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Breast Cancer RESEARCH

REVIEW

# Disparities in breast cancer outcomes between Caucasian and African American women: a model for describing the relationship of biological and nonbiological factors

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**Abstract**

Breast cancer is the most common malignancy in women in the United States but significant disparities exist for African American women compared to Caucasian women. African American women present with breast cancer at a younger age and with a greater incidence under the age of 50 years, develop histologically more aggressive tumors that are at a more advanced stage at presentation, and have a worse disease-free and overall survival than Caucasian women. The biological characteristics of the primary tumor play an important role in determining the outcome of the disparity, and significant differences have been identified between African American and Caucasian breast cancer in steroid receptor and growth factor receptor content, mutations in cell cycle components, chromosomal abnormalities, and tumor suppressor and other cancer genes. The consequences of the biological factors are influenced by a variety of nonbiological factors, including socioeconomic, health care access, reproductive, and confounding factors. The nonbiological factors may act directly to enhance (or inhibit) the consequences of the biological changes, indirectly to facilitate outcome of the disparity, or as a cofounding factor, driving the association between the biological factors and the disparity. The prevention and management of the disparities will require an understanding of the relationship of biological and nonbiological factors. The present review was undertaken to promote this understanding by describing the biological basis of the four major disparities - early age of onset, more advanced stage of disease, more aggressive histologic changes, and worse survival - and the important relationship to the nonbiological factors. A model is proposed to provide a comprehensive view of this relationship, with the goal of facilitating an understanding of each disparity and the issues that need to be addressed to eliminate the disparity.

## Introduction

Breast cancer is the most common malignancy in women, with over 229,000 cases annually in the United States [1]. While the overall incidence of breast cancer among African American women (114.7 cases per 100,000) is lower than that for Caucasian women (121.7 cases per 100,000 [2]), significant disparities in the presentation and outcome exist between these two groups. Breast cancer in African American women presents at a younger age, presents at a more advanced stage with more aggressive histologic characteristics, and is associated with a worse survival for all stages and at all ages than that of Caucasian women. Many biological and nonbiological factors are felt to contribute to these disparities. Significant differences have been identified in the biological properties between Caucasian and African American women in the plasma levels of growth factors and hormones [3], in reproductive factors [4-7], in susceptibility loci [8-10], and in primary tumor characteristics, including the presence and expression of steroid and growth factor receptors [7,11-16], cell cycle proteins [17-21], tumor suppressor genes [21,22], and chromosomal abnormalities [23]. These differences have the potential to influence, or even explain, multiple aspects of the disparities and outcomes for breast cancer between these two ethnic groups. Many of these molecular changes, especially estrogen receptor (ER) and triple negative (TN) status [7,11-16], expression of p16 [17-19], cyclins D and E [17-21], and the tumor suppressor genes *p53* [22] and *RASSF1A* [21,24], have been studied for their

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effect on survival; however, their role in defining the other disparities - age of onset, stage of presentation, and aggressive histologic features - has not been addressed. An understanding of these molecular differences and how they contribute to each of the four disparities is critical to formulating a comprehensive understanding of the marked differences in development, presentation, and outcome of breast cancer between Caucasian and African American women. The nonbiological factors have been studied more extensively and include differences in reproductive factors, socioeconomic characteristics, access to health care and mammography, delivery of treatment modalities, psychological/behavioral/cultural factors, and comorbidities. The nonbiological factors may act to inhibit these processes, such as through breastfeeding or breast cancer treatment, they may act to facilitate the biological activity or disparity, such as through a delay in diagnosis, or they may represent a confounding factor that is associated with both the biological factor and the disparity. Many of these nonbiological factors are modifiable, and when effectively addressed may lead to improvement in outcome. Importantly, an understanding of both biological and nonbiological factors and their interaction is necessary to design effective and comprehensive management programs, especially those that might be tailored to ethnic-specific differences in outcome. The present review has been undertaken to examine the differences in biological characteristics of breast cancer in African American and Caucasian women, how they may contribute to each of the four categories of disparities - age of onset, stage of presentation, histologic characteristics, and survival - and how they are influenced by the nonbiological factors that are felt to contribute to the disparity, providing a comprehensive view of the development and outcome of the disparity. A model is proposed to indicate the nature of the interaction of biological and nonbiological factors on the disparities both to understand their relationship and to guide future efforts.

## Materials and methods

Articles for this review were identified through a Pubmed search conducted using the following queries: African American or Black breast cancer, breast cancer disparities, African American or Black breast cancer age of onset, stage, histologic features, survival, breast cancer and race or ethnicity. Articles were also identified through cross-references. Studies examining United States, European or African-based populations were included. An attempt was made to include all relevant references examining clinical aspects of the disparities and potential contributing biological and nonbiological activities and their analysis. For review of nonbiological factors, hazard ratios, odds ratios (ORs) and confidence intervals (CIs) are included when available. The specificity of nonbiological factors for which adjustments were made in the analysis of outcomes for disparities was identified and indicated. The designation of the proposed manner in which biological abnormalities influenced the outcome of individual disparities was based on evidence of the biological activity and supporting articles for that activity. The development of the model and the proposed manner in which the nonbiological factors influenced the biological activities and the disparities (promote/inhibit, facilitate, confounding factors), as indicated in the model, is the author's interpretation.

## A model for the initiation and development of breast cancer disparities in African American versus Caucasian women

The development and outcome of the four major breast cancer disparities between African American and Caucasian women are influenced by a variety of biological and nonbiological factors. To promote an understanding of these factors and how they interact, a model is proposed depicting the relationship of the disparities, the biological factors, and the nonbiological factors to each other (Figure 1). The four major disparities are indicated at the top of the figure. Multiple biological abnormalities have been identified in the primary breast cancer of African American women to a greater extent than in Caucasian women, and these are considered to be important contributors to the disparities. These abnormalities, alone or in combination, may contribute to the earlier onset, advanced stage, more aggressive histologic features, and worse survival of the breast cancers. Concomitantly, a variety of nonbiological factors have been identified that are more frequent in African American women and that have the potential for influencing the tumor biological activities and each of the disparities. These nonbiological factors are organized according to how they are considered to influence these events, although there may be overlap between the nonbiological factors of different categories. The nonbiologic factors may act: i) to either promote or inhibit biological activities and disparities, such as through the action of reproductive factors or treatment, respectively; ii) to facilitate biological activities and disparities, such as through a delay in diagnosis; or iii) as confounding factors driving the association between the biological factor and the disparity, such as socioeconomic factors. The nonbiological factors are depicted in three separate but overlapping circles to indicate that they may have different patterns of influence but that they may also interact with each other to further promote the disparity. The direction of influence is indicated by the arrows. This model emphasizes the role of the biological and nonbiological factors and the interaction between them in influencing the development

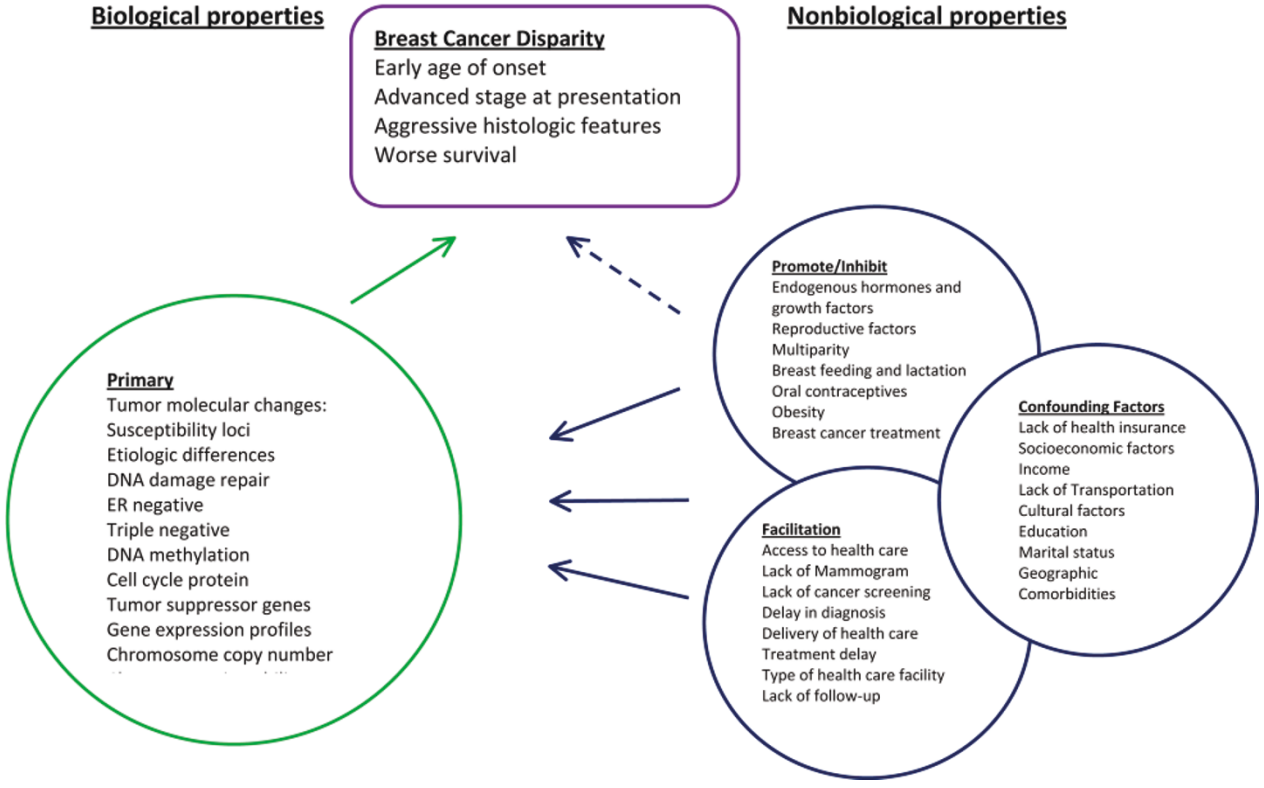


**Figure 1. A model for the initiation and development of breast cancer disparities in African American versus Caucasian women.** The model depicts the relationship of biological abnormalities that occur to a greater extent in the tumors of African American women, and nonbiological factors that are more frequent in African Americans, in the initiation and development of breast cancer disparities. The biological activities are considered to be the main contributing factors to the type and outcome of the disparities. The nonbiological activities are considered to influence primarily the biological activities, and are organized according to what is considered to be the main manner of influence on the biological activities - to promote or inhibit, to facilitate, or to act as confounding factors. It is through this influence on biological activities that the nonbiological factors influence disparity outcome. The nonbiological factors may also influence the disparity directly, although this is considered to be less common. The nonbiological factors are depicted in overlapping circles to indicate that they may interact with each other, and the nonbiological factors may act alone or in combination to influence these outcomes. ER, estrogen receptor.

and outcome of the disparities. The nonbiological factors are considered to influence the disparities primarily through their influence on the biological activities, although a more direct influence on the disparity is also possible. These relationships, and the versatility of each biological and nonbiological factor to influence different, and multiple, disparities will be reviewed in the following sections to suggest a comprehensive picture of the events responsible for the differences in breast cancer outcome in African American versus Caucasian women.

## Early age of onset of breast cancer

### Evidence for presentation with breast cancer at an earlier age in African American women

African American women present with breast cancer at an earlier age than Caucasian women (median age 54 versus 61 years, respectively) [2,25-28]. This is particularly striking for young African American women, where among women aged <35 years, significant predictors of breast cancer risk include African American race (relative risk 2.66, 95% CI 1.4 to 4.9) [29]. This is consistent with the analysis of a five-state registry by Johnson [30], who found more than 10% of breast cancer cases in African American women were diagnosed at <40 years of age versus 5% in white women ($P < 0.001$), and SEER data indicating an age-specific incidence rate in the 30 to 39 years age group of 48.36/100,000 (95% CI 44.78 to 52.15) for African Americans versus 40.79 (95% CI 39.45 to 42.18) for white women. Johnson considered African-American women in the 30 to 39 years age category to represent a high-risk group [30]. On average, approximately 5.7% of Caucasians and 12.4% of African Americans with breast cancer present under the age of 40 years, and 17.3% of Caucasians versus 25.1% of African Americans present in the 40 to 49 years age group [27,28,31,32]). The earlier onset is emphasized by a prominent crossover pattern to the incidence of breast cancer between these two ethnic groups, resulting in a

lower incidence among older African American women [30,33].

### Biological activities contributing to earlier onset of breast cancer in African American women

The increased incidence of breast cancer at a younger age among African American women may be the result of either different susceptibilities, different etiologies, and/or acceleration of the development and presentation of breast cancer among young African Americans. Recent genome-wide association studies have identified a common risk variant at the *TERT-CLPTM1L* locus on chromosome 5p15 (OR = 1.25, $P = 1.1 \times 10^{-9}$), which was present at greater frequency in African Americans than in women of European ancestry, and was significantly associated with TN breast cancer in younger women (aged <50 years; OR = 1.48, $P = 1.9 \times 10^{-9}$) [8]. A genetic variant in the *LOC643714* gene has also been identified that is African American specific and is associated with a 23% increased risk for breast cancer in African American women (OR 1.23, 95% CI 1.05 to 1.44) [34].

The greater breast cancer risk among African American women aged <35 years has suggested the possibility that breast cancers diagnosed at very young ages may be etiologically distinct. Chen and colleagues [5] raised the possibility that the carcinogenic insult to the target cell may be more profound for black than for white women, or possibly represents racial differences in the metabolism of carcinogens. In support of this, estrogen is a known carcinogen for breast cancer [35], and studies examining single nucleotide polymorphisms (SNPs) in genes involved in estrogen metabolism or action identified a *Msp1* polymorphism in the *CYP1A1* gene significantly associated with breast cancer in African Americans (OR 9.7, 95% CI 2.0 to 47.9) but not in Caucasians [9,10], and others have reported the *HSD17B1* 312 Gly allele was specifically associated with premenopausal breast cancer risk in African Americans (OR 3.00, 95% CI 1.29 to 6.99) [9]. The higher incidence of basal-like tumors in African American than in Caucasian women has also suggested a distinct etiology [17,36].

There is evidence for the presence of molecular abnormalities that are associated with greater proliferation of breast cancer in African American than in Caucasian women (Figure 2), potentially accelerating the development, appearance, and timing of breast cancer. These abnormalities include an increased incidence of ER-negative and TN breast cancer, an increased incidence of high grade breast cancers, and an increased incidence of alterations in a variety of cell cycle regulatory proteins, including cyclin E, and an increased loss of critical tumor suppressor genes, including *p53*, *RASSF1A*, *RARβ*, and *HIN-l*. African American women have an increased incidence of high grade tumors, which are commonly

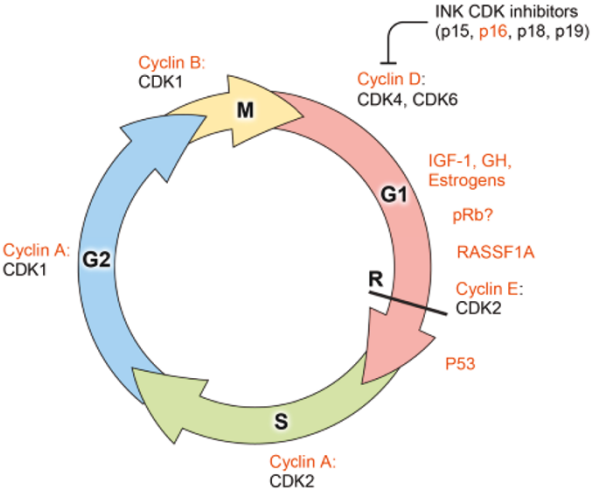


**Figure 2. Cell cycle phases and the regulatory components important in breast cancer disparities.** Abnormalities (highlighted in red) have been identified in multiple regulatory components of the cell cycle in the breast cancer of African American compared with Caucasian women. These include cyclins A, B, D, and E, p16/INK4A, the tumor suppressor genes *p53* and *RASSF1A*, as well as endogenous hormones and growth factors. Retinoblastoma protein (pRb) has not been studied in African American breast cancer, but evidence suggests this may be altered as well.

associated with high proliferative rates (see below, section on more aggressive histologic characteristics). There is a higher incidence of ER-negative and TN/basal-like (ER-/progesterone receptor (PR)-/HER2/neu-) tumors in African American compared with Caucasian women [7,11-13,16]. Basal-like tumors are homogeneously highly proliferative and likely to grow quickly, a result in part of common deficiencies in retinoblastoma and p53 proteins [36]. Breast cancer in African American women is characterized by enhanced expression of cyclin E [17-19], which regulates entry into S-phase. Increased levels of cyclin E may reflect disruption of alternative pathways, resulting in unrestrained cell proliferation [17,37]. High levels of cyclin E expression are also associated with larger, ER-negative tumors, consistent with tumors in African American women [38]. The tumor suppressor gene p53, an important regulator of cell cycle progression and DNA damage repair, has been found to be mutated in African American breast cancer in most [17,18,39,40], but not all, studies [13]. Expression of mutant p53 protein is associated with high tumor proliferation rate [41]. If there is an increased estrogenic carcinogenic potential in these women, and this is combined with enhanced proliferation, reduced DNA damage repair, and the accumulation of genetic errors, this could facilitate initiation and development of tumors in these women.

The tumor suppressor gene *RASSF1A* modulates multiple apoptotic and cell cycle checkpoint pathways,

restricting exit from G1 [42]. *RASSF1A* in breast cancer among women aged <50 years was found to be methylated in 76% of cases of African American women versus 29% of cases of Caucasian women ($P < 0.0001$) [21]. *RARβ* (trend, $P = 0.01$) and *HIN-1* ($P < 0.0001$) are more often methylated in the tumors of African American women [21]). RARβ causes cell cycle arrest, growth inhibition and induction of apoptosis, and HIN-1 in exponentially dividing cells inhibits cell cycle reentry [43]. Breast cancer in young women is also considered to be a distinct biological entity, enriched with abnormalities in genes involved in extracellular signal-related kinase and phosphoinositide 3-kinase signaling [44,45]. Insulin-like growth factor (IGF)-1 (which is increased in the plasma of premenopausal African American women [3]) acts through the phosphoinositide 3-kinase signaling pathway, providing a mechanism for further enhancement of these tumors. These G1/S abnormalities are accompanied by evidence of increased proliferation in the tumors of African American women, including increased Ki-67, [39,46] increased progression into S-phase [13,46], and higher quantitative gene expression of all five genes in the Oncotype Rx proliferation group (*CCNB1*, *MKI17*, *MYBL2*, *BIRC5* ($P < 0.05$), *AURKA* ($P = 0.051$) [47].

Together, these findings indicate that the breast cancer of African American women contains multiple biological abnormalities that may represent a different mutational landscape of breast cancer than in Caucasian women, and that is associated with accelerated proliferation and growth, and could play an important role in the earlier appearance of breast cancer in African American women.

#### Nonbiological activities contributing to earlier onset of breast cancer in African American women

There is good evidence for the presence of nonbiological factors in African American women that may influence the activity of biological processes to promote the early onset of breast cancer. These are primarily reproductive factors that may serve to promote or inhibit the biological processes, but may include confounding socioeconomic factors as well. Multiple childbirths and earlier initiation of childbearing are more common among African American women [4-7]. This may confer a more prominent carcinogenic insult and an increased risk for breast cancer among African American women. A short-term increase in the risk for breast cancer occurs following full-term pregnancy [48], and several authors have proposed that if African Americans have children at intervals of 3 years or less, and have multiple children at younger ages, the higher prevalence of this factor could serve to elevate the risk for younger African Americans [4,49]. Full-term pregnancy is characterized by a significant elevation of growth hormone, which can cause oncologic transformation [50], and IGF-1, which is a known risk factor for breast cancer [51]. IGF-1 is an important mitogen for breast cancer, and elevated levels through multiple pregnancies could further accelerate growth and the appearance of breast cancer in these women. Estrogens and IGF-1 plasma levels are also elevated in premenopausal African American women versus Caucasian women ($P < 0.01$) [3], and would be expected to enhance cell cycle progression, especially in cells in which the G1/S checkpoint is compromised by loss of tumor suppressor genes and elevation of cyclin E.

Breastfeeding and waist-hip ratio (a measure of adiposity) are important nonbiological (reproductive and socioeconomic) factors associated with breast cancer risk in African American women. Millikan and colleagues [52] found younger African-American women had a higher prevalence of each of the principal risk factors for basal-like breast cancer: higher parity, lower breastfeeding, higher parity combined with lower breastfeeding, greater use of lactation suppressants, and elevated waist-hip ratio. Women with multiple live births who did not breastfeed and women who used medications to suppress lactation were at increased risk of basal-like breast cancer. Li and colleagues [53] also demonstrated that socioeconomic status had a bigger impact on breastfeeding practice among African Americans.

Together, these findings suggest an important interaction between reproductive factors, socioeconomic and cultural factors and biological activities in the initiation and development of breast cancer in young African American women. These nonbiological factors may act in a promotional manner, such as the hormonal mediation of pregnancy (and perhaps adiposity), in an inhibitory manner, such as through breastfeeding, or through confounding factors, such as socioeconomic and cultural patterns. The ability of cultural factors to influence breastfeeding illustrates the potential interaction among nonbiological factors, as suggested by the model. Importantly, many of these factors are modifiable, which emphasizes the importance of their identification among these young women.

## Stage of presentation of breast cancer

#### Evidence for presentation of breast cancer at a more advanced stage in African American women

African American women with breast cancer present at a more advanced stage, with less localized and more regional disease than Caucasian women. African American women are significantly more likely to receive a diagnosis at a regional stage than Caucasians in all age groups (<40, 40 to 49, >50 years), and among African American women, those aged <40 years, compared with women in other race-age subgroups, were more likely to be diagnosed at a regional stage [54]. This disparity extends to all degrees of tumor involvement, from tumor size, to

localization within the breast, to regionally advanced disease, to stage IV breast cancer with distant metastatic disease [2,13,39,55,56]. It has been shown that African American females had less early stage disease in every age group for each ER status and had more late-stage disease in every age group for all breast tumors and ER-positive tumors only [57]. These findings have been observed following analysis of both regional and national registries [26,56]. Porter and colleagues [17] found the weighted odds that African American women had AJCC stage III/IV rather than stage I disease were three times (OR 3.0, 95% CI 1.5 to 5.7) the corresponding odds for white women. The age-adjusted rates for inflammatory breast cancer, a very aggressive form of breast cancer, were also approximately 1.4-fold greater than in Caucasians, and the age-specific rates among African Americans were greater than among Caucasians at all ages [58].

#### Biological activities contributing to presentation at a more advanced stage of breast cancer in African American women

The presentation of breast cancer at a more advanced stage in African American women may be the result of significant biological abnormalities promoting tumor proliferation, as well as the higher incidence of more aggressive forms of breast cancer, including TN, ER-negative, and high grade tumors, which are associated with a higher stage. Multiple molecular abnormalities have been identified in cell cycle proteins and tumor suppressor genes, including cyclin E [17-19], p53 [41], RASSF1A [21,42], RARβ, HIN-1 [21], and proliferative gene signatures [47], which enhance proliferation and would be capable of propelling these tumors to a larger size and more advanced stage. The contribution of these abnormalities to enhanced proliferation was discussed in the preceding section on early age of onset. TN tumors [11,19,59] and ER-negative tumors [7,12-14,16] are more common in African American women. TN tumors are associated with a larger tumor size and higher incidence of axillary node positivity [60]. ER-negative tumors are larger, present at a more advanced disease stage, and are more likely to present with axillary lymph node metastases [61]. High grade tumors, more common in African American women, are significantly associated with higher disease stage [62]. Interestingly, the tumors of African American women have a trend toward a greater incidence of methylation of RARβ [21], which has been shown to be associated with a higher incidence of sentinel lymph node metastasis [63].

#### Nonbiological factors contributing to presentation of breast cancer at a more advanced stage in African American women

Multiple nonbiological factors have been identified in each of the three corresponding categories of Figure 1 and these may serve to influence the biological activities and the disparity of advanced stage. These may act to promote or facilitate these events or act as confounding factors, and this process is further encouraged by multiple interactions between these factors. Clinical studies have indicated an important role for a delay in diagnosis and the multiple factors contributing to this delay, which would allow for continuing activity of the tumor molecular properties and increased time for tumor progression. It has been estimated that, among women with private health insurance, the mean diagnostic delay time was 55 days for African American women versus 43 days for Caucasian women [64]. In another study, >25% of African American women experienced 3 or more months of clinical delay [65]. This is a considerable period of time during which tumors with multiple aggressive characteristics, especially multiple proliferative molecular changes, may progress. Stage at presentation measures the impact of events affecting diagnosis, and these may be multiple [57], including access to health care and the lack of a mammogram [55], socioeconomic variables plus cultural belief and attitude variables [66], lower frequency of, and longer intervals between, mammograms and lack of timely follow-up of suspicious results [67], and method of disease detection and access to health care [28,56]. This is well summarized by Joslyn and West ([26] and references therein), who noted that lower socioeconomic status, including variables such as low income, no private health insurance, lack of transportation, and lack of access to health care, is associated with less cancer screening, delay in the diagnosis of cancer, and more advanced tumor stage at the time of diagnosis. TN tumors are more likely to be detected through clinical examination than through mammography and ultrasound, which may reflect a more rapid growth rate or may be due to intrinsic differences in detectability [68]. TN breast cancers are also more likely than other breast cancers to present in the interval between regular mammograms, which may relate to differences in the density of breast tissue in women with TN breast cancer, or to more accelerated growth [69].

The nonbiological factors of breastfeeding, obesity, and plasma hormone levels may also promote a more advanced stage of breast cancer. Lack of breast feeding, as noted above, is more common in African American women and may be associated with a greater incidence of TN tumors [52] and an accompanying advanced stage. Obesity is also more prevalent in African American women and has been associated in some [62,70], but not all [71], series with advanced stage of breast cancer. Elevated plasma IGF-1 and estradiol levels, present in premenopausal African American women [3], may promote tumor proliferation and thus, potentially, tumor size and tumor stage.

Together, these findings indicate that biological and nonbiological factors may influence progression of breast cancer to a more advanced stage in African American women. The biological factors may act to increase tumor size and/or lymph node metastases. The nonbiological factors interact with the biological factors in a variety of ways: they may act more directly through reproductive factors; they may act to facilitate biological activity through a variety of health care deficiencies that result in a delay in diagnosis and treatment; or they may act through confounding factors such as socioeconomic deficiencies and cultural beliefs. The large number of nonbiological factors that may contribute, especially the many events that may result in a delay in diagnosis, illustrate the potential magnitude of the problem, as well as the number of pathways (from nonbiological factors to biological factors to advanced stage) that must be addressed to reduce the outcome of this disparity. Lastly, it should be noted that several of the factors influencing more advanced stage also played a role in promoting the earlier onset of breast cancer, including the molecular factors promoting increased proliferation, ER and TN tumors, and reproductive factors. As suggested in the model, this indicates the multiple consequences of some of these abnormalities and the close relationship of some of the disparities to each other.

## Aggressive histologic characteristics of breast cancer

### Evidence for more aggressive histologic characteristics in African American breast cancer

African American women are at increased odds of having a higher grade tumor, with a higher mitotic index, marked tumor necrosis, more poorly differentiated, and less well defined tubular formation then Caucasian women [5,17,54,72,73]. It was noted above that African Americans have a higher incidence of basal-like tumors, and it has been shown that basal-like tumors, compared to luminal A tumors, have more *TP53* mutations (44% versus 15%, $P < 0.001$), a higher mitotic index (OR 11.0, 95% CI 5.6 to 21.7), more marked nuclear pleomorphism (OR 9.7, 95% CI 5.3 to 18.0), and higher combined grade (OR 8.3, 95% CI 4.4 to 15.6) [74]. Many series [17,25, 26,54] but not all [5] have also found a higher prevalence of medullary carcinomas and a lower prevalence of lobular carcinomas in African American than Caucasian women. Breast cancer is most commonly the infiltrating ductal type in both African American and Caucasian women [5,17,54,73].

### Biological activities contributing to presentation with more aggressive histologic features in African American women

There is evidence for abnormalities in the breast cancer of African American women that affect several biological processes and may contribute to the more advanced histologic characteristics. The presence of molecular changes that contribute to enhanced proliferation and growth were reviewed previously in the sections discussing biological activities contributing to early age of onset and to more advanced stage at presentation. When rapid growth exceeds the blood supply of the tumor, central necrosis may result, a common finding in these tumors. Porter and colleagues [17], for example, found the constellation of low expression of cyclin D1, and overexpression of cyclin E, p16, and p53 at diagnosis were associated with increased odds of having a higher-grade tumor, a higher mitotic index, and marked tumor necrosis. Increased cyclin E expression, characteristic of breast cancer in African Americans, is associated with ER-negative, high grade tumors in younger women [75]. Martin and colleagues [18] observed increased expression of cyclin B, which controls G2-M transition and is required for mitosis, in the tumors of African American women. Enhanced expression of cyclin B has been shown to be associated with high grade, advanced stage tumors [76]. The enhanced proliferation rate would also decrease the time for DNA damage repair and increase the accumulation of genetic errors in multiple signaling pathways, which would be further compounded by the higher incidence of p53 mutations resulting in an important loss of DNA damage control and repair. It has been shown that African American women with breast cancer had significantly higher ionizing radiation-induced gamma-H2AX phosphorylation levels in peripheral lymphocytes than Caucasians ($P < 0.05$), particularly in the younger age group (<50 years) and higher body mass index (>25 kg/m$^2$), suggesting an increased potential for carcinogen-induced double-strand breaks, chromosome aberrations and genomic instability in African American women [77]. Aneuploidy is common in high grade tumors [78,79], and loss of p53 also results in an increased incidence of centrosome duplication, an important cause of chromosome mis-segration and aneuploidy [80]. A difference in the frequency of copy number alterations, reflecting chromosomal instability, between tumors of African American and Caucasian women has also been demonstrated [23].

The higher incidence of TN tumors in African American women also contributes to, and may partially explain, the increased incidence of a more aggressive histology in these women. Basal-like tumors have the highest prevalence of unfavorable histologies (metaplastic, anaplastic, undifferentiated high grade) [74]. Carey and colleagues [74] suggested that the association of race with high-grade breast tumors and ER negativity is driven by the increased prevalence of basal-like tumors. Basal-like tumors have distinct gene expression profiles [36,81] and have many cell cycle abnormalities (high expression of p16, p53, and cyclin E, and low cyclin

D1 expression) [19], which are associated with the other disparities, and thus might be expected to contribute broadly to the phenotypic changes in the tumors of African American versus Caucasian women. There is thus a range of biological abnormalities in the breast cancer of African American women that could contribute to mitotic defects, aneuploidy, an increase in histologic grade or dedifferentiation, increased nuclear grade, pleomorphism, and central necrosis, all characteristics of histologically more aggressive tumors observed in African American breast cancer.

#### Nonbiological activities contributing to presentation with more aggressive histologic features

Nonbiological factors may influence the histologic pattern of African American breast cancer, but appear to play a more limited role than in other disparities. Essentially all of the studies examining this question found the disparity of more aggressive histologic features to be only partially reduced after adjustment for age, stage, and other nonbiologic factors [5,17,72,73]. Chen and colleagues [5] studied histologic characteristics and their relation to nonbiological factors in 963 women. They reported tumor characteristics (high grade nuclear atypia, high mitotic activity, grade 3 tumors, and necrosis) persisted after adjustment for age, stage and metropolitan area, groups of socioeconomic factors (marital status, education, poverty index, and occupation), host factor and lifestyle (body mass index, smoking, and alcohol consumption), reproductive factors (parity, age at first pregnancy), and health care access and utilization (usual source of care and insurance coverage). Porter and colleagues [17] found partial reduction in the OR from 5.3 (95% CI 2.4 to 11.8) to 4.3 (95% CI 1.7 to 9.2) for histologic grade with adjustment for age and stage. Consistent with this, they also found that adjustment for stage and age resulted in the partial reduction of the OR for cyclin E (OR 4.3, 95% CI 2.0 to 9.2) and p53 (OR 1.7, 95% CI 1.0 to 2.9) in the breast cancer of African Americans, suggesting an important link between biological activities, nonbiological factors and the disparities. Elmore and colleagues [72] reported that controlling for the method of detection removed the racial difference in the presence of vascular and lymphatic invasion; however, the racial differences in the presence of necrosis remained even after controlling for differences in income, insurance, and method of detection. In another study, adjustment for age and stage corrected for aneuploidy, and for combined grade (architectural, mitotic, nuclear) in older women aged 60 to 74 years but not for combined grade in the 20 to 39 and 40 to 59 years age groups [73]. The finding that adjustment for these nonbiological factors was incomplete for aggressive histologic features suggests the influence of many nonbiological factors on this disparity may be less than on early age of onset or stage of presentation. If correct, this would suggest an important feature of the proposed model, that the nonbiological events influencing one disparity may differ (in part) from those influencing another. The possibility that the incomplete adjustment represents lack of inclusion of other potentially important confounding factors, however, cannot be excluded.

### Breast cancer mortality

#### Evidence for a worse survival from breast cancer in African American women

African American women with breast cancer have higher mortality rates when analyzed according to localized or regional disease [2,25,54,82-84], according to stage of presentation [26,27,57,85], among all age groups [54,57, 83,86], in premenopausal versus postmenopausal women [87], and in ER-negative and ER-positive tumors [19,27,57]. In the period 2003 to 2007, African American women had a 39% higher breast cancer death rate than Caucasian women, despite a lower incidence rate [2].

#### Biological activities contributing to increased mortality for breast cancer in African American women

The biological abnormalities that are more pronounced in the primary tumor of African Americans, in addition to contributing to early onset, advanced stage of presentation, and aggressive histology, may have important adverse effects on survival. These include reduced expression of cyclin D [17,19-21], enhanced expression of cyclin E [17-19], enhanced expression of p16/INK4A (p16) [17-19], enhanced expression of p53 [22], reduced expression of RASSF1A [21], and increased expression of cyclins A and B [18]. Mehrotra and colleagues [21] examined DNA methylation of genes in breast cancer and observed that African American women aged <50 years with ER-negative tumors had a significantly higher frequency of hypermethylation of cyclin D2 (64% versus 19% in Caucasian women), which was significantly associated with cancer-related death (hazard ratio 3.82, $P = 0.01$). This is consistent with Gillett and colleagues [88], who found decreased cyclin D1 protein expression together with negative ER status was associated with a poor prognosis in breast cancer. Overexpression of p16, which binds to CDK4/6 to prevent cyclin D binding, has been observed in tumors of African American compared with Caucasian women [17-19] and is associated with a worse prognosis, an aggressive breast carcinoma phenotype, poor clinical outcome, and poor outcome in patients treated with specific chemotherapy regimens, suggesting that altered expression can also affect response to therapy ([17] and references therein).

Cyclin E partners with CDK2 to regulate the G1/S phase transition, and overexpression of cyclin E can

accelerate G1 phase of the cell cycle [89]. Increased cyclin E expression is associated with higher grade/stage breast cancers, and increased mortality [76]. Importantly, abnormalities of cyclin D and cyclin E frequently occur together [17]. Nielsen and colleagues [90] found 25 out of 34 tumors with overexpression of cyclin E to have uniform low cyclin D1 expression, and tumors with high cyclin E and low D1 expression were generally ER-negative. Among 114 primary breast cancer specimens, the group of patients with tumors showing high cyclin E and low D1 expression had the worst prognosis [90]. Cyclins A and B function in S-phase, G2, and early mitosis. Martin and colleagues [18] demonstrated that CDKN2A (p16; which complexes with cyclin A), cyclin A2 and cyclin B1 were expressed at significantly higher levels ($P < 0.01$) in the tumor epithelium of African Americans than in European Americans. Elevated cyclin A2 is associated with high recurrence and significantly shorter disease-free survival periods [91], and elevated cyclin B1 is a predictor of poor outcome and associated with poor survival in breast cancer [92,93].

The tumor suppressor gene *p53* is frequently mutated in breast cancers of African Americans (see above, section on early age of onset), and in addition there is evidence that the pattern of p53 mutations in African American women is different from that in Caucasian women [94,95]. In the study by Shiao and colleagues [94] G:C to A:T transitions at non-CpG sites were found in 80.0% of blacks and 62.3% of whites, with significantly poorer survival associated with *p53* gene alterations being observed for blacks ($P = 0.012$), but not for whites, suggesting that the types of *p53* gene alterations may contribute to the racial difference in breast cancer survival. A recent study found p53 status to be an independent predictor of survival after adjustment for stage, tumor grade, and subtype, and indicating p53 may be useful in identifying African American women at high risk of breast cancer mortality [22].

TN breast cancer is more common in African Americans, and is associated with a worse survival than other subtypes [11,96]. It also shares some biological abnormalities with other tumors (cyclin E, p53, p16, cyclin D) [19]. However, it has been shown that the outcomes in premenopausal African American cases did not become more similar to the other groups when basal-like cases were removed, suggesting that factors other than subtype could also be influencing survival in younger African American women [74].

Abnormalities in other genes have been identified that may be associated with a worse prognosis in African American women. Methylation of the tumor suppressor gene *RASSF1A* has been observed, especially in ER-/PR- tumors of young (aged <50 years) African American women [21]. Studies, including a meta-analysis, have indicated that *RASSF1A* promoter hypermethylation confers a higher risk of relapse and a worse survival in patients with breast cancer [24]. Lastly, abnormalities in chromosome copy numbers have been identified in African American tumors, with twice the frequency of copy number gain in 13q31-13q34 for TN tumors for African American (20%) versus Caucasian (9%) women [23]. This locus contains two 'driver' genes, cullin4A (*CUL4A*) and transcription factor Dp-1 (*TFDP1*), both of which have been associated with shorter overall and disease-free survival. Together, these findings suggest multiple molecular abnormalities in the breast cancer of African American women that may contribute to a worse survival compared to Caucasian women. In addition, these molecular abnormalities provide a range of opportunities for interaction with nonbiological factors to further influence outcome of this disparity.

### Nonbiological activities contributing to increased mortality for breast cancer in African American women

The increased mortality from breast cancer in African Americans compared with Caucasians may be influenced, at least in part, by multiple nonbiological factors, especially those involving health care availability and socioeconomic factors. The magnitude of their contribution has been clarified by a large number of studies examining the impact of adjustment for given nonbiological factors on mortality. These studies are reviewed in Table 1, and it can be seen that, in virtually all cases, adjustment for even multiple factors may lead to partial but still incomplete improvement in outcome. Importantly, these include adjustment for the major prognostic indicators for breast cancer - age, stage, histology, and ER-negative and TN tumors - as well as for all major components of access to health care and delivery, comorbidity, treatment, and many socioeconomic factors. This is well summarized by van Ravesteyn and colleagues [97], who examined models that accurately reproduced observed breast cancer incidence, stage and tumor size distributions, and felt the higher mortality for African American women could be attributed to differences in natural history parameters (26% to 44%), use of adjuvant therapy (11% to 19%), and uptake of mammography screening (7% to 8%); however, 38% to 46% remained unexplained.

Table 1 contains many of the promotional, facilitatory and confounding factors described in the model and for which adjustment was made in the different studies, either directly or through correction for age, stage and histology. The incomplete adjustment by these factors underscores the complexity of factors contributing to the survival disparity. There may, however, be several possible explanations for this failure of adjustment. First is the possibility that nonbiological factors may interact

**Table 1. Effect of adjustment for clinical and demographic factors on survival outcome in African American breast cancer**

| Reference | Adjusted factors | Effect on survival |
|---|---|---|
| Field *et al.* [84] | Unfavorable tumor characteristics (age at diagnosis, stage, grade, tumor size, and ER and progesterone receptor status, treatment, health insurance, access to health care) | Controlling for these characteristics did not fully explain the higher risk of breast cancer death |
| van Ravesteyn *et al.* [97] | Natural history parameters (stage distribution and survival in the absence of screening and adjuvant treatment), use of adjuvant therapy, and uptake of mammography screening | Despite adjustment, 38 to 46% of higher breast cancer mortality remained unexplained |
| Curtis *et al.* [100] | Mammography screening, tumor characteristics at diagnosis, biologic markers, treatment, comorbidity, and demographics (type of community, income) | Controlling for predictor variables reduced, but did not eliminate, the breast cancer survival disparities for stage II/III disease |
| Carey *et al.* [74] | Basal-like cases | The breast cancer-specific survival outcomes in premenopausal African American cases did not become more similar to the other groups when basal-like cases were removed |
| Boyer-Chammard *et al.* [25] | Age, stage, histology and treatment | Black patients had a higher risk of death from breast cancer relative to non-Hispanic white patients even when data were adjusted for age, stage, histology and treatment |
| Adams *et al.* [27] | Age, insurance, stage, Elston grade, ER, and HER2 | After controlling for age, insurance, stage, Elston grade, ER, and HER2, African American women still had a higher risk of death from both breast cancer and all-cause mortality |
| Lund *et al.* [19] | Triple-negative subtype - age, stage, grade, poverty index | Correction for age, stage, grade, poverty index had no effect on the all-cause mortality |
| Porter *et al.* [17] | Age and stage | Observed differences for cyclin E, p16, p53, cyclin D1 between tumor specimens were independent of stage and age at diagnosis |

ER, estrogen receptor.

with each other, as is suggested in Figure 1, and certain factors may have a greater effect in combination with other factors than either alone, and the simple adjustment for each separately may not identify and correct for this influence. Second are unrecognized promotional reproductive and other factors. For example, African Americans have greater parity, beginning at a younger age and at shorter intervals, and have a higher incidence of breast cancer at a younger age. It has been shown that women whose last birth occurred within <2 years of diagnosis of breast cancer had a worse survival (48.2% died) compared with women whose last birth occurred 5 or more years after diagnosis (24.4% died; $P = 0.02$) [98]. This increased predictor of mortality remained after adjustment for tumor characteristics and treatment. Third are potentially unique molecular events contributing to mortality that do not contribute to age, stage, or histology. Intuitively, the molecular abnormalities affecting survival must ultimately be associated with disseminated disease and may thus possess characteristics in addition to those influencing early onset, advanced stage, or aggressive histology. These might include events regulating epithelial-mesenchymal transition [99], a critical event in initiating metastases. African American versus Caucasian breast cancer has not been studied for differences in epithelial-mesenchymal transition biology. If differences do exist, they may also occur very early in breast carcinogenesis and be amenable to influence by nonbiological factors in addition to those already described. These are important questions for future studies. Importantly, as this information becomes available, the model has been designed with flexibility to include new biological or nonbiological factors as they are identified to further clarify factors influencing the disparities.

## Conclusion

African American women with breast cancer have a worse outcome than Caucasian women according to four breast cancer characteristics: earlier age of onset, more advanced stage, more aggressive histologic features, and worse survival. The outcome of a disparity is considered to result from the influence of both biological activities and nonbiological factors. A model has been proposed to indicate the important relationship of the biological and nonbiological factors to each other and to the disparity. This model proposes that the development and outcome of these disparities is primarily determined by a variety of biological abnormalities of the primary tumor that are more common in African American than Caucasian women. The biological activities are versatile, and each may contribute to one or more disparity. The nonbiological factors include a variety of reproductive, health care access and socioeconomic factors that may act to promote or inhibit, to facilitate, or to act as confounding

factors for biological activities. The nonbiological factors may also interact with each other to further influence outcome, and there is evidence to suggest that certain nonbiological factors may influence the outcome of some disparities more than others. As our knowledge and understanding of these disparities advances, additional biological differences and nonbiological factors will be identified. The proposed model has been designed with flexibility to incorporate additional biological and nonbiological factors to further clarify the initiation and development of the disparities. Ultimately, it is hoped this model will facilitate identification of targets that may be modified to reduce or eliminate these disparities.

Finally, while the proposal and conclusions in this review are based on a large number of studies, one must recognize the potential influence of the heterogeneity of breast cancer and the diversity of these ethnic populations. It has been proposed that the disparities in outcome for breast cancer are the result of differences in the biological and nonbiological factors between African American and Caucasian women. The possibility that these differences could be explained by tumor heterogeneity or population genetics or structure should also be considered. Recent studies have demonstrated the heterogeneity in the mutational pattern of breast cancer and the limited number of driver genes that may be mutated in a given tumor; however, these sequencing studies were done without regard to ethnicity. It has been proposed in the present review that there may be different etiologies or different reproductive patterns according to race, and thus one might expect differences in the heterogeneity of gene expression between the races. Whole genome sequencing and expression studies are needed to further define how these differences may contribute to the disparity. It is also important to recognize that captured among African American women as a category for data collection are blacks from the Caribbean, Africa and other parts of the world where there are women of African descent. This tremendously diverse group is influenced by many factors that likely influence prevention, treatment, adherence and overall survival. Similarly, the genome-wide association studies provide evidence for a potential genetic influence for breast cancer disparities between African American and Caucasian women. The degree to which population structure and confounding variables influence these findings is unclear, and clarification of population characteristics will be important. This having been said, there appears to be strong evidence for the influence of the biological activities of the primary tumor and nonbiological factors on the outcomes of the disparities, and for the proposed model describing these relationships. Future studies, especially those that address whole genome abnormalities, population genetics and population structure of these ethnic groups, should further clarify the initiation and development of these important disparities.

#### Abbreviations

CI, confidence interval; ER, estrogen receptor; IGF, insulin-like growth factor; OR, odds ratio; TN, triple negative.

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#### Competing interests

The author declares that he has no competing interests and no non-financial competing interests to declare in relation to this manuscript.

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#### References

1. Siegel R, Naishadham D, Jemal A: **Cancer statistics, 2012.** *CA Cancer J Clin* 2012, **62:**10-29.
2. Thun M, Ward E: **Cancer Facts and Figures for African Americans 2011-2012** [http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027765.pdf]
3. Pinheiro SP, Holmes MD, Pollak MN, Barbieri RL, Hankinson SE: **Racial differences in premenopausal endogenous hormones.** *Cancer Epidemiol Biomarkers Prev* 2005, **14:**2147-2153.
4. Hall IJ, Moorman PG, Millikan RC, Newman B: **Comparative analysis of breast cancer risk factors among African-American women and White women.** *Am J Epidemiol* 2005, **161:**40-51.
5. Chen VW, Correa P, Kurman RJ, Wu XC, Eley JW, Austin D, Muss H, Hunter CP, Redmond C, Sobhan M: **Histological characteristics of breast carcinoma in blacks and whites.** *Cancer Epidemiol Biomarkers Prev* 1994, **3:**127-135.
6. Weiss SE, Tartter PI, Ahmed S, Brower ST, Brusco C, Bossolt K, Amberson JB, Bratton J: **Ethnic differences in risk and prognostic factors for breast cancer.** *Cancer* 1995, **76:**268-274.
7. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, Dolan NC, Paskett ED, McTiernan A, Hubbell FA, Adams-Campbell LL, Prentice R: **Ethnicity and breast cancer: factors influencing differences in incidence and outcome.** *J Natl Cancer Inst* 2005, **97:**439-448.
8. Haiman CA, Chen GK, Vachon CM, Canzian F, Dunning A, Millikan RC, Wang X, Ademuyiwa F, Ahmed S, Ambrosone CB, Baglietto L, Balleine R, Bandera EV, Beckmann MW, Berg CD, Bernstein L, Blomqvist C, Blot WJ, Brauch H, Buring JE, Carey LA, Carpenter JE, Chang-Claude J, Chanock SJ, Chasman DI, Clarke CL, Cox A, Cross SS, Deming SL, Diasio RB, *et al.*: **A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer.** *Nat Genet* 2011, **43:**1210-1214.
9. Kato I, Cichon M, Yee CL, Land S, Korczak JF: **African American-preponderant single nucleotide polymorphisms (SNPs) and risk of breast cancer.** *Cancer Epidemiol* 2009, **33:**24-30.
10. Taioli E, Trachman J, Chen X, Toniolo P, Garte SJ: **A CYP1A1 restriction fragment length polymorphism is associated with breast cancer in African-American women.** *Cancer Res* 1995, **55:**3757-3758.
11. Ray M, Polite BN: **Triple-negative breast cancers: a view from 10,000 feet.** *Cancer J* 2010, **16:**17-22.
12. Joslyn SA: **Hormone receptors in breast cancer: racial differences in distribution and survival.** *Breast Cancer Res Treat* 2002, **73:**45-59.
13. Elledge RM, Clark GM, Chamness GC, Osborne CK: **Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States.** *J Natl Cancer Inst* 1994, **86:**705-712.
14. Setiawan VW, Monroe KR, Wilkens LR, Kolonel LN, Pike MC, Henderson BE: **Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study.** *Am J Epidemiol* 2009, **169:**1251-1259.
15. Dunnwald LK, Rossing MA, Li CI: **Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients.** *Breast Cancer Res* 2007, **9:**R6.
16. Chu KC, Anderson WF, Fritz A, Ries LA, Brawley OW: **Frequency distributions**

of breast cancer characteristics classified by estrogen receptor and progesterone receptor status for eight racial/ethnic groups. *Cancer* 2001, **92:**37-45.
17. Porter PL, Lund MJ, Lin MG, Yuan X, Liff JM, Flagg EW, Coates RJ, Eley JW: **Racial differences in the expression of cell cycle-regulatory proteins in breast carcinoma.** *Cancer* 2004, **100:**2533-2542.
18. Martin DN, Boersma BJ, Yi M, Reimers M, Howe TM, Yfantis HG, Tsai YC, Williams EH, Lee DH, Stephens RM, Weissman AM, Ambs S: **Differences in the tumor microenvironment between African-American and European-American breast cancer patients.** *PLoS ONE* 2009, **4:**e4531.
19. Lund MJ, Trivers KF, Porter PL, Coates RJ, Leyland-Jones B, Brawley OW, Flagg EW, O'Regan RM, Gabram SG, Eley JW: **Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA.** *Breast Cancer Res Treat* 2009, **113:**357-370.
20. Gukas ID, Girling AC, Mandong BM, Prime W, Jennings BA, Leinster SJ: **A comparison of clinicopathological features and molecular markers in british and nigerian women with breast cancer.** *Clin Med Oncol* 2008, **2:**347-351.
21. Mehrotra J, Ganpat MM, Kanaan Y, Fackler MJ, McVeigh M, Lahti-Domenici J, Polyak K, Argani P, Naab T, Garrett E, Parmigiani G, Broome C, Sukumar S: **Estrogen receptor/progesterone receptor-negative breast cancers of young African-American women have a higher frequency of methylation of multiple genes than those of Caucasian women.** *Clin Cancer Res* 2004, **10:**2052-2057.
22. Dookeran KA, Dignam JJ, Ferrer K, Sekosan M, McCaskill-Stevens W, Gehlert S: **p53 as a marker of prognosis in African-American women with breast cancer.** *Ann Surg Oncol* 2010, **17:**1398-1405.
23. Loo LW, Wang Y, Flynn EM, Lund MJ, Bowles EJ, Buist DS, Liff JM, Flagg EW, Coates RJ, Eley JW, Hsu L, Porter PL: **Genome-wide copy number alterations in subtypes of invasive breast cancers in young white and African American women.** *Breast Cancer Res Treat* 2011, **127:**297-308.
24. Jiang Y, Cui L, Chen WD, Shen SH, Ding LD: **The prognostic role of RASSF1A promoter methylation in breast cancer: a meta-analysis of published data.** *PLoS ONE* 2012, **7:**e36780.
25. Boyer-Chammard A, Taylor TH, Anton-Culver H: **Survival differences in breast cancer among racial/ethnic groups: a population-based study.** *Cancer Detect Prev* 1999, **23:**463-473.
26. Joslyn SA, West MM: **Racial differences in breast carcinoma survival.** *Cancer* 2000, **88:**114-123.
27. Adams SA, Butler WM, Fulton J, Heiney SP, Williams EM, Delage AF, Khang L, Hebert JR: **Racial disparities in breast cancer mortality in a multiethnic cohort in the Southeast.** *Cancer* 2011, **118:**2693-2699.
28. Zaloznik AJ: **Breast cancer stage at diagnosis: Caucasians versus Afro-Americans.** *Breast Cancer Res Treat* 1995, **34:**195-198.
29. Althuis MD, Brogan DD, Coates RJ, Daling JR, Gammon MD, Malone KE, Schoenberg JB, Brinton LA: **Breast cancers among very young premenopausal women (United States).** *Cancer Causes Control* 2003, **14:**151-160.
30. Johnson ET: **Breast cancer racial differences before age 40 – implications for screening.** *J Natl Med Assoc* 2002, **94:**149-156.
31. Kurian AW, Fish K, Shema SJ, Clarke CA: **Lifetime risks of specific breast cancer subtypes among women in four racial/ethnic groups.** *Breast Cancer Res* 2010, **12:**R99.
32. Aziz H, Hussain F, Sohn C, Mediavillo R, Saitta A, Hussain A, Brandys M, Homel P, Rotman M: **Early onset of breast carcinoma in African American women with poor prognostic factors.** *Am J Clin Oncol* 1999, **22:**436-440.
33. Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID, Jatoi I: **Racial disparities in breast cancer outcome: insights into host-tumor interactions.** *Cancer* 2007, **110:**1880-1888.
34. Ruiz-Narvaez EA, Rosenberg L, Cozier YC, Cupples LA, Adams-Campbell LL, Palmer JR: **Polymorphisms in the TOX3/LOC643714 locus and risk of breast cancer in African-American women.** *Cancer Epidemiol Biomarkers Prev* 2010, **19:**1320-1327.
35. Yager JD, Davidson NE: **Estrogen carcinogenesis in breast cancer.** *N Engl J Med* 2006, **19:**270-282.
36. Perou CM: **Molecular stratification of triple-negative breast cancers.** *Oncologist* 2011, **16 Suppl 1:**61-70.
37. Loden M, Stighall M, Nielsen NH, Roos G, Emdin SO, Ostlund H, Landberg G: **The cyclin D1 high and cyclin E high subgroups of breast cancer: separate pathways in tumorogenesis based on pattern of genetic aberrations and inactivation of the pRb node.** *Oncogene* 2002, **21:**4680-4690.
38. Nielsen NH, Arnerlov C, Emdin SO, Landberg G: **Cyclin E overexpression, a negative prognostic factor in breast cancer with strong correlation to oestrogen receptor status.** *Br J Cancer* 1996, **74:**874-880.
39. Morris GJ, Naidu S, Topham AK, Guiles F, Xu Y, McCue P, Schwartz GF, Park PK, Rosenberg AL, Brill K, Mitchell EP: **Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database.** *Cancer* 2007, **110:**876-884.
40. Caleffi M, Teague MW, Jensen RA, Vnencak-Jones CL, Dupont WD, Parl FF: **p53 gene mutations and steroid receptor status in breast cancer. Clinicopathologic correlations and prognostic assessment.** *Cancer* 1994, **73:**2147-2156.
41. Allred DC, Clark GM, Elledge R, Fuqua SA, Brown RW, Chamness GC, Osborne CK, McGuire WL: **Association of p53 protein expression with tumor cell proliferation rate and clinical outcome in node-negative breast cancer.** *J Natl Cancer Inst* 1993, **85:**200-206.
42. Donninger H, Vos MD, Clark GJ: **The RASSF1A tumor suppressor.** *J Cell Sci* 2007, **120:**3163-3172.
43. Krop I, Parker MT, Bloushtain-Qimron N, Porter D, Gelman R, Sasaki H, Maurer M, Terry MB, Parsons R, Polyak K: **HIN-1, an inhibitor of cell growth, invasion, and AKT activation.** *Cancer Res* 2005, **65:**9659-9669.
44. Anders CK, Hsu DS, Broadwater G, Acharya CR, Foekens JA, Zhang Y, Wang Y, Marcom PK, Marks JR, Febbo PG, Nevins JR, Potti A, Blackwell KL: **Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression.** *J Clin Oncol* 2008, **26:**3324-3330.
45. Azim HA Jr, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, Haibe-Kains B, Piccart MJ, Sotiriou C, Loi S: **Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling.** *Clin Cancer Res* 2012, **18:**1341-1351.
46. Ihemelandu CU, Leffall LD Jr, Dewitty RL, Naab TJ, Mezghebe HM, Makambi KH, Adams-Campbell L, Frederick WA: **Molecular breast cancer subtypes in premenopausal African-American women, tumor biologic factors and clinical outcome.** *Ann Surg Oncol* 2007, **14:**2994-3003.
47. Albain S, Barlow WE, Shak S, Hortobagyi GN, Hayes DF: **Potential biologic causes of the racial survival disparity in adjuvant trials of ER-positive breast cancer.** *J Clin Oncol* 2010, **28 (Suppl):**511.
48. Bruzzi P, Negri E, La VC, Decarli A, Palli D, Parazzini F, Del Turco MR: **Short term increase in risk of breast cancer after full term pregnancy.** *BMJ* 1988, **297:**1096-1098.
49. Pathak DR, Osuch JR, He J: **Breast carcinoma etiology: current knowledge and new insights into the effects of reproductive and hormonal risk factors in black and white populations.** *Cancer* 2000, **88:**1230-1238.
50. Mukhina S, Mertani HC, Guo K, Lee KO, Gluckman PD, Lobie PE: **Phenotypic conversion of human mammary carcinoma cells by autocrine human growth hormone.** *Proc Natl Acad Sci U S A* 2004, **101:**15166-15171.
51. Key TJ, Appleby PN, Reeves GK, Roddam AW: **Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies.** *Lancet Oncol* 2010, **11:**530-542.
52. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, Smith LV, Labbok MH, Geradts J, Bensen JT, Jackson S, Nyante S, Livasy C, Carey L, Earp HS, Perou CM: **Epidemiology of basal-like breast cancer.** *Breast Cancer Res Treat* 2008, **109:**123-139.
53. Li R, Fridinger F, Grummer-Strawn L: **Racial/ethnic disparities in public opinion about breastfeeding: the 1999–2000 healthstyles surveys in the United States.** *Adv Exp Med Biol* 2004, **554:**287-291.
54. Baquet CR, Mishra SI, Commiskey P, Ellison GL, DeShields M: **Breast cancer epidemiology in blacks and whites: disparities in incidence, mortality, survival rates and histology.** *J Natl Med Assoc* 2008, **100:**480-488.
55. Hunter CP: **Epidemiology, stage at diagnosis, and tumor biology of breast carcinoma in multiracial and multiethnic populations.** *Cancer* 2000, **88:**1193-1202.
56. Lantz PM, Mujahid M, Schwartz K, Janz NK, Fagerlin A, Salem B, Liu L, Deapen D, Katz SJ: **The influence of race, ethnicity, and individual socioeconomic factors on breast cancer stage at diagnosis.** *Am J Public Health* 2006, **96:**2173-2178.
57. Chu KC, Lamar CA, Freeman HP: **Racial disparities in breast carcinoma survival rates: seperating factors that affect diagnosis from factors that affect treatment.** *Cancer* 2003, **97:**2853-2860.
58. Reihani S, Akushevich I, Schildkraut J, Il'yasova D: **Inflammatory breast cancer rates among different ethnic and rcial groups in the United States.** *Cancer Res* 2011, **71 (Suppl 1):**3732.
59. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V: **Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and**

HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. *Cancer* 2007, **109:**1721-1728.
60. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA: **Triple-negative breast cancer: clinical features and patterns of recurrence.** *Clin Cancer Res* 2007, **13:**4429-4434.
61. Dunnwald LK, Rossing MA, Li CI: **Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients.** *Breast Cancer Res* 2007, **9:**R6.
62. Hunter CP, Redmond CK, Chen VW, Austin DF, Greenberg RS, Correa P, Muss HB, Forman MR, Wesley MN, Blacklow RS: **Breast cancer: factors associated with stage at diagnosis in black and white women. Black/White Cancer Survival Study Group.** *J Natl Cancer Inst* 1993, **85:**1129-1137.
63. Shinozaki M, Hoon DS, Giuliano AE, Hansen NM, Wang HJ, Turner R, Taback B: **Distinct hypermethylation profile of primary breast cancer is associated with sentinel lymph node metastasis.** *Clin Cancer Res* 2005, **11:**2156-2162.
64. Hoffman HJ, LaVerda NL, Levine PH, Young HA, Alexander LM, Patierno SR: **Having health insurance does not eliminate race/ethnicity-associated delays in breast cancer diagnosis in the District of Columbia.** *Cancer* 2011, **117:**3824-3832.
65. Sheinfeld SN, Gorin J, Heck E, Gorin JE: **Delay in breast cancer diagnosis by race/ethnicity.** *J Clin Oncol* 2005, **23 (Suppl):**16S.
66. Lannin DR, Mathews HF, Mitchell J, Swanson MS, Swanson FH, Edwards MS: **Influence of socioeconomic and cultural factors on racial differences in late-stage presentation of breast cancer.** *JAMA* 1998, **279:**1801-1807.
67. Trock BJ: **Breast cancer in African American women: epidemiology and tumor biology.** *Breast Cancer Res Treat* 1996, **40:**11-24.
68. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA: **Triple-negative breast cancer: clinical features and patterns of recurrence.** *Clin Cancer Res* 2007, **13:**4429-4434.
69. Collett K, Stefansson IM, Eide J, Braaten A, Wang H, Eide GE, Thoresen SO, Foulkes WD, Akslen LA: **A basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors.** *Cancer Epidemiol Biomarkers Prev* 2005, **14:**1108-1112.
70. Bandera EV, Chandran U, Zirpoli G, Ciupak G, Hwang H, McCann S, Pawlish K, Jandorf L, Bovbjerg D, Ambrosone C: **Anthropometric factors and breast cancer among African American women participating in the Women's Circle of Health Study.** *Cancer Res* 2012, **72:**649.
71. Ownby HE, Frederick J, Russo J, Brooks SC, Swanson GM, Heppner GH, Brennan MJ: **Racial differences in breast cancer patients.** *J Natl Cancer Inst* 1985, **75:**55-60.
72. Elmore JG, Moceri VM, Carter D, Larson EB: **Breast carcinoma tumor characteristics in black and white women.** *Cancer* 1998, **83:**2509-2515.
73. Furberg H, Millikan R, Dressler L, Newman B, Geradts J: **Tumor characteristics in African American and white women.** *Breast Cancer Res Treat* 2001, **68:**33-43.
74. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC: **Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study.** *JAMA* 2006, **295:**2492-2502.
75. Landberg G: **Multiparameter analyses of cell cycle regulatory proteins in human breast cancer: a key to definition of separate pathways in tumorigenesis.** *Adv Cancer Res* 2002, **84:**35-56.
76. Keyomarsi K, Tucker SL, Buchholz TA, Callister M, Ding Y, Hortobagyi GN, Bedrosian I, Knickerbocker C, Toyofuku W, Lowe M, Herliczek TW, Bacus SS: **Cyclin E and survival in patients with breast cancer.** *N Engl J Med* 2002, **347:**1566-1575.
77. Rodriguez-Gil J, Hill J, Allen G, Thomas V, Hu J: **Racial/ethnic differences in double-strand break repair signaling in breast cancer.** *Cancer Res* 2010, **70:**4704.
78. Dowle CS, Owainati A, Robins A, Burns K, Ellis IO, Elston CW, Blamey RW: **Prognostic significance of the DNA content of human breast cancer.** *Br J Surg* 1987, **74:**133-136.
79. Kallioniemi OP, Hietanen T, Mattila J, Lehtinen M, Lauslahti K, Koivula T: **Aneuploid DNA content and high S-phase fraction of tumour cells are related to poor prognosis in patients with primary breast cancer.** *Eur J Cancer Clin Oncol* 1987, **23:**277-282.
80. Tarapore P, Fukasawa K: **Loss of p53 and centrosome hyperamplification.** *Oncogene* 2002, **21:**6234-6240.
81. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de RM, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Eystein LP, Borresen-Dale AL: **Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications.** *Proc Natl Acad Sci U S A* 2001, **98:**10869-10874.
82. Tammemagi CM: **Racial/ethnic disparities in breast and gynecologic cancer treatment and outcomes.** *Curr Opin Obstet Gynecol* 2007, **19:**31-36.
83. Schairer C, Mink PJ, Carroll L, Devesa SS: **Probabilities of death from breast cancer and other causes among female breast cancer patients.** *J Natl Cancer Inst* 2004, **96:**1311-1321.
84. Field TS, Buist DS, Doubeni C, Enger S, Fouayzi H, Hart G, Korner EJ, Lamerato L, Bachman DJ, Ellis J, Herrinton L, Hornbrook MC, Krajenta R, Liu L, Yao J: **Disparities and survival among breast cancer patients.** *J Natl Cancer Inst Monogr* 2005:88-95.
85. Henson DE, Chu KC, Levine PH: **Histologic grade, stage, and survival in breast carcinoma: comparison of African American and Caucasian women.** *Cancer* 2003, **98:**908-917.
86. Hirschman J, Whitman S, Ansell D: **The black:white disparity in breast cancer mortality: the example of Chicago.** *Cancer Causes Control* 2007, **18:**323-333.
87. Lu Y, Ma H, Malone KE, Norman SA, Sullivan-Halley J, Strom BL, Marchbanks PA, Spirtas R, Burkman RT, Deapen D, Folger SG, Simon MS, Press MF, McDonald JA, Bernstein L: **Obesity and survival among black women and white women 35 to 64 years of age at diagnosis with invasive breast cancer.** *J Clin Oncol* 2011, **29:**3358-3365.
88. Gillett C, Smith P, Gregory W, Richards M, Millis R, Peters G, Barnes D: **Cyclin D1 and prognosis in human breast cancer.** *Int J Cancer* 1996, **69:**92-99.
89. Donnellan R, Kleinschmidt I, Chetty R: **Cyclin E immunoexpression in breast ductal carcinoma: pathologic correlations and prognostic implications.** *Hum Pathol* 2001, **32:**89-94.
90. Nielsen NH, Emdin SO, Cajander J, Landberg G: **Deregulation of cyclin E and D1 in breast cancer is associated with inactivation of the retinoblastoma protein.** *Oncogene* 1997, **14:**295-304.
91. Li HP, Ji JF, Hou KY, Lei YT, Zhao HM, Wang J, Zheng J, Liu JY, Wang MP, Xiao Y, Wang YF, Lu YY, Sun Y: **Prediction of recurrence risk in early breast cancer using human epidermal growth factor 2 and cyclin A2.** *Chin Med J (Engl )* 2010, **123:**431-437.
92. Agarwal R, Gonzalez-Angulo AM, Myhre S, Carey M, Lee JS, Overgaard J, Alsner J, Stemke-Hale K, Lluch A, Neve RM, Kuo WL, Sorlie T, Sahin A, Valero V, Keyomarsi K, Gray JW, Borresen-Dale AL, Mills GB, Hennessy BT: **Integrative analysis of cyclin protein levels identifies cyclin b1 as a classifier and predictor of outcomes in breast cancer.** *Clin Cancer Res* 2009, **15:**3654-3662.
93. Aaltonen K, Amini RM, Heikkila P, Aittomaki K, Tamminen A, Nevanlinna H, Blomqvist C: **High cyclin B1 expression is associated with poor survival in breast cancer.** *Br J Cancer* 2009, **100:**1055-1060.
94. Shiao YH, Chen VW, Scheer WD, Wu XC, Correa P: **Racial disparity in the association of p53 gene alterations with breast cancer survival.** *Cancer Res* 1995, **55:**1485-1490.
95. Blaszyk H, Vaughn CB, Hartmann A, McGovern RM, Schroeder JJ, Cunningham J, Schaid D, Sommer SS, Kovach JS: **Novel pattern of p53 gene mutations in an American black cohort with high mortality from breast cancer.** *Lancet* 1994, **343:**1195-1197.
96. Ihemelandu CU, Naab TJ, Mezghebe HM, Makambi KH, Siram SM, Leffall LD Jr, DeWitty RL Jr, Frederick WA: **Treatment and survival outcome for molecular breast cancer subtypes in black women.** *Ann Surg* 2008, **247:**463-469.
97. van Ravesteyn NT, Schechter CB, Near AM, Heijnsdijk EA, Stoto MA, Draisma G, de Koning HJ, Mandelblatt JS: **Race-specific impact of natural history, mammography screening, and adjuvant treatment on breast cancer mortality rates in the United States.** *Cancer Epidemiol Biomarkers Prev* 2011, **20:**112-122.
98. Daling JR, Malone KE, Doody DR, Anderson BO, Porter PL: **The relation of reproductive factors to mortality from breast cancer.** *Cancer Epidemiol Biomarkers Prev* 2002, **11:**235-241.
99. Wang Y, Zhou BP: **Epithelial-mesenchymal transition in breast cancer progression and metastasis.** *Chin J Cancer* 2011, **30:**603-611.
100. Curtis E, Quale C, Haggstrom D, Smith-Bindman R: **Racial and ethnic differences in breast cancer survival: how much is explained by screening, tumor severity, biology, treatment, comorbidities, and demographics?** *Cancer* 2008, **112:**171-180.

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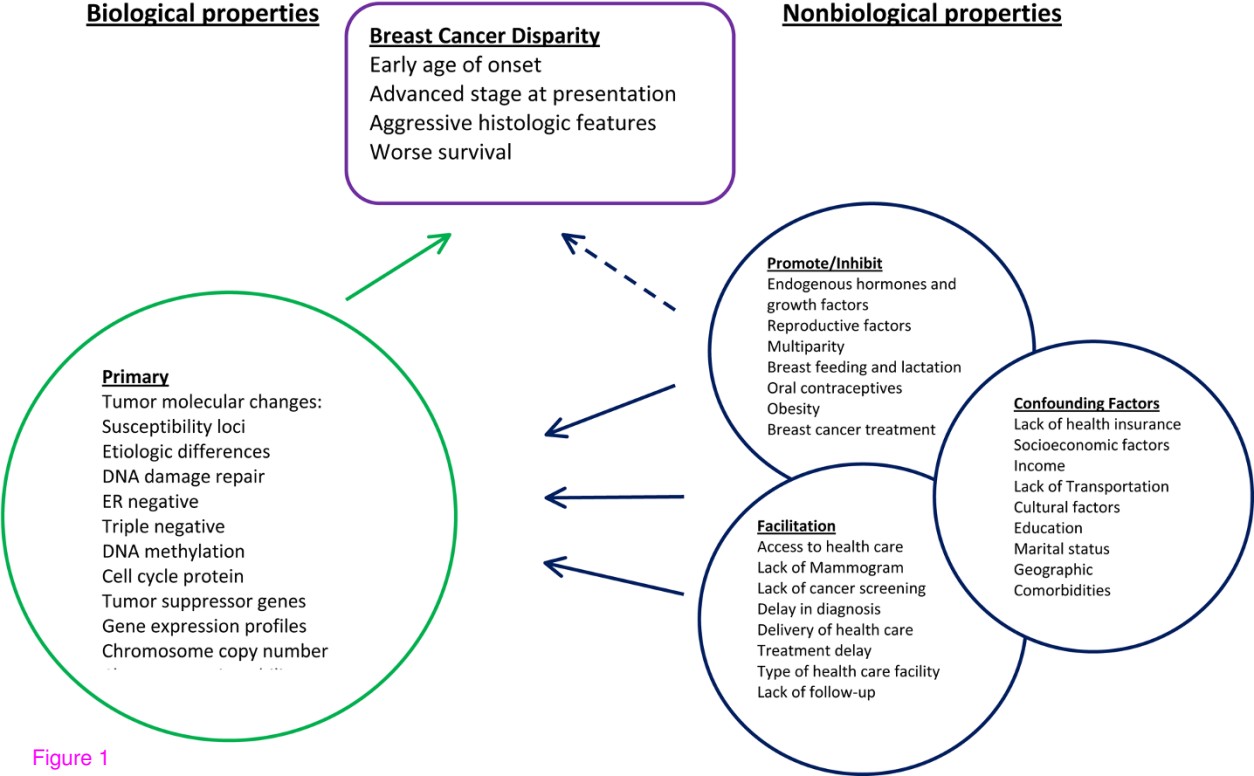
Biological properties
Nonbiological properties
Breast Cancer Disparity
Early age of onset
Advanced stage at presentation
Aggressive histologic features
Worse survival
Primary
Tumor molecular changes:
Susceptibility loci
Etiologic differences
DNA damage repair
ER negative
Triple negative
DNA methylation
Cell cycle protein
Tumor suppressor genes
Gene expression profiles
Chromosome copy number
Promote/Inhibit
Endogenous hormones and growth factors
Reproductive factors
Multiparity
Breast feeding and lactation
Oral contraceptives
Obesity
Breast cancer treatment
Confounding Factors
Lack of health insurance
Socioeconomic factors
Income
Lack of Transportation
Cultural factors
Education
Marital status
Geographic
Comorbidities
Facilitation
Access to health care
Lack of Mammogram
Lack of cancer screening
Delay in diagnosis
Delivery of health care
Treatment delay
Type of health care facility
Lack of follow-up

Figure 1

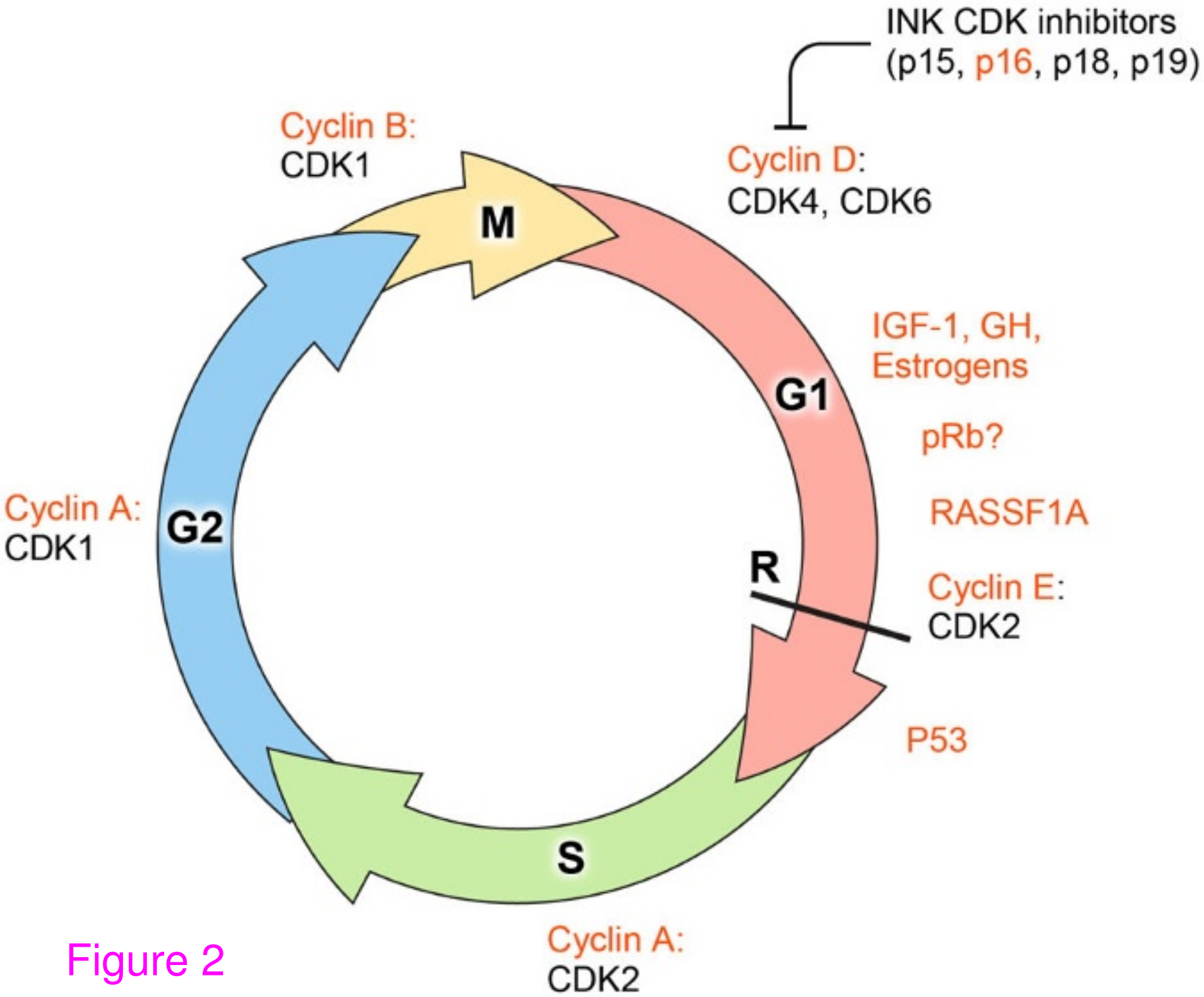
INK CDK inhibitors
(p15, p16, p18, p19)
Cyclin B:
CDK1
Cyclin D:
CDK4, CDK6
M
G1
IGF-1, GH,
Estrogens
pRb?
RASSF1A
Cyclin E:
CDK2
P53
R
Cyclin A:
CDK1
G2
S
Cyclin A:
CDK2

Figure 2