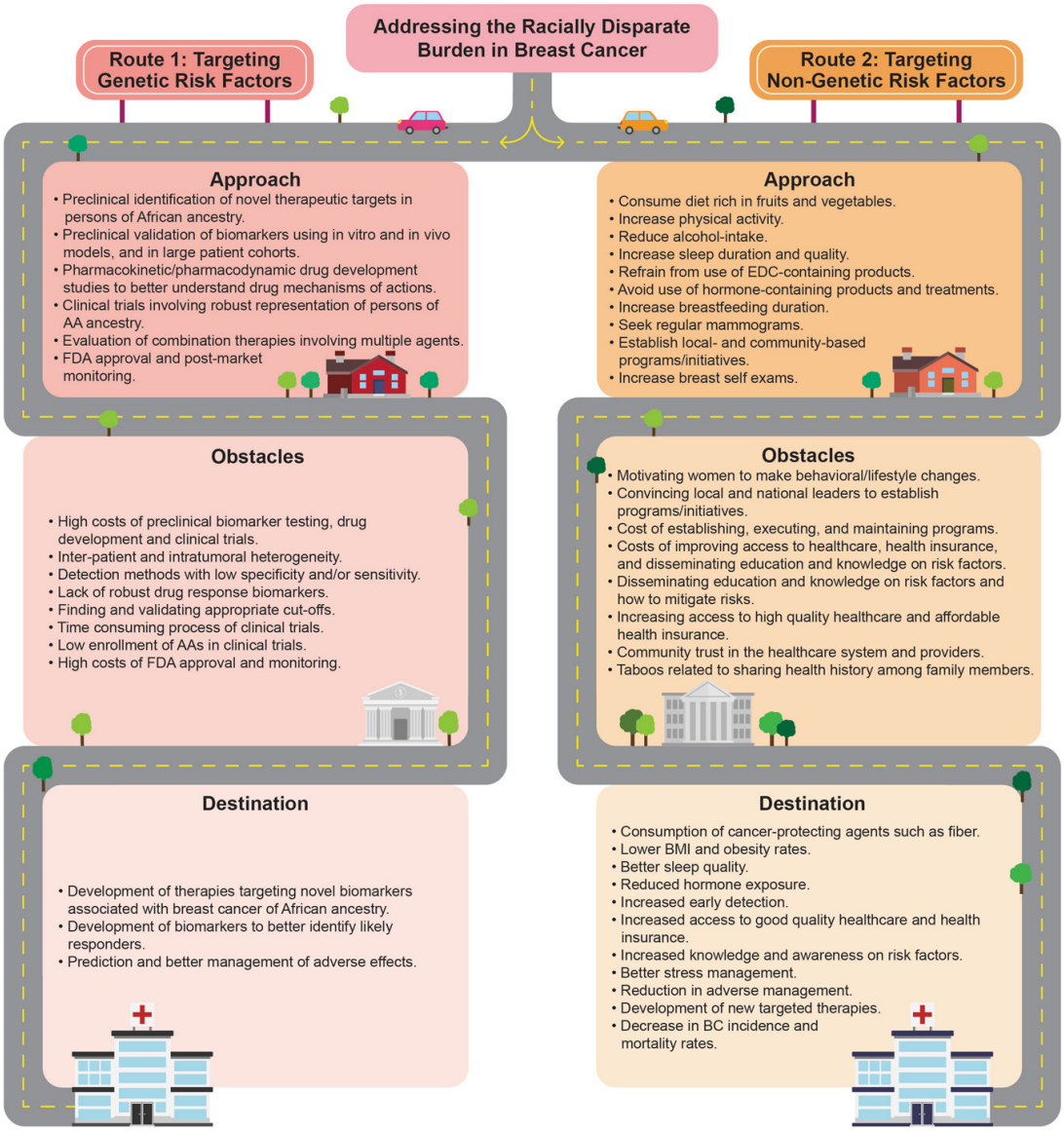

Figure 1. Genetic vs. Non-genetic route to reducing racial health disparity. Comparison of approaches and obstacles between addressing genetic versus non-genetic risk factors to reduce the racially disparate burden in BC.

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

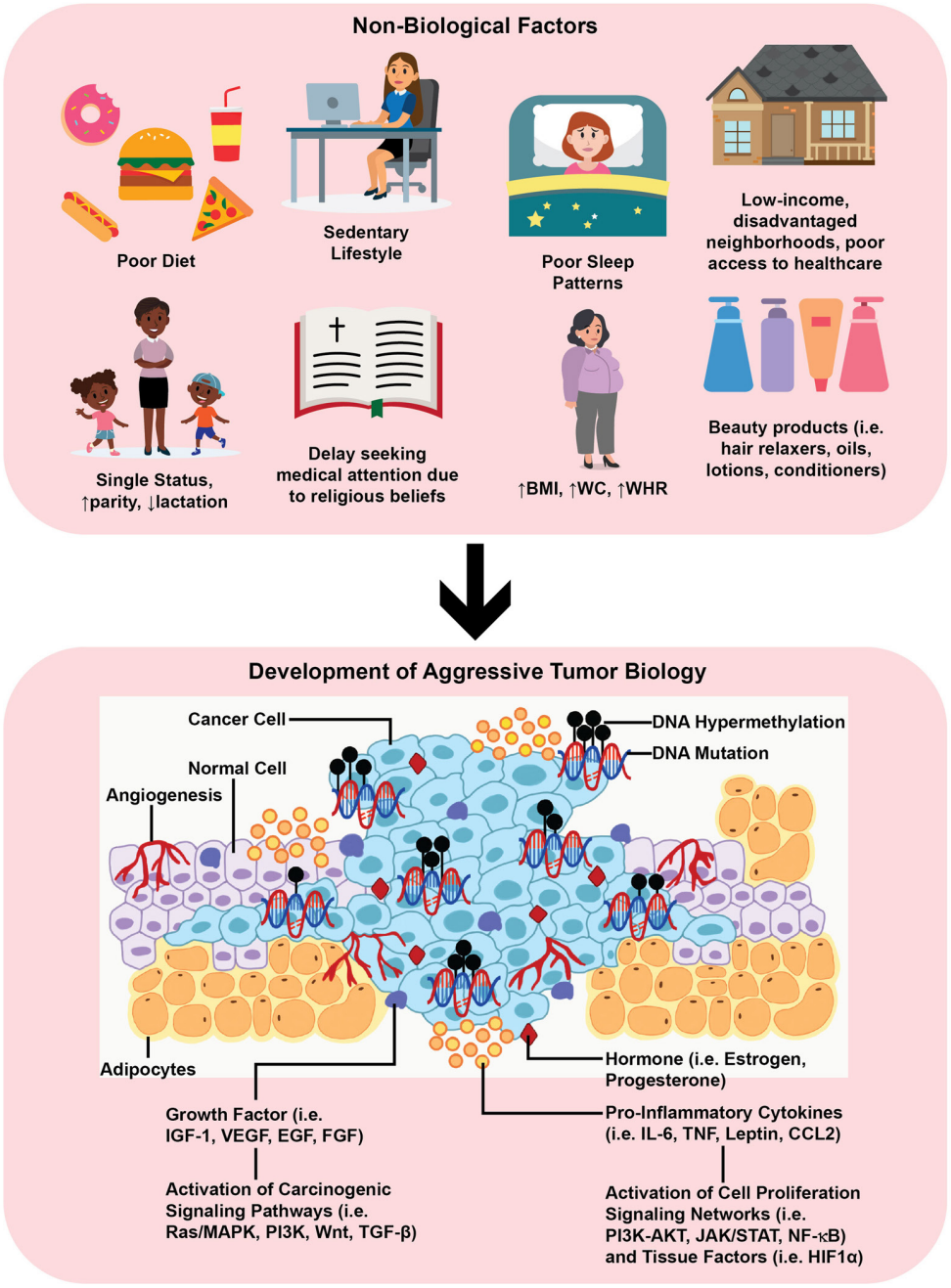

Figure 2. Influence of non-genetic risk factors on tumor biology**.** Schematic of various lifestyle and environmental factors that alter genetic and epigenetic programs to promote aggressive breast tumor biology. An increase in practicing of these lifestyle behaviors and exposure to these environmental carcinogens can lead to an increase in genetic and epigenetic modifications that underlie faster tumor progression.

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 (26). 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

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

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

neighborhoods, 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

Risk factor	Mechanism of breast tumorigenesis/tumor progression	Behavioral modifications
Lifestyle risk factors		
• High fat intake	Promotes the accumulation of adipose tissue, which is a site for the conversion of androstenedione to estrone or estrogen, linked to epigenetic alterations	Consume a low fat or plant-based diet; Avoid processed foods
• High cholesterol intake	Plasma levels in mice mammary tumors can increase cyclin D1 expression and decrease expression of proteins that protect against BC	Avoid or reduce intake of cholesterol-rich foods such as meat, eggs, and dairy
• Low dietary fiber intake	Increase the excretion of estrogens to inhibit the absorption of estrogens into the gut	Consume fiber-rich foods such as fruits, vegetables, legumes, and whole grains
• Low vitamin D levels	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.	Consume vitamin-D rich foods such as fatty fish, mushrooms, fortified milk, and tofu
• Lack of physical activity	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	Engage in regular moderate to low intensity exercise
• Alcohol intake	Increases levels of endogenous estrogens while byproducts of alcohol metabolism can be toxic and lead to DNA modifications that promote cancer	Reduce or avoid alcoholic beverages
• Lack of folate intake	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	Consume diet rich in fruits, vegetables, and legumes
• Poor sleep patterns	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 circadium rhythms that can reprogram circadian genes; Suppress the immune system and promote an increase in the presence of cancer-stimulatory cytokines	Increase sleep duration and avoid sleep disturbances and circadian disruption
Reproductive risk factors		
• Parity	Induce differentiation of target structures, terminal-end buds, and terminal ducts for carcinogenesis	Increase awareness among nulliparous women and encourage their participation in regular mammograms and breast self-exams
• Lack of breastfeeding	Lactation delays the reestablishment of ovulation after a woman gives birth	Engage in and increase duration of breastfeeding after giving birth
• Early age at menarche	Exposure to greater cumulative levels of estrogen and progesterone during adolescent years	Avoid risk factors for early onset of menarche such as poor diet and physical inactivity
• Oral contraceptives	Mimic the pregnancy state of a woman through raising the levels of estrogen and progestin (a type of progesterone) in the body	Use non-hormonal or natural based contraceptive methods
• Hormone replacement therapy	Increases exposure to estrogen	Use non-hormonal treatments to alleviate menopausal symptoms
Anthropometric/family history risk factors		
• High BMI	Conversion of the androgen precursor, androstenedione, to estrone or endogenous estrogens occurs in adipose tissue	Consume low fat diet and increase level of physical activity
• High breast density	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	Participate in annual BC screenings
• Positive family history	Inherited gene mutations associated with increased risk for BC, such as BRCA1 and BRCA2, and shared lifestyle factors that increase risk for breast pathogenesis	Record and share family history with family members and primary care doctors, participate in annual BC screenings
Environmental risk factors		
• Endocrine-disrupting chemicals (EDC)	Mimic the activity of estrogen in the body which may stimulate cancer cell proliferation, and accelerate cell invasion and migration	Avoid use of EDC-containing products such as hair products and lotions

Socioeconomic risk factors		
• Late diagnosis	Allows more time for tumors to growth, invade, and metastasize	Participate in regular mammograms or seek immediate medical attention upon suspicion of disease presence
• Poor access to quality healthcare	Prevent control of tumor progression	Local- and community-based programs/initiatives that implement strategies to improve access of the medically-underserved population to quality healthcare facilities and well-trained clinicians
• Lack of health insurance	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	Local- and community-based programs/initiatives that help gain access to healthcare insurance for the medically-underserved population
• Area of residence	Decrease in access to quality facilities, education, early detection screening, recreational facilities, and supermarkets that sell fruits and vegetables	Local- and community-based programs/initiatives that increase access to quality healthcare and early screening facilities as well as promote the incorporation of recreational facilities and grocery stores in disadvantaged neighborhoods
• Stress	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	Local- and community- based programs/ initiatives that provide support and psychological services that encourage strategies to help individuals cope positively in highly stressful circumstances and environments
• Lack of education	Lack of early detection screening and unawareness of engagement in behaviors that promote tumorigenesis	Local- and community- based programs/ initiatives that encourage the provision of services that provide current information on BC risk factors, biology of the disease, and early-detection methods
• Single marital status	Less access to early detection screening and quality healthcare and increased engagement in reproductive behaviors that foster breast tumorigenesis	Increase awareness among single mothers and local/community-based efforts dedicated to increasing access of single mothers to health insurance, quality healthcare, and knowledge on BC risk factors
Co-morbid diseases risk factors		
• Obesity	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-κB, 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	Consume low fat diet and increase level of physical activity
• Diabetes mellitus	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	Consume diet rich in fruits, vegetables, legumes, and whole grains; Increase physical activity
• Hypertension	Promote chronic tissue inflammation and block and modify apoptosis	Consume low fat diet and increase level of physical activity
Culturally-derived beliefs risk factors		
• Cultural perceptions	Lower perceived need for mammography screening and delays in seeking medical attention which can control tumor progression	Local- and community-based programs that increase awareness of the repercussions of not seeking immediate medical attention or participating in early-detection screening
• Religious beliefs	Decreased adherence to clinical breast examinations, mammogram recommendations, and seeking medical attention which can prevent tumor progression	Local- and community-based programs that increase awareness of the repercussions of not seeking immediate medical attention or participating in early-detection screening
• Fears	Avoid seeking medical exam and treatment which can prevent tumor progression	Local/community-based efforts that dispel myths and false perceptions of the cancer screening and treatment process as well as reduce discrimination in healthcare facilities

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).

Figure 3. Preventable disparity. Recommendations on how to address the racial disparity in modifiable risk factors at the individual-, community-, and system-level to proactively prevent or reduce the racially disparate burden in BC.

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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12. REFERENCES

1. C. DeSantis, J. Ma, L. Bryan and A. Jemal: Breast cancer statistics, 2013. *CA Cancer J Clin*, 64 (1), 52-62 (2014)
DOI: 10.3322/caac.21203

2. C. E. DeSantis, J. Ma, A. Goding Sauer, L. A. Newman and A. Jemal: Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin*, 67 (6), 439-448 (2017)
DOI: 10.3322/caac.21412

3. C. G. Yedjou, P. B. Tchounwou, M. Payton, L. Miele, D. D. Fonseca, L. Lowe and R. A. Alo: Assessing the Racial and Ethnic Disparities in Breast Cancer Mortality in the United States. *Int J Environ Res Public Health*, 14 (5) (2017)
DOI: 10.3390/ijerph14050486

4. K. R. Bauer, M. Brown, R. D. Cress, C. A. Parise and V. Caggiano: 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*, 109 (9), 1721-8 (2007)
DOI: 10.1002/cncr.22618

5. E. C. Dietze, C. Sistrunk, G. Miranda-Carboni, R. O'Regan and V. L. Seewaldt: Triple-negative breast cancer in African-American women: disparities versus biology. *Nat Rev Cancer*, 15 (4), 248-54 (2015)
DOI: 10.1038/nrc3896

6. M. J. Lund, K. F. Trivers, P. L. Porter, R. J. Coates, B. Leyland-Jones, O. W. Brawley, E. W. Flagg, R. M. O'Regan, S. G. Gabram and J. W. Eley: Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. *Breast Cancer Res Treat*, 113 (2), 357-70 (2009)
DOI: 10.1007/s10549-008-9926-3

7. C. Printz: Failure rate: Why many cancer drugs don't receive FDA approval, and what can be done about it. *Cancer*, 121 (10), 1529-30 (2015)
DOI: 10.1002/cncr.28994

8. D. A. Gewirtz, M. L. Bristol and J. C. Yalowich: Toxicity issues in cancer drug development. *Curr Opin Investig Drugs*, 11 (6), 612-4 (2010)
PMid:20496255

9. T. Hermanson, L. B. Norris, J. Bian, O. Sartor and C. L. Bennett: Toxicity and costs of toxicity associated with new cancer drugs: international implications. *J Clin Oncol*, 32 (32), 3591-2 (2014)
DOI: 10.1200/JCO.2014.57.2404

10. S. Niraula, B. Seruga, A. Ocana, T. Shao, R. Goldstein, I. F. Tannock and E. Amir: The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. *J Clin Oncol*, 30 (24), 3012-9 (2012)
DOI: 10.1200/JCO.2011.40.3824

11. D. Olsen and J. T. Jorgensen: Companion diagnostics for targeted cancer drugs - clinical and regulatory aspects. *Front Oncol*, 4, 105 (2014)
DOI: 10.3389/fonc.2014.00105

12. S. J. Mandrekar and D. J. Sargent: Design of clinical trials for biomarker research in oncology. *Clin Investig (Lond)*, 1 (12), 1629-1636 (2011)
DOI: 10.4155/cli.11.152

13. C. S. Wilhelm-Benartzi, S. Mt-Isa, F. Fiorentino, R. Brown and D. Ashby: Challenges and methodology in the incorporation of biomarkers in cancer clinical trials. *Crit Rev Oncol Hematol*, 110, 49-61 (2017)
DOI: 10.1016/j.critrevonc.2016.12.008

14. S. Amin and O. F. Bathe: Response biomarkers: re-envisioning the approach to tailoring drug therapy for cancer. *BMC Cancer*, 16 (1), 850 (2016)
DOI: 10.1186/s12885-016-2886-9

15. M. Werner, A. Chott, A. Fabiano and H. Battifora: Effect of formalin tissue fixation and processing on immunohistochemistry. *Am J Surg Pathol*, 24 (7), 1016-9 (2000)
DOI: 10.1097/00000478-200007000-00014
PMid:10895825

16. V. K. Anagnostou, A. W. Welsh, J. M. Giltnane, S. Siddiqui, C. Liceaga, M. Gustavson, K. N. Syrigos, J. L. Reiter and D. L. Rimm: Analytic variability in immunohistochemistry biomarker studies. *Cancer Epidemiol Biomarkers Prev*, 19 (4), 982-91 (2010)
DOI: 10.1158/1055-9965.EPI-10-0097

17. S. J. Potts, J. S. Krueger, N. D. Landis, D. A. Eberhard, G. D. Young, S. C. Schmechel and H. Lange: Evaluating tumor heterogeneity in immunohistochemistry-stained breast cancer tissue. *Lab Invest*, 92 (9), 1342-57 (2012)
DOI: 10.1038/labinvest.2012.91

18. C. R. Taylor and R. M. Levenson: Quantification of immunohistochemistry--issues concerning methods, utility and semiquantitative assessment II. *Histopathology*, 49 (4), 411-24 (2006)
DOI: 10.1111/j.1365-2559.2006.02513.x

19. R. F. Brown, D. L. Cadet, R. H. Houlihan, M. D. Thomson, E. C. Pratt, A. Sullivan and L. A. Siminoff: Perceptions of participation in a phase I, II, or III clinical trial among African American patients with cancer: what do refusers say? *J Oncol Pract*, 9 (6), 287-93 (2013)
DOI: 10.1200/JOP.2013.001039

20. K. McPherson, C. M. Steel and J. M. Dixon: ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. *BMJ*, 321 (7261), 624-8 (2000)
DOI: 10.1136/bmj.321.7261.624
PMid:10977847 PMCid:PMC1118507

21. R. L. Siegel, K. D. Miller and A. Jemal: Cancer Statistics, 2017. *CA Cancer J Clin*, 67 (1), 7-30 (2017)
DOI: 10.3322/caac.21387

22. D. P. Rose: Effects of dietary fatty acids on breast and prostate cancers: evidence from *in vitro* experiments and animal studies. *Am J Clin Nutr*, 66 (6 Suppl), 1513S-1522S (1997)
DOI: 10.1093/ajcn/66.6.1513S
PMid:9394709

23. M. A. Moore, C. B. Park and H. Tsuda: Soluble and insoluble fiber influences on cancer development. *Crit Rev Oncol Hematol*, 27 (3), 229-42 (1998)
DOI: 10.1016/S1040-8428(98)00006-7

24. G. Llaverias, C. Danilo, I. Mercier, K. Daumer, F. Capozza, T. M. Williams, F. Sotgia, M. P. Lisanti and P. G. Frank: Role of cholesterol in the development and progression of breast cancer. *Am J Pathol*, 178 (1), 402-12 (2011)
DOI: 10.1016/j.ajpath.2010.11.005

25. M. Hewison: Vitamin D and immune function: an overview. *Proc Nutr Soc*, 71 (1), 50-61 (2012)
DOI: 10.1017/S0029665111001650

26. R. A. Forshee, M. L. Storey and C. Ritenbaugh: Breast cancer risk and lifestyle differences among premenopausal and postmenopausal African-American women and white women. *Cancer*, 97 (1 Suppl), 280-8 (2003)
DOI: 10.1002/cncr.11020

27. S. Nesby-O'Dell, K. S. Scanlon, M. E. Cogswell, C. Gillespie, B. W. Hollis, A. C. Looker, C. Allen, C. Doughertly, E. W. Gunter and B. A. Bowman: Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr*, 76 (1), 187-92 (2002)
DOI: 10.1093/ajcn/76.1.187

28. S. Yao and C. B. Ambrosone: Associations between vitamin D deficiency and risk of aggressive breast cancer in African-American women. *J Steroid Biochem Mol Biol*, 136, 337-41 (2013)
DOI: 10.1016/j.jsbmb.2012.09.010

29. P. Gordon-Larsen, R. G. McMurray and B. M. Popkin: Adolescent physical activity and inactivity vary by ethnicity: The National Longitudinal Study of Adolescent Health. *J Pediatr*, 135 (3), 301-6 (1999)
DOI: 10.1016/S0022-3476(99)70124-1

30. S. Schmidt, J. M. Monk, L. E. Robinson and M. Mourtzakis: The integrative role of leptin, oestrogen and the insulin family in obesity-associated breast cancer: potential effects of exercise. *Obes Rev*, 16 (6), 473-87 (2015)
DOI: 10.1111/obr.12281

31. V. B. Sheppard, K. Makambi, T. Taylor, S. F. Wallington, J. Sween and L. Adams-Campbell: Physical activity reduces breast cancer risk in African American women. *Ethn Dis*, 21 (4), 406-11 (2011)
PMid:22428342 PMCid:PMC3760197

32. G. D. Coronado, J. Beasley and J. Livaudais: Alcohol consumption and the risk of breast cancer. *Salud Publica Mex*, 53 (5), 440-7 (2011)
PMid:22218798

33. T. E. Fuller-Rowell, D. S. Curtis, M. El-Sheikh, D. H. Chae, J. M. Boylan and C. D. Ryff: Racial disparities in sleep: the role of neighborhood disadvantage. *Sleep Med*, 27-28, 1-8 (2016)
DOI: 10.1016/j.sleep.2016.10.008

34. A. Soucise, C. Vaughn, C. L. Thompson, A. E. Millen, J. L. Freudenheim, J. Wactawski-Wende, A. I. Phipps, L. Hale, L. Qi and H. M. Ochs-Balcom: Sleep quality, duration, and breast cancer aggressiveness. *Breast Cancer Res Treat*, 164 (1), 169-178 (2017)
DOI: 10.1007/s10549-017-4245-1

35. Q. Xiao, L. B. Signorello, L. A. Brinton, S. S. Cohen, W. J. Blot and C. E. Matthews: Sleep duration and breast cancer risk among black and white women. *Sleep Med*, 20, 25-9 (2016)
DOI: 10.1016/j.sleep.2015.11.010

36. V. N. Anisimov: The role of pineal gland in breast cancer development. *Crit Rev Oncol Hematol*, 46 (3), 221-34 (2003)
DOI: 10.1016/S1040-8428(03)00021-0

37. D. Aeschbach, L. Sher, T. T. Postolache, J. R. Matthews, M. A. Jackson and T. A. Wehr: A longer biological night in long sleepers than in short sleepers. *J Clin Endocrinol Metab*, 88 (1), 26-30 (2003)
DOI: 10.1210/jc.2002-020827

38. A. V. Gandhi, E. A. Mosser, G. Oikonomou and D. A. Prober: Melatonin is required for the circadian regulation of sleep. *Neuron*, 85 (6), 1193-9 (2015)
DOI: 10.1016/j.neuron.2015.02.016

39. C. L. Jackson, S. Redline, I. Kawachi, M. A. Williams and F. B. Hu: Racial disparities in short sleep duration by occupation and industry. *Am J Epidemiol*, 178 (9), 1442-51 (2013)
DOI: 10.1093/aje/kwt159

40. D. E. Blask: Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev*, 13 (4), 257-64 (2009)
DOI: 10.1016/j.smrv.2008.07.007

41. J. L. Kelsey, M. D. Gammon and E. M. John: Reproductive factors and breast cancer. *Epidemiol Rev*, 15 (1), 36-47 (1993)
DOI: 10.1093/oxfordjournals.epirev.a036115
PMid:8405211

42. M. D. Althuis, J. H. Fergenbaum, M. Garcia-Closas, L. A. Brinton, M. P. Madigan and M. E. Sherman: Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev*, 13 (10), 1558-68 (2004)
PMid:15466970

43. H. Ma, L. Bernstein, M. C. Pike and G. Ursin: Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res*, 8 (4), R43 (2006)
DOI: 10.1186/bcr1525

44. L. Rajkumar, R. C. Guzman, J. Yang, G. Thordarson, F. Talamantes and S. Nandi: Short-term exposure to pregnancy levels of estrogen prevents mammary carcinogenesis. *Proc Natl Acad Sci U S A*, 98 (20), 11755-9 (2001)
DOI: 10.1073/pnas.201393798

45. C. B. Ambrosone, G. Zirpoli, M. Ruszczyk, J. Shankar, C. C. Hong, D. McIlwain, M. Roberts, S. Yao, S. E. McCann, G. Ciupak, H. Hwang, T. Khoury, L. Jandorf, D. H. Bovbjerg, K. Pawlish and E. V. Bandera: Parity and breastfeeding among African-American women: differential effects on breast cancer risk by estrogen receptor status in the Women's Circle of Health Study. *Cancer Causes Control*, 25 (2), 259-65 (2014)
DOI: 10.1007/s10552-013-0323-9

46. M. L. Kwan, L. H. Kushi, E. Weltzien, B. Maring, S. E. Kutner, R. S. Fulton, M. M. Lee, C. B. Ambrosone and B. J. Caan: Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res*, 11 (3), R31 (2009)
DOI: 10.1186/bcr2261

47. S. J. Lord, L. Bernstein, K. A. Johnson, K. E. Malone, J. A. McDonald, P. A. Marchbanks, M. S. Simon, B. L. Strom, M. F. Press, S. G. Folger, R. T. Burkman, D. Deapen, R. Spirtas and G. Ursin: Breast cancer risk and hormone receptor status in older women by parity, age of first birth, and breastfeeding: a case-control study. *Cancer Epidemiol Biomarkers Prev*, 17 (7), 1723-30 (2008)
DOI: 10.1158/1055-9965.EPI-07-2824

48. R. C. Millikan, B. Newman, C. K. Tse, P. G. Moorman, K. Conway, L. G. Dressler, L. V. Smith, M. H. Labbok, J. Geradts, J. T. Bensen, S. Jackson, S. Nyante, C. Livasy, L. Carey, H. S. Earp and C. M. Perou: Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat*, 109 (1), 123-39 (2008)
DOI: 10.1007/s10549-007-9632-6

49. J. R. Palmer, D. A. Boggs, L. A. Wise, C. B. Ambrosone, L. L. Adams-Campbell and L. Rosenberg: Parity and lactation in relation to estrogen receptor negative breast cancer in African American women. *Cancer Epidemiol Biomarkers Prev*, 20 (9), 1883-91 (2011)
DOI: 10.1158/1055-9965.EPI-11-0465

50. S. S. Shinde, M. R. Forman, H. M. Kuerer, K. Yan, F. Peintinger, K. K. Hunt, G. N. Hortobagyi, L. Pusztai and W. F. Symmans: Higher parity and shorter breastfeeding duration: association with triple-negative phenotype of breast cancer. *Cancer*, 116 (21), 4933-43 (2010)
DOI: 10.1002/cncr.25443

51. J. R. Palmer, L. A. Wise, N. J. Horton, L. L. Adams-Campbell and L. Rosenberg: Dual effect of parity on breast cancer risk in African-American women. *J Natl Cancer Inst*, 95 (6), 478-83 (2003)
DOI: 10.1093/jnci/95.6.478
PMid:12644541

52. D. E. Ramos: Breastfeeding: a bridge to addressing disparities in obesity and health. *Breastfeed Med*, 7 (5), 354-7 (2012)
DOI: 10.1089/bfm.2012.0076

53. L. Bernstein, C. R. Teal, S. Joslyn and J. Wilson: Ethnicity-related variation in breast cancer risk factors. *Cancer*, 97 (1 Suppl), 222-9 (2003)
DOI: 10.1002/cncr.11014

54. J. R. Palmer, E. Viscidi, M. A. Troester, C. C. Hong, P. Schedin, T. N. Bethea, E. V. Bandera, V. Borges, C. McKinnon, C. A. Haiman, K. Lunetta, L. N. Kolonel, L. Rosenberg,

A. F. Olshan and C. B. Ambrosone: Parity, lactation, and breast cancer subtypes in African American women: results from the AMBER Consortium. *J Natl Cancer Inst*, 106 (10) (2014)
DOI: 10.1093/jnci/dju237

55. D. Apter and R. Vihko: Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles. *J Clin Endocrinol Metab*, 57 (1), 82-6 (1983)
DOI: 10.1210/jcem-57-1-82

56. G. L. Burke, P. J. Savage, T. A. Manolio, J. M. Sprafka, L. E. Wagenknecht, S. Sidney, L. L. Perkins, K. Liu and D. R. Jacobs, Jr.: Correlates of obesity in young black and white women: the CARDIA Study. *Am J Public Health*, 82 (12), 1621-5 (1992)
DOI: 10.2105/AJPH.82.12.1621
PMid:1456336 PMCid:PMC1694535

57. W. A. Wattigney, S. R. Srinivasan, W. Chen, K. J. Greenlund and G. S. Berenson: Secular trend of earlier onset of menarche with increasing obesity in black and white girls: the Bogalusa Heart Study. *Ethn Dis*, 9 (2), 181-9 (1999)
PMid:10421080

58. N. Krieger, M. V. Kiang, A. Kosheleva, P. D. Waterman, J. T. Chen and J. Beckfield: Age at menarche: 50-year socioeconomic trends among US-born black and white women. *Am J Public Health*, 105 (2), 388-97 (2015)
DOI: 10.2105/AJPH.2014.301936

59. C. B. Ambrosone, G. Zirpoli, C. C. Hong, S. Yao, M. A. Troester, E. V. Bandera, P. Schedin, T. N. Bethea, V. Borges, S. Y. Park, D. Chandra, L. Rosenberg, L. N. Kolonel, A. F. Olshan and J. R. Palmer: Important Role of Menarche in Development of Estrogen Receptor-Negative Breast Cancer in African American Women. *J Natl Cancer Inst*, 107 (9) (2015)
DOI: 10.1093/jnci/djv172

60. L. Aksglaede, A. Juul, H. Leffers, N. E. Skakkebaek and A. M. Andersson: The sensitivity of the child to sex steroids: possible impact of exogenous estrogens. *Hum Reprod Update*, 12 (4), 341-9 (2006)
DOI: 10.1093/humupd/dml018

61. L. Aksglaede, A. Juul, L. W. Olsen and T. I. Sorensen: Age at puberty and the emerging obesity epidemic. *PLoS One*, 4 (12), e8450 (2009)
DOI: 10.1371/journal.pone.0008450

62. G. Cheng, S. Gerlach, L. Libuda, S. Kranz, A. L. Gunther, N. Karaolis-Danckert, A. Kroke and A. E. Buyken: Diet quality in childhood is prospectively associated with the timing of puberty but not with body composition at puberty onset. *J Nutr*, 140 (1), 95-102 (2010)
DOI: 10.3945/jn.109.113365

63. E. Diamanti-Kandarakis, J. P. Bourguignon, L. C. Giudice, R. Hauser, G. S. Prins, A. M. Soto, R. T. Zoeller and A. C. Gore: Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev*, 30 (4), 293-342 (2009) 2
DOI: 10.1210/er.2009-0002

64. A. L. Gunther, N. Karaolis-Danckert, A. Kroke, T. Remer and A. E. Buyken: Dietary protein intake throughout childhood is associated with the timing of puberty. *J Nutr*, 140 (3), 565-71 (2010)
DOI: 10.3945/jn.109.114934

65. P. B. Kaplowitz: Link between body fat and the timing of puberty. *Pediatrics*, 121 Suppl 3, S208-17 (2008)
DOI: 10.1542/peds.2007-1813F

66. I. S. Rogers, K. Northstone, D. B. Dunger, A. R. Cooper, A. R. Ness and P. M. Emmett: Diet throughout childhood and age at menarche in a contemporary cohort of British girls. *Public Health Nutr*, 13 (12), 2052-63 (2010) d
DOI: 10.1017/S1368980010001461

67. J. R. Roy, S. Chakraborty and T. R. Chakraborty: Estrogen-like endocrine disrupting chemicals affecting puberty in humans--a review. *Med Sci Monit*, 15 (6), RA137-45 (2009)
PMid:19478717

68. M. J. Vandeloo, L. M. Bruckers and J. P. Janssens: Effects of lifestyle on the onset of puberty as determinant for breast cancer. *Eur J Cancer Prev*, 16 (1), 17-25 (2007)
DOI: 10.1097/01.cej.0000220635.38847.6e

69. J. D. Veldhuis, J. N. Roemmich, E. J. Richmond, A. D. Rogol, J. C. Lovejoy, M. Sheffield-Moore, N. Mauras and C. Y. Bowers: Endocrine control of body composition in infancy, childhood, and puberty. *Endocr Rev*, 26 (1), 114-46 (2005)
DOI: 10.1210/er.2003-0038

70. A. S. Wiley: Milk intake and total dairy consumption: associations with early menarche in NHANES 1999-2004. *PLoS*

One, 6 (2), e14685 (2011)
DOI: 10.1371/journal.pone.0014685

71. Z. Huang, S. E. Hankinson, G. A. Colditz, M. J. Stampfer, D. J. Hunter, J. E. Manson, C. H. Hennekens, B. Rosner, F. E. Speizer and W. C. Willett: Dual effects of weight and weight gain on breast cancer risk. *JAMA*, 278 (17), 1407-11 (1997)
DOI: 10.1001/jama.1997.03550170037029
DOI: 10.1001/jama.278.17.1407
PMid:9355998

72. D. J. Hunter and W. C. Willett: Diet, body size, and breast cancer. *Epidemiol Rev*, 15 (1), 110-32 (1993)
DOI: 10.1093/oxfordjournals.epirev.a036096
PMid:8405195

73. P. A. van den Brandt, D. Spiegelman, S. S. Yaun, H. O. Adami, L. Beeson, A. R. Folsom, G. Fraser, R. A. Goldbohm, S. Graham, L. Kushi, J. R. Marshall, A. B. Miller, T. Rohan, S. A. Smith-Warner, F. E. Speizer, W. C. Willett, A. Wolk and D. J. Hunter: Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*, 152 (6), 514-27 (2000)
DOI: 10.1093/aje/152.6.514
PMid:10997541

74. J. R. Daling, K. E. Malone, D. R. Doody, L. G. Johnson, J. R. Gralow and P. L. Porter: Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. *Cancer*, 92 (4), 720-9 (2001)
DOI: 10.1002/1097-0142(20010815)92:4<720::AID-CNCR1375>3.0.CO;2-T

75. P. J. Goodwin and N. F. Boyd: Body size and breast cancer prognosis: a critical review of the evidence. *Breast Cancer Res Treat*, 16 (3), 205-14 (1990)
DOI: 10.1007/BF01806329
PMid:2085672

76. A. Y. El-Bastawissi, E. White, M. T. Mandelson and S. Taplin: Variation in mammographic breast density by race. *Ann Epidemiol*, 11 (4), 257-63 (2001)
DOI: 10.1016/S1047-2797(00)00225-8

77. L. A. Habel, A. M. Capra, N. Oestreicher, G. A. Greendale, J. A. Cauley, J. Bromberger, C. J. Crandall, E. B. Gold, F. Modugno, M. Salane, C. Quesenberry and B. Sternfeld: Mammographic density in a multiethnic cohort. *Menopause*, 14 (5), 891-9 (2007)
DOI: 10.1097/gme.0b013e318032569c

78. G. Ursin, H. Ma, A. H. Wu, L. Bernstein, M. Salane, Y. R. Parisky, M. Astrahan, C. C. Siozon and M. C. Pike: Mammographic density and breast cancer in three ethnic groups. *Cancer Epidemiol Biomarkers Prev*, 12 (4), 332-8 (2003)
PMid:12692108

79. L. J. Martin and N. F. Boyd: Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. *Breast Cancer Res*, 10 (1), 201 (2008)
DOI: 10.1186/bcr1831

80. T. A. Sellers, C. M. Vachon, V. S. Pankratz, C. A. Janney, Z. Fredericksen, K. R. Brandt, Y. Huang, F. J. Couch, L. H. Kushi and J. R. Cerhan: Association of childhood and adolescent anthropometric factors, physical activity, and diet with adult mammographic breast density. *Am J Epidemiol*, 166 (4), 456-64 (2007)
DOI: 10.1093/aje/kwm112

81. A. Pettersson and R. M. Tamimi: Breast fat and breast cancer. *Breast Cancer Res Treat*, 135 (1), 321-3 (2012)
DOI: 10.1007/s10549-012-2186-2

82. S. Ching, S. Kashinkunti, M. D. Niehaus and G. M. Zinser: Mammary adipocytes bioactivate 25-hydroxyvitamin D (3) and signal via vitamin D (3) receptor, modulating mammary epithelial cell growth. *J Cell Biochem*, 112 (11), 3393-405 (2011) d
DOI: 10.1002/jcb.23273

83. V. Brower: Homing in on mechanisms linking breast density to breast cancer risk. *J Natl Cancer Inst*, 102 (12), 843-5 (2010)
DOI: 10.1093/jnci/djq230

84. P. P. Provenzano, D. R. Inman, K. W. Eliceiri and P. J. Keely: Matrix density-induced mechanoregulation of breast cell phenotype, signaling and gene expression through a FAK-ERK linkage. *Oncogene*, 28 (49), 4326-43 (2009)
DOI: 10.1038/onc.2009.299

85. L. Ronnov-Jessen and M. J. Bissell: Breast cancer by proxy: can the microenvironment

be both the cause and consequence? *Trends Mol Med*, 15 (1), 5-13 (2009)
DOI: 10.1016/j.molmed.2008.11.001

86. K. A. Metcalfe, A. Finch, A. Poll, D. Horsman, C. Kim-Sing, J. Scott, R. Royer, P. Sun and S. A. Narod: Breast cancer risks in women with a family history of breast or ovarian cancer who have tested negative for a BRCA1 or BRCA2 mutation. *Br J Cancer*, 100 (2), 421-5 (2009)
DOI: 10.1038/sj.bjc.6604830

87. J. R. Palmer, D. A. Boggs, L. L. Adams-Campbell and L. Rosenberg: Family history of cancer and risk of breast cancer in the Black Women's Health Study. *Cancer Causes Control*, 20 (9), 1733-7 (2009)
DOI: 10.1007/s10552-009-9425-9

88. M. Donovan, C. M. Tiwary, D. Axelrod, A. J. Sasco, L. Jones, R. Hajek, E. Sauber, J. Kuo and D. L. Davis: Personal care products that contain estrogens or xenoestrogens may increase breast cancer risk. *Med Hypotheses*, 68 (4), 756-66 (2007)
DOI: 10.1016/j.mehy.2006.09.039

89. L. A. Brinton, J. Benichou, M. D. Gammon, D. R. Brogan, R. Coates and J. B. Schoenberg: Ethnicity and variation in breast cancer incidence. *Int J Cancer*, 73 (3), 349-55 (1997)
DOI: 10.1002/(SICI)1097-0215(19971104)73:3<349::AID-IJC8>3.0.CO;2-#

90. T. N. Bethea, L. Rosenberg, C. C. Hong, M. A. Troester, K. L. Lunetta, E. V. Bandera, P. Schedin, L. N. Kolonel, A. F. Olshan, C. B. Ambrosone and J. R. Palmer: A case-control analysis of oral contraceptive use and breast cancer subtypes in the African American Breast Cancer Epidemiology and Risk Consortium. *Breast Cancer Res*, 17, 22 (2015)
DOI: 10.1186/s13058-015-0535-x

91. P. G. Moorman, R. C. Millikan and B. Newman: Oral contraceptives and breast cancer among African-american women and white women. *J Natl Med Assoc*, 93 (9), 329-34 (2001)
PMid:11560288 PMCid:PMC2593962

92. J. R. Palmer, L. Rosenberg, R. S. Rao, B. L. Strom, M. E. Warshauer, S. Harlap, A. Zauber and S. Shapiro: Oral contraceptive use and breast cancer risk among African-American women. *Cancer Causes Control*, 6 (4), 321-31 (1995)
DOI: 10.1007/BF00051407
PMid:7548719

93. P. M. Marcus, D. D. Baird, R. C. Millikan, P. G. Moorman, B. Qaqish and B. Newman: Adolescent reproductive events and subsequent breast cancer risk. *Am J Public Health*, 89 (8), 1244-7 (1999)
DOI: 10.2105/AJPH.89.8.1244
PMid:10432916 PMCid:PMC1508686

94. L. Rosenberg, D. A. Boggs, L. A. Wise, L. L. Adams-Campbell and J. R. Palmer: Oral contraceptive use and estrogen/progesterone receptor-negative breast cancer among African American women. *Cancer Epidemiol Biomarkers Prev*, 19 (8), 2073-9 (2010)
DOI: 10.1158/1055-9965.EPI-10-0428

95. A. K. Charles and P. D. Darbre: Combinations of parabens at concentrations measured in human breast tissue can increase proliferation of MCF-7 human breast cancer cells. *J Appl Toxicol*, 33 (5), 390-8 (2013)
DOI: 10.1002/jat.2850

96. T. H. Hsieh, C. F. Tsai, C. Y. Hsu, P. L. Kuo, E. Hsi, J. L. Suen, C. H. Hung, J. N. Lee, C. Y. Chai, S. C. Wang and E. M. Tsai: n-Butyl benzyl phthalate promotes breast cancer progression by inducing expression of lymphoid enhancer factor 1. *PLoS One*, 7 (8), e42750 (2012)
DOI: 10.1371/journal.pone.0042750

97. S. Khanna and P. D. Darbre: Parabens enable suspension growth of MCF-10A immortalized, non-transformed human breast epithelial cells. *J Appl Toxicol*, 33 (5), 378-82 (2013)
DOI: 10.1002/jat.2753

98. S. Khanna, P. R. Dash and P. D. Darbre: Exposure to parabens at the concentration of maximal proliferative response increases migratory and invasive activity of human breast cancer cells *in vitro*. *J Appl Toxicol*, 34 (9), 1051-9 (2014)
DOI: 10.1002/jat.3003

99. T. James-Todd, R. Senie and M. B. Terry: Racial/ethnic differences in hormonally-active hair product use: a plausible risk factor for health disparities. *J Immigr Minor Health*, 14 (3), 506-11 (2012)
DOI: 10.1007/s10903-011-9482-5

100. T. James-Todd, M. B. Terry, J. Rich-Edwards, A. Deierlein and R. Senie: Childhood hair product use and earlier age at menarche in a racially diverse study population: a pilot study. *Ann Epidemiol*, 21 (6), 461-5 (2011)
DOI: 10.1016/j.annepidem.2011.01.009

101. J. V. Marsh, K. M. Brett and L. C. Miller: Racial differences in hormone replacement therapy prescriptions. *Obstet Gynecol*, 93 (6), 999-1003 (1999)

102. A. F. Brown, E. J. Perez-Stable, E. E. Whitaker, S. F. Posner, M. Alexander, J. Gathe and A. E. Washington: Ethnic differences in hormone replacement prescribing patterns. *J Gen Intern Med*, 14 (11), 663-9 (1999)
DOI: 10.1046/j.1525-1497.1999.10118.x

103. L. Rosenberg, T. N. Bethea, E. Viscidi, C. C. Hong, M. A. Troester, E. V. Bandera, C. A. Haiman, L. N. Kolonel, A. F. Olshan, C. B. Ambrosone and J. R. Palmer: Postmenopausal Female Hormone Use and Estrogen Receptor-Positive and -Negative Breast Cancer in African American Women. *J Natl Cancer Inst*, 108 (4) (2016)
DOI: 10.1093/jnci/djv361

104. S. Lee, L. Kolonel, L. Wilkens, P. Wan, B. Henderson and M. Pike: Postmenopausal hormone therapy and breast cancer risk: the Multiethnic Cohort. *Int J Cancer*, 118 (5), 1285-91 (2006)
DOI: 10.1002/ijc.21481

105. L. Rosenberg, J. R. Palmer, L. A. Wise and L. L. Adams-Campbell: A prospective study of female hormone use and breast cancer among black women. *Arch Intern Med*, 166 (7), 760-5 (2006)
DOI: 10.1001/archinte.166.7.760

106. S. B. Wheeler, K. E. Reeder-Hayes and L. A. Carey: Disparities in breast cancer treatment and outcomes: biological, social, and health system determinants and opportunities for research. *Oncologist*, 18 (9), 986-93 (2013)
DOI: 10.1634/theoncologist.2013-0243

107. C. A. Parise and V. Caggiano: Disparities in race/ethnicity and socioeconomic status: risk of mortality of breast cancer patients in the California Cancer Registry, 2000-2010. *BMC Cancer*, 13, 449 (2013)
DOI: 10.1186/1471-2407-13-449

108. L. A. Newman, J. Mason, D. Cote, Y. Vin, K. Carolin, D. Bouwman and G. A. Colditz: African-American ethnicity, socioeconomic status, and breast cancer survival: a meta-analysis of 14 studies involving over 10,000 African-American and 40,000 White American patients with carcinoma of the breast. *Cancer*, 94 (11), 2844-54 (2002)
DOI: 10.1002/cncr.10575

109. C. J. Bradley, C. W. Given and C. Roberts: Race, socioeconomic status, and breast cancer treatment and survival. *J Natl Cancer Inst*, 94 (7), 490-6 (2002)
DOI: 10.1093/jnci/94.7.490

110. J. O. DeLancey, M. J. Thun, A. Jemal and E. M. Ward: Recent trends in Black-White disparities in cancer mortality. *Cancer Epidemiol Biomarkers Prev*, 17 (11), 2908-12 (2008)
DOI: 10.1158/1055-9965.EPI-08-0131

111. N. T. van Ravesteyn, C. B. Schechter, A. M. Near, E. A. Heijnsdijk, M. A. Stoto, G. Draisma, H. J. de Koning and J. S. Mandelblatt: Race-specific impact of natural history, mammography screening, and adjuvant treatment on breast cancer mortality rates in the United States. *Cancer Epidemiol Biomarkers Prev*, 20 (1), 112-22 (2011)
DOI: 10.1158/1055-9965.EPI-10-0944

112. C. DeSantis, D. Naishadham and A. Jemal: Cancer statistics for African Americans, 2013. *CA Cancer J Clin*, 63 (3), 151-66 (2013)
DOI: 10.3322/caac.21173

113. C. Centers for Disease and Prevention: Breast cancer screening and socioeconomic status--35 metropolitan areas, 2000 and 2002. *MMWR Morb Mortal Wkly Rep*, 54 (39), 981-5 (2005)

114. S. Whitman, A. M. Shah, A. Silva and D. Ansell: Mammography screening in six diverse communities in Chicago--a population study. *Cancer Detect Prev*, 31 (2), 166-72 (2007)
DOI: 10.1016/j.cdp.2006.12.008

115. P. George, S. Chandwani, M. Gabel, C. B. Ambrosone, G. Rhoads, E. V. Bandera and K. Demissie: Diagnosis and surgical delays in African American and white women with early-stage breast cancer. *J Womens Health (Larchmt)*, 24 (3), 209-17 (2015)
DOI: 10.1089/jwh.2014.4773

116. K. Patel, M. Kanu, J. Liu, B. Bond, E. Brown, E. Williams, R. Theriot, S. Bailey, M. Sanderson and M. Hargreaves: Factors influencing breast cancer screening in low-income African Americans in Tennessee. *J Community Health*, 39 (5), 943-50 (2014)
DOI: 10.1007/s10900-014-9834-x

117. J. H. Silber, P. R. Rosenbaum, A. S. Clark, B. J. Giantonio, R. N. Ross, Y. Teng, M. Wang, B. A. Niknam, J. M. Ludwig, W. Wang, O. Even-Shoshan and K. R. Fox: Characteristics associated with differences in survival among black and white women with breast cancer. *JAMA*, 310 (4), 389-97 (2013)
DOI: 10.1001/jama.2013.8272

118. B. A. Balasubramanian, K. Demissie, B. F. Crabtree, P. A. Strickland, K. Pawlish and G. G. Rhoads: Black Medicaid beneficiaries experience breast cancer treatment delays more frequently than whites. *Ethn Dis*, 22 (3), 288-94 (2012)

119. D. Ansell, P. Grabler, S. Whitman, C. Ferrans, J. Burgess-Bishop, L. R. Murray, R. Rao and E. Marcus: A community effort to reduce the black/white breast cancer mortality disparity in Chicago. *Cancer Causes Control*, 20 (9), 1681-8 (2009)
DOI: 10.1007/s10552-009-9419-7

120. C. I. Li, K. E. Malone and J. R. Daling: Differences in breast cancer stage, treatment, and survival by race and ethnicity. *Arch Intern Med*, 163 (1), 49-56 (2003)
DOI: 10.1001/archinte.163.1.49

121. J. J. Griggs, M. E. Sorbero, A. T. Stark, S. E. Heininger and A. W. Dick: Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy. *Breast Cancer Res Treat*, 81 (1), 21-31 (2003)
DOI: 10.1023/A:1025481505537

122. N. A. Bickell, J. J. Wang, S. Oluwole, D. Schrag, H. Godfrey, K. Hiotis, J. Mendez and A. A. Guth: Missed opportunities: racial disparities in adjuvant breast cancer treatment. *J Clin Oncol*, 24 (9), 1357-62 (2006)
DOI: 10.1200/JCO.2005.04.5799

123. A. Jemal, A. S. Robbins, C. C. Lin, W. D. Flanders, C. E. DeSantis, E. M. Ward and R. A. Freedman: Factors That Contributed to Black-White Disparities in Survival Among Nonelderly Women With Breast Cancer Between 2004 and 2013. *J Clin Oncol*, 36 (1), 14-24 (2018)
DOI: 10.1200/JCO.2017.73.7932

124. M. A. Gerend and M. Pai: Social determinants of Black-White disparities in breast cancer mortality: a review. *Cancer Epidemiol Biomarkers Prev*, 17 (11), 2913-23 (2008)
DOI: 10.1158/1055-9965.EPI-07-0633

125. A. B. Dailey, S. V. Kasl, T. R. Holford, L. Calvocoressi and B. A. Jones: Neighborhood-level socioeconomic predictors of nonadherence to mammography screening guidelines. *Cancer Epidemiol Biomarkers Prev*, 16 (11), 2293-303 (2007)
DOI: 10.1158/1055-9965.EPI-06-1076

126. D. Dai: Black residential segregation, disparities in spatial access to health care facilities, and late-stage breast cancer diagnosis in metropolitan Detroit. *Health Place*, 16 (5), 1038-52 (2010)
DOI: 10.1016/j.healthplace.2010.06.012

127. E. T. Warner and S. L. Gomez: Impact of neighborhood racial composition and metropolitan residential segregation on disparities in breast cancer stage at diagnosis and survival between black and white women in California. *J Community Health*, 35 (4), 398-408 (2010)
DOI: 10.1007/s10900-010-9265-2

128. C. Rainville, Y. Khan and G. Tisman: Triple negative breast cancer patients presenting with low serum vitamin D levels: a case series. *Cases J*, 2, 8390 (2009)
DOI: 10.4076/1757-1626-2-8390

129. S. S. Harris: Vitamin D and African Americans. *J Nutr*, 136 (4), 1126-9 (2006)
DOI: 10.1093/jn/136.4.1126

130. N. I. Larson, M. T. Story and M. C. Nelson: Neighborhood environments: disparities in access to healthy foods in the U.S. *Am J Prev Med*, 36 (1), 74-81 (2009)
DOI: 10.1016/j.amepre.2008.09.025

131. A. Hilmers, D. C. Hilmers and J. Dave: Neighborhood disparities in access to healthy foods and their effects on environmental justice. *Am J Public Health*, 102 (9), 1644-54 (2012)
DOI: 10.2105/AJPH.2012.300865

132. V. W. Chang, A. E. Hillier and N. K. Mehta: Neighborhood Racial Isolation, Disorder

and Obesity. *Soc Forces*, 87 (4), 2063-2092 (2009)
DOI: 10.1353/sof.0.0188

133. T. D. Hill, A. M. Burdette and L. Hale: Neighborhood disorder, sleep quality, and psychological distress: testing a model of structural amplification. *Health Place*, 15 (4), 1006-13 (2009)
DOI: 10.1016/j.healthplace.2009.04.001

134. E. Tarlov, S. N. Zenk, R. T. Campbell, R. B. Warnecke and R. Block: Characteristics of mammography facility locations and stage of breast cancer at diagnosis in Chicago. *J Urban Health*, 86 (2), 196-213 (2009)
DOI: 10.1007/s11524-008-9320-9

135. K. J. Mueller, S. T. Ortega, K. Parker, K. Patil and A. Askenazi: Health status and access to care among rural minorities. *J Health Care Poor Underserved*, 10 (2), 230-49 (1999)
DOI: 10.1353/hpu.2010.0249

136. J. C. Probst, C. G. Moore, S. H. Glover and M. E. Samuels: Person and place: the compounding effects of race/ethnicity and rurality on health. *Am J Public Health*, 94 (10), 1695-703 (2004)
DOI: 10.2105/AJPH.94.10.1695

137. J. C. Probst, J. D. Bellinger, K. M. Walsemann, J. Hardin and S. H. Glover: Higher risk of death in rural blacks and whites than urbanites is related to lower incomes, education, and health coverage. *Health Aff (Millwood)*, 30 (10), 1872-9 (2011)
DOI: 10.1377/hlthaff.2011.0668

138. F. Williams, S. Jeanetta, D. J. O'Brien and J. L. Fresen: Rural-urban difference in female breast cancer diagnosis in Missouri. *Rural Remote Health*, 15 (3), 3063 (2015)

139. D. R. Williams, S. A. Mohammed and A. E. Shields: Understanding and effectively addressing breast cancer in African American women: Unpacking the social context. *Cancer*, 122 (14), 2138-49 (2016)
DOI: 10.1002/cncr.29935

140. D. R. Williams, S. A. Mohammed, J. Leavell and C. Collins: Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. *Ann N Y Acad Sci*, 1186, 69-101 (2010)
DOI: 10.1111/j.1749-6632.2009.05339.x

141. D. R. Williams, N. Priest and N. B. Anderson: Understanding associations among race, socioeconomic status, and health: Patterns and prospects. *Health Psychol*, 35 (4), 407-11 (2016)
DOI: 10.1037/hea0000242

142. J. W. Robinette, S. T. Charles, D. M. Almeida and T. L. Gruenewald: Neighborhood features and physiological risk: An examination of allostatic load. *Health Place*, 41, 110-118 (2016)
DOI: 10.1016/j.healthplace.2016.08.003

143. A. D. Crosswell, J. E. Bower and P. A. Ganz: Childhood adversity and inflammation in breast cancer survivors. *Psychosom Med*, 76 (3), 208-14 (2014)
DOI: 10.1097/PSY.0000000000000041

144. C. Wildeman, N. Emanuel, J. M. Leventhal, E. Putnam-Hornstein, J. Waldfogel and H. Lee: The prevalence of confirmed maltreatment among US children, 2004 to 2011. *JAMA Pediatr*, 168 (8), 706-13 (2014)
DOI: 10.1001/jamapediatrics.2014.410

145. L. Witek Janusek, D. Tell, K. Albuquerque and H. L. Mathews: Childhood adversity increases vulnerability for behavioral symptoms and immune dysregulation in women with breast cancer. *Brain Behav Immun*, 30 Suppl, S149-62 (2013)
DOI: 10.1016/j.bbi.2012.05.014

146. N. J. Park and D. H. Kang: Inflammatory cytokine levels and breast cancer risk factors: racial differences of healthy Caucasian and African American women. *Oncol Nurs Forum*, 40 (5), 490-500 (2013)
DOI: 10.1188/13.ONF.40-05AP

147. P. A. McDonald, D. D. Thorne, J. C. Pearson and L. L. Adams-Campbell: Perceptions and knowledge of breast cancer among African-American women residing in public housing. *Ethn Dis*, 9 (1), 81-93 (1999)

148. M. Allicock, N. Graves, K. Gray and M. A. Troester: African American women's perspectives on breast cancer: implications for communicating risk of basal-like breast cancer. *J Health Care Poor Underserved*, 24 (2), 753-67 (2013)
DOI: 10.1353/hpu.2013.0082

149. D. M. Harris, J. E. Miller and D. M. Davis: Racial differences in breast cancer

screening, knowledge and compliance. *J Natl Med Assoc*, 95 (8), 693-701 (2003)

150. I. J. Hall, P. G. Moorman, R. C. Millikan and B. Newman: Comparative analysis of breast cancer risk factors among African-American women and White women. *Am J Epidemiol*, 161 (1), 40-51 (2005)
DOI: 10.1093/aje/kwh331

151. C. Dehlendorf, L. H. Harris and T. A. Weitz: Disparities in abortion rates: a public health approach. *Am J Public Health*, 103 (10), 1772-9 (2013)
DOI: 10.2105/AJPH.2013.301339

152. S. H. Taplin, L. Ichikawa, M. U. Yood, M. M. Manos, A. M. Geiger, S. Weinmann, J. Gilbert, J. Mouchawar, W. A. Leyden, R. Altaras, R. K. Beverly, D. Casso, E. O. Westbrook, K. Bischoff, J. G. Zapka and W. E. Barlow: Reason for late-stage breast cancer: absence of screening or detection, or breakdown in follow-up? *J Natl Cancer Inst*, 96 (20), 1518-27 (2004)
DOI: 10.1093/jnci/djh284

153. J. Barry and N. Breen: The importance of place of residence in predicting late-stage diagnosis of breast or cervical cancer. *Health Place*, 11 (1), 15-29 (2005)
DOI: 10.1016/j.healthplace.2003.12.002

154. S. Wadhera and W. J. Millar: Marital status and abortion. *Health Rep*, 9 (3), 19-26 (Eng); 19-27 (Fre) (1997)

155. K. E. Heck, P. Braveman, C. Cubbin, G. F. Chavez and J. L. Kiely: Socioeconomic status and breastfeeding initiation among California mothers. *Public Health Rep*, 121 (1), 51-9 (2006)
DOI: 10.1177/003335490612100111

156. E. Hood: Dwelling disparities: how poor housing leads to poor health. *Environ Health Perspect*, 113 (5), A310-7 (2005)
DOI: 10.1289/ehp.113-a310
PMid:15866753 PMCid:PMC1257572

157. G. Beccuti and S. Pannain: Sleep and obesity. *Curr Opin Clin Nutr Metab Care*, 14 (4), 402-12 (2011)
DOI: 10.1097/MCO.0b013e3283479109

158. M. Donat, C. Brown, N. Williams, A. Pandey, C. Racine, S. I. McFarlane and G. Jean-Louis: Linking sleep duration and obesity among black and white US adults. *Clin Pract (Lond)*, 10 (5) (2013)
DOI: 10.2217/cpr.13.47

159. Y. C. Cozier, J. Yu, P. F. Coogan, T. N. Bethea, L. Rosenberg and J. R. Palmer: Racism, segregation, and risk of obesity in the Black Women's Health Study. *Am J Epidemiol*, 179 (7), 875-83 (2014)
DOI: 10.1093/aje/kwu004

160. R. Lindner, C. Sullivan, O. Offor, K. Lezon-Geyda, K. Halligan, N. Fischbach, M. Shah, V. Bossuyt, V. Schulz, D. P. Tuck and L. N. Harris: Molecular phenotypes in triple negative breast cancer from African American patients suggest targets for therapy. *PLoS One*, 8 (11), e71915 (2013)
DOI: 10.1371/journal.pone.0071915

161. E. C. Dietze, T. A. Chavez and V. L. Seewaldt: Obesity and Triple-Negative Breast Cancer: Disparities, Controversies, and Biology. *Am J Pathol*, 188 (2), 280-290 (2018)
DOI: 10.1016/j.ajpath.2017.09.018

162. M. A. Beydoun and Y. Wang: Gender-ethnic disparity in BMI and waist circumference distribution shifts in US adults. *Obesity (Silver Spring)*, 17 (1), 169-76 (2009)
DOI: 10.1038/oby.2008.492

163. L. A. Sturtz, J. Melley, K. Mamula, C. D. Shriver and R. E. Ellsworth: Outcome disparities in African American women with triple negative breast cancer: a comparison of epidemiological and molecular factors between African American and Caucasian women with triple negative breast cancer. *BMC Cancer*, 14, 62 (2014)
DOI: 10.1186/1471-2407-14-62

164. C. X. Xu, H. H. Zhu and Y. M. Zhu: Diabetes and cancer: Associations, mechanisms, and implications for medical practice. *World J Diabetes*, 5 (3), 372-80 (2014)
DOI: 10.4239/wjd.v5.i3.372

165. C. Garcia-Jimenez, J. M. Garcia-Martinez, A. Chocarro-Calvo and A. De la Vieja: A new link between diabetes and cancer: enhanced WNT/beta-catenin signaling by high glucose. *J Mol Endocrinol*, 52 (1), R51-66 (2014)
DOI: 10.1530/JME-13-0152

166. T. Y. Ryu, J. Park and P. E. Scherer: Hyperglycemia as a risk factor for cancer

progression. *Diabetes Metab J*, 38 (5), 330-6 (2014)
DOI: 10.4093/dmj.2014.38.5.330

167. F. Imamura, L. O'Connor, Z. Ye, J. Mursu, Y. Hayashino, S. N. Bhupathiraju and N. G. Forouhi: Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *BMJ*, 351, h3576 (2015)
DOI: 10.1136/bmj.h3576

168. M. R. Martins, A. C. Ambrosio, M. Nery, C. Aquino Rde and M. S. Queiroz: Assessment guidance of carbohydrate counting method in patients with type 2 diabetes mellitus. *Prim Care Diabetes*, 8 (1), 39-42 (2014)
DOI: 10.1016/j.pcd.2013.04.009

169. U. Riserus, W. C. Willett and F. B. Hu: Dietary fats and prevention of type 2 diabetes. *Prog Lipid Res*, 48 (1), 44-51 (2009)
DOI: 10.1016/j.plipres.2008.10.002

170. A. H. Mokdad, E. S. Ford, B. A. Bowman, W. H. Dietz, F. Vinicor, V. S. Bales and J. S. Marks: Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*, 289 (1), 76-9 (2003)
DOI: 10.1001/jama.289.1.76
PMid:12503980

171. M. E. Peek, A. Cargill and E. S. Huang: Diabetes health disparities: a systematic review of health care interventions. *Med Care Res Rev*, 64 (5 Suppl), 101S-56S (2007)
DOI: 10.1177/1077558707305409

172. J. R. Palmer, N. Castro-Webb, K. Bertrand, T. N. Bethea and G. V. Denis: Type II Diabetes and Incidence of Estrogen Receptor Negative Breast Cancer in African American Women. *Cancer Res*, 77 (22), 6462-6469 (2017)
DOI: 10.1158/0008-5472.CAN-17-1903

173. K. Masuo, M. L. Tuck and G. W. Lambert: Hypertension and diabetes in obesity. *Int J Hypertens*, 2011, 695869 (2011)
DOI: 10.4061/2011/695869

174. D. T. Lackland: Racial differences in hypertension: implications for high blood pressure management. *Am J Med Sci*, 348 (2), 135-8 (2014)
DOI: 10.1097/MAJ.0000000000000308

175. D. Braithwaite, C. M. Tammemagi, D. H. Moore, E. M. Ozanne, R. A. Hiatt, J. Belkora, D. W. West, W. A. Satariano, M. Liebman and L. Esserman: Hypertension is an independent predictor of survival disparity between African-American and white breast cancer patients. *Int J Cancer*, 124 (5), 1213-9 (2009)
DOI: 10.1002/ijc.24054

176. D. R. Lannin, H. F. Mathews, J. Mitchell, M. S. Swanson, F. H. Swanson and M. S. Edwards: Influence of socioeconomic and cultural factors on racial differences in late-stage presentation of breast cancer. *JAMA*, 279 (22), 1801-7 (1998)
DOI: 10.1001/jama.279.22.1801
PMid:9628711

177. D. R. Lannin, H. F. Mathews, J. Mitchell and M. S. Swanson: Impacting cultural attitudes in African-American women to decrease breast cancer mortality. *Am J Surg*, 184 (5), 418-23 (2002)
DOI: 10.1016/S0002-9610(02)01009-7

178. S. W. Vernon, V. G. Vogel, S. Halabi and M. L. Bondy: Factors associated with perceived risk of breast cancer among women attending a screening program. *Breast Cancer Res Treat*, 28 (2), 137-44 (1993)
DOI: 10.1007/BF00666426
PMid:8173066

179. J. H. Price, S. M. Desmond, S. Slenker, D. Smith and P. W. Stewart: Urban black women's perceptions of breast cancer and mammography. *J Community Health*, 17 (4), 191-204 (1992)
DOI: 10.1007/BF01321652
PMid:1527241

180. M. E. Peek, J. V. Sayad and R. Markwardt: Fear, fatalism and breast cancer screening in low-income African-American women: the role of clinicians and the health care system. *J Gen Intern Med*, 23 (11), 1847-53 (2008)
DOI: 10.1007/s11606-008-0756-0

181. P. J. Loehrer, Sr., H. A. Greger, M. Weinberger, B. Musick, M. Miller, C. Nichols, J. Bryan, D. Higgs and D. Brock: Knowledge and beliefs about cancer in a socioeconomically disadvantaged population. *Cancer*, 68 (7), 1665-71 (1991)
DOI: 10.1002/1097-0142(19911001)68:7<1665::AID-CNCR2820680734>3.0.CO;2-3

182. K. S. Johnson, K. I. Elbert-Avila and J. A. Tulsky: The influence of spiritual beliefs and practices on the treatment preferences of African Americans: a review of the literature. *J Am Geriatr Soc*, 53 (4), 711-9 (2005) DOI: 10.1111/j.1532-5415.2005.53224.x

183. R. J. Taylor, L. M. Chatters, K. Lincoln and A. T. Woodward: Church-Based Exchanges of Informal Social Support among African Americans. *Race Soc Probl*, 9 (1), 53-62 (2017) DOI: 10.1007/s12552-017-9195-z

184. C. L. Holt, S. N. Lukwago and M. W. Kreuter: Spirituality, breast cancer beliefs and mammography utilization among urban African American women. *J Health Psychol*, 8 (3), 383-96 (2003) DOI: 10.1177/13591053030083008

185. J. Mitchell, D. R. Lannin, H. F. Mathews and M. S. Swanson: Religious beliefs and breast cancer screening. *J Womens Health (Larchmt)*, 11 (10), 907-15 (2002) DOI: 10.1089/154099902762203740

186. M. M. Gullatte, O. Brawley, A. Kinney, B. Powe and K. Mooney: Religiosity, spirituality, and cancer fatalism beliefs on delay in breast cancer diagnosis in African American women. *J Relig Health*, 49 (1), 62-72 (2010) DOI: 10.1007/s10943-008-9232-8

187. J. M. Phillips, M. Z. Cohen and G. Moses: Breast cancer screening and African American women: fear, fatalism, and silence. *Oncol Nurs Forum*, 26 (3), 561-71 (1999) PMid:10214597

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