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## Triple-negative breast cancer in African-American women: disparities versus biology

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### Abstract

Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype that disproportionately affects *BRCA1* mutation carriers and young women of African origin. There is evidence that African-American women with TNBC have worse clinical outcomes than women of European descent. However, it is unclear whether survival differences persist after adjusting for disparities in access to health-care treatment, co-morbid disease and income. It remains controversial whether TNBC in African-American women is a molecularly distinct disease or whether African-American women have a higher incidence of aggressive biology driven by disparities: there is evidence in support of both. Understanding the relative contributions of biology and disparities is essential for improving the poor survival rate of African-American women with TNBC.

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Triple-negative breast cancer (TNBC) represents a diverse group of cancers that are characterized by lack of expression of the oestrogen receptor (ER) and progesterone receptor (PR) and absence of *ERBB2* (also known as *HER2*) amplification<sup>1</sup>. There is a high prevalence of TNBC in women of African descent and women who carry a mutated copy of the *BRCA1* gene<sup>2</sup>. The basal subset of TNBC is characterized by the expression of basal-

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#### Competing interests statement

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#### FURTHER INFORMATION

Black Women's Health Study: <http://www.bu.edu/bwhs/>

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type cytokeratin 5 and cytokeratin 6 and high expression of epidermal growth factor receptor (EGFR), and frequently exhibits aggressive clinical behaviour<sup>2</sup>. Women with TNBC have a high frequency of metastasis to the lung, liver and brain, and survival is generally poor<sup>3</sup>.

There is evidence that African-American women with TNBC have worse clinical outcomes compared with women of European descent who have the disease. However, published reports of survival outcomes for African-American women with TNBC, relative to European-American women, are conflicting<sup>4–10</sup>. Furthermore, it is unclear whether survival differences persist after adjusting for disparities in access to health-care treatment, co-morbid disease and income. African-American women experience lack of access to breast cancer screening, lack of access to oncology care and delays in treatment<sup>11</sup>. There is strong evidence that disparities in health-care provision, co-morbid disease and income affect the stage of presentation and survival of African-American women with TNBC<sup>11,12</sup>. Emerging data also indicate that disparities may drive aggressive biology in African-American women with TNBC. It is essential that we understand the potential molecular mechanism by which biology and disparities may intersect to drive the aggressive TNBC subtypes in African-American women: such knowledge may lead to the development of models that specifically capture the risk of women of African descent for TNBC, to increased access to effective early detection and to the implementation of health policies to eliminate disparities.

## Demographics and prognosis

### TNBC is a distinct subtype

In 2001, Perou and colleagues used cDNA microarray profiling to identify breast cancer subtypes<sup>2,13,14</sup>. These subtypes were subsequently integrated with traditional hormone-receptor-based clinical subtyping to define four integrated subtypes: basal-like (ER<sup>-</sup>, PR<sup>-</sup>, no *ERBB2* amplification, cytokeratin 5<sup>+</sup>, cytokeratin 6<sup>+</sup> and EGFR<sup>+</sup>); ERBB2<sup>+</sup> (*ERBB2* amplified) and ER<sup>-</sup> and PR<sup>-</sup> (ERBB2<sup>+</sup>, ER<sup>-</sup> and PR<sup>-</sup>); luminal A (ER<sup>+</sup> and/or PR<sup>+</sup>, no *ERBB2* amplification); and luminal B (ER<sup>+</sup> and/or PR<sup>+</sup>, and ERBB2<sup>+</sup>). Over 75% of TNBCs express basal markers and cluster with the basal-like subtype by gene expression profiling<sup>2,13,14</sup>.

### Demographics

Many studies show that premenopausal African-American and African women have a high prevalence of TNBC relative to women of European descent (TABLE 1). The Carolina Breast Cancer Study showed that the highest prevalence of the basal-like subtype of TNBC (39%; 38/97 invasive cancers) occurred in premenopausal African-American women. This was substantially higher than the prevalence of TNBC observed in post-menopausal African-American women (14%; 14/99 invasive cancers) or American women of European descent (16%; 48/300 invasive cancers) ( $p < 0.001$  for both comparisons)<sup>3</sup>. The high frequency of TNBC in African-American women has also been observed in population-based studies in Philadelphia<sup>15</sup>, Boston<sup>16</sup>, Georgia<sup>4</sup> and Michigan<sup>17</sup> (TABLE 1).

Several studies show that TNBC occurs in sub-Saharan and West African women at a higher frequency and a younger age than in African-American women<sup>17–19</sup>. Although breast cancer

incidence rates among sub-Saharan African women are low (10–40 per 100,000), these women experience higher mortality rates (5–20 per 100,000) and are more often diagnosed at a younger age than either African-American or European-American women (peak incidence: 35–45 years). In a population-based study that evaluated African-American and European-American women with invasive breast cancer at Henry Ford Hospital in Detroit, Michigan, USA, and Ghanaian women with invasive breast cancer at Komfo Anokye Hospital in Kumasi, Ghana, 83% ( $n = 507$ ) of Ghanaian women had TNBC, whereas 41.9% ( $n = 507$ ) of African-American women and 15.4% of European-American women had TNBC. Most of the Ghanaian women (83%) presented with advanced, high-grade tumours<sup>17</sup>. One of the strengths of this study was that all biopsy samples underwent central pathology review and analysis of expression of ERBB2, ER and PR at the University of Michigan in Ann Arbor, USA. A second study evaluated a collection of 507 invasive breast cancers from six sites in Nigeria and Senegal; most of the tumours were basal-like or unclassified subtypes (27% and 28%, respectively), 29% were luminal A or B, 15% were the ERBB2<sup>+</sup> and ER<sup>-</sup> subtype, and 1% were unclassified<sup>20</sup>. However, not all studies of African women show an increased incidence of TNBC or a younger age of presentation. In a population-based study of 1,218 consecutive women (91% black) diagnosed with invasive breast cancer from 2006 to 2012 at a public hospital in Soweto, South Africa, the age-specific incidence of TNBC in black South African women was similar to that in African-American women<sup>21</sup>.

## Prognosis

African-American women have higher overall breast cancer mortality compared with women of European descent<sup>3,8,22</sup>. Contributing factors include disparities in income, barriers to screening, differences in treatment, higher stage of disease at diagnosis and increased incidence of TNBC<sup>23–27</sup>. Although Western nations have a higher incidence of breast cancer in comparison to developing nations, mortality is highest in developing nations. The factors influencing a woman's survival are affected by cultural and economic barriers to care and vary greatly throughout the world<sup>27</sup>.

Newman and her colleagues<sup>28</sup> conducted a meta-analysis of over 13,000 African-American women with breast cancer compared with 75,000 women of European descent. In this study, African-American identity was associated with a statistically significant, nearly 30% higher mortality rate (mortality hazard, 1.27; 95% confidence interval, 1.18–1.38). Although African-American identity is associated with poor prognosis, it is unclear whether poor survival is due to differences at the molecular level, beyond an increased frequency of TNBC<sup>3</sup>.

Studies of the impact of race on survival in women with TNBC have yielded mixed results. Dean-Colomb *et al.*<sup>10</sup> compared transcriptional profiles of tumours of 98 women with TNBC who received cytotoxic chemotherapy and observed no differences in pathologic complete response (pCR) rates by ethnicity or race, and no differences in gene expression between African-American and Caucasian women. Dawood *et al.*<sup>9</sup> investigated the impact of race on pCR in 471 women with TNBC who were receiving anthracycline-based chemotherapy and showed that race did not significantly affect outcome. Shen *et al.*<sup>8</sup>

reported shorter survival rates among African-American women compared with women of European descent ( $n = 6,054$ ). Woodward *et al.*<sup>7</sup> explored the effect of race on survival outcome in patients treated at the University of Texas MD Anderson Cancer Center in Houston, USA, and reported that, despite a uniform distribution of treatment, African-American race was independently associated with poorer survival. Albain's group<sup>6</sup> found that African-American women with early-stage premenopausal breast cancer participating in Phase III Southwest Oncology Group (SWOG) trials had a significantly worse prognosis than age- and prognosis-matched European-American women. Bauer *et al.*<sup>5</sup> and Lund *et al.*<sup>4</sup> also reported a worse survival for African-American women with TNBC after controlling for socioeconomic factors, treatment delay and breast cancer receptor expression (FIG. 1). Taken together, these studies provide evidence that even after controlling for treatment disparities, biological differences may contribute to the poor survival of women with TNBC. However, the data are inconsistent, and molecular studies are needed to better define potential biological differences.

## Genetic risk

### Frequency of *BRCA1* mutations in African-American women with TNBC is low relative to women of European descent

*BRCA1* is a tumour suppressor gene and has a key role in homology-directed repair of DNA double-strand breaks<sup>29–31</sup>. Most breast cancers (69%) in women with *BRCA1* mutations are TNBCs<sup>32</sup>. Although the incidence of TNBC is high in African-American women, several studies show that the incidence of germline *BRCA1* mutations is low relative to the incidence in women of European descent. In a study of 155 high-risk families evaluated at the University of Chicago in Illinois, USA, African Americans had a lower rate of deleterious germline *BRCA1* mutations compared with non-Hispanic, non-Jewish Caucasians (27.9% versus 46.2%, respectively) but a higher rate of sequence variations (44.2% versus 11.5%, respectively;  $p < 0.001$ )<sup>33,34</sup>. Deleterious mutations in *BRCA1* were highest for Ashkenazi-Jewish women (69.0%)<sup>33</sup>. Similarly, whereas 50% of Caucasian non-Ashkenazi-Jewish women with TNBC had germline *BRCA1* mutations, fewer than 20% of African-American women with TNBC had germline *BRCA1* mutations<sup>35</sup>. This suggests that another genetic mechanism (or mechanisms) beyond germline mutation of *BRCA1* may promote TNBC in African-American women.

A diverse spectrum of *BRCA1* mutations and sequence variations unique to African women has been reported<sup>36–42</sup>. A complete review of the founder mutations identified in African-American women is beyond the scope of this article (see Oluwagbemiga *et al.*<sup>36</sup> for a full review). However, although many sequence variations of *BRCA1* have been found in women of African descent, only a small number of the mutations result in known structural defects that block BRCA1 function (for example, protein-truncating mutations)<sup>37–42</sup>, and these known structural mutations occur in women of African origin at a lower rate than is observed in women of European descent<sup>37</sup>.

BROCA profiling tests for 18–40 genes (in addition to BRCA) that repair DNA. These new 'panel tests' use a combination of targeted genomic capture and next-generation sequencing and are becoming widely available. It is anticipated that such panel tests will provide

important insights into the genetic mutations that contribute to TNBC risk. BROCA profiling of 249 African-American women with breast cancer found that approximately 20% carried an inherited abnormality in at least 1 of 18 genes associated with breast cancer susceptibility; 56 of 249 women (22%) had at least one clinically relevant mutation<sup>43</sup>. Most women carried a single mutation, and most mutations (79%) were in *BRCA1* and *BRCA2*. However, 21% of the mutations were in other cancer-associated genes, including ataxia telangiectasia mutated (*ATM*), checkpoint kinase 2 (*CHEK2*; also known as *CHK2*), partner and localizer of BRCA2 (*PALB2*) and *PTEN*. Mutations were most common in patients with a second primary cancer in the breast (49%), TNBC (30%) and/or a family history of either breast or ovarian cancer in a close relative (30%), and/or in patients diagnosed before the age of 45 years (27%)<sup>43</sup>.

A recent study in women of European descent identified that loss-of-function mutations in *PALB2* are an important cause of hereditary breast cancer<sup>44</sup>. Another recent study evaluated the contribution of germline *PALB2* mutations in 279 African-American women with breast cancer; novel monoallelic truncating mutations were identified in three patients (1.08%) together with 50 sequence variants. This study showed that rare *PALB2* mutations accounted for a small but substantial proportion of breast cancer in women of African descent<sup>45</sup>.

### Genome-wide studies

Most genome-wide association studies (GWASs) have been carried out in European-ancestry populations; no risk variants for TNBC have been identified solely in women of African ancestry. As the Black Women's Health Study matures (see Further information), it is anticipated that GWASs focusing on women of African ancestry will provide important insights into the genetic basis of TNBC in African-American women. GWASs of African-American women identified a common risk variant at the telomerase reverse transcriptase (*TERT*)–CLPTM1-like (*CLPTMIL*) locus on chromosome 5p15 (odds ratio (OR) = 1.25;  $p = 1.1 \times 10^{-9}$ ) that was present at a greater frequency in African-American women than in women of European ancestry and was significantly associated with TNBC in women less than 50 years old (OR = 1.48;  $p = 1.9 \times 10^{-9}$ )<sup>46</sup>. A genetic variant in the *LOC643714* gene has also been identified that predicts a 23% increased risk for breast cancer in African-American women but not in women of European ancestry (OR = 1.23; 95% confidence interval, 1.05–1.44)<sup>47</sup>. A nested case–control study of breast cancer in the Black Women's Health Study (1,199 cases/1,948 controls) identified two single-nucleotide polymorphisms — rs10069690 in 5p13.33 (*TERT* gene) and rs8170 in 19p13.11 — that were significantly associated with TNBC in African-American women, with higher ORs relative to controls<sup>48</sup>.

## Biology of TNBC

### Unique biology versus higher frequency of poor prognosis subtypes

As outlined above, disparities in treatment, co-morbid disease, income and access to health care all affect survival. It is unclear whether women of African descent have worse survival owing to an increased frequency of TNBC subtypes that have poor prognosis or whether TNBC in women of African descent has a uniquely aggressive biology. Studies comparing biological differences between TNBC in African-American and European-American women

have yielded conflicting results. Some studies have been complicated by the combined analysis of multiple breast cancers<sup>49,50</sup>. A key emerging area of study is the potential interaction between disparities and signalling pathways that are known to promote aggressive biology and genomic instability (FIGS 2,3).

### The Cancer Genome Atlas

The Cancer Genome Atlas recently analysed primary breast cancers from 627 women, 53 of whom (8.5%) were African American<sup>51</sup>. Relative to breast cancers in women of European descent, breast cancers from African-American women showed increased expression of members of the p53, BRCA1, Aurora A, Aurora B and polo-like kinase signalling networks<sup>52</sup>.

Comparisons of TNBC arising in African-American versus European-American women have yielded varied results. The gene expression profiles of the disease have been shown to be highly similar between these two groups<sup>53</sup>. In a study by Lindner *et al.* comparing a total of 128 TNBC tumour samples from European-American women (54%) and African-American women (39%) — the remaining 7% were of Hispanic origin — the transcriptional profiles from African-American women demonstrated a gene expression signature that was consistent with increased loss of BRCA1 expression, increased activation of insulin-like growth factor 1 receptor (IGF1R) and increased expression of vascular endothelial growth factor-activated genes, as compared with the transcriptional profiles of European-American women<sup>54</sup>. Although these studies directly compared TNBC in African-American women versus European-American women, they did not control for body mass index. Increased expression of IGF1R may be attributable to obesity (which is on average higher in African-American women) and increased insulin signalling.

### EZH2 network signalling

Enhancer of zeste homologue 2 (EZH2) is a member of the Polycomb group (PcG) family. PcG family members form multimeric protein complexes that maintain the transcriptional repressive state of genes over successive cell generations<sup>55–57</sup>. EZH2 overexpression is observed in TNBC and is associated with poor prognosis in women of European descent<sup>55,57</sup>. EZH2 has been shown to induce AKT-dependent genomic instability and block BRCA1 function<sup>58</sup>. There is emerging evidence that EZH2 may also have a role in the aggressive biology of TNBC in African women. A joint study by Kleer and Newman<sup>59</sup> investigated the role of EZH2 expression in 100 invasive breast cancers obtained from Ghanaian women. Of the 100 invasive carcinomas, 89% were ductal, 2% were lobular and 9% were metaplastic; 30% of the tumours were basal-type TNBC. Nuclear EZH2 overexpression was significantly associated with the basal-like subtype of TNBC ( $p = 0.03$ ) in women of African descent, and was seen in 42% of basal-type TNBC cases in women of African descent. Similarly, in a set of 295 patients with breast cancer from the Netherlands, 40.3% of cases showed high EZH2 expression and a significant association with basal-type cancer ( $p < 0.0001$ )<sup>60</sup>. Therefore, EZH2 might play a part in TNBC regardless of patient ethnicity.

## WNT

WNT genes encode a family of signalling molecules that are involved in embryologic development and progenitor cell renewal, and WNT- $\beta$ -catenin signalling is known to be activated in TNBC arising in women of all races<sup>61</sup>. Studies specifically investigating WNT- $\beta$ -catenin signalling in TNBC in women of African descent are limited. A pilot study comparing expression of *WNT10B* and the WNT10B target gene high mobility group AT-hook 2 (*HMGA2*) in TNBC from women living in Los Angeles (California, USA), Chicago (Illinois, USA), Berlin (Germany) and North Carolina (USA) shows that *WNT10B* and *HMGA2* expression are increased in TNBCs in both women of African descent (15/17 (88%) and 15/17 (88%), respectively) and women of European descent (33/45 (73%) and 36/45 (80%), respectively)<sup>62</sup>. Differential gene expression studies comparing stage- and age-matched TNBC in women of African origin ( $n = 31$ ) and women of European origin ( $n = 13$ ) showed that dysregulated genes associated with the WNT- $\beta$ -catenin pathway were significantly enriched (fold-change  $>3.0$ ;  $p < 0.05$ ) in women of African origin compared with the women of European descent, suggesting that activation of this pathway may contribute to the more aggressive phenotype of TNBC in women of African origin<sup>63</sup>.

### Progenitor-like cells

Breast cancers have been reported to contain a subpopulation of cells with the ability to self-renew and undergo differentiation to phenotypically diverse populations of tumour cells<sup>64</sup>. Cell surface markers associated with self-renewal capacity include CD44 and aldehyde dehydrogenase 1 (ALDH1; also known as retinal dehydrogenase 1 and ALDH1A1) and low or no CD24 expression<sup>64–66</sup>. A study by Nalwoga *et al.*<sup>67</sup> tested for ALDH1 in 192 breast cancers from women of African descent. ALDH1 expression was detected in 88 breast cancer specimens from Uganda (48%) and was associated with p53 ( $p = 0.034$ ) and basal-type markers ( $p = 0.008$ )<sup>67</sup>. For comparison, 19% and 30% of breast tumours were ALDH1<sup>+</sup> in tissue collected from non-African women in Michigan (USA) and France, respectively<sup>65</sup>.

## A link to aggressive biology?

### Survival has improved in European-American but not in African-American women

Women of European descent diagnosed with breast cancer experienced increased survival rates in 1999–2005 relative to 1991–1998 (REF. 68). By contrast, African-American women did not experience improved breast cancer survival during this same time period<sup>68</sup>. Poor survival rates for African-American women are attributed to advanced disease presentation, co-morbid disease<sup>11</sup>, disparities in income, lack of access to breast cancer screening and oncology care, and delays in treatment<sup>11</sup>. African-American women experience an unequal burden of co-morbid disease, including obesity, diabetes and hypertension<sup>69</sup>.

There is a clear association between unequal living standards and increased levels of co-morbid disease. Disparities that promote disease include unsafe neighbourhoods, lack of access to grocery stores, stress and exposures to environmental carcinogens<sup>70</sup>. There is increasing evidence that disparities in health and co-morbid diseases may play a part in defining the biology of TNBC in women of African descent, but more work is needed before definite conclusions can be drawn (FIG. 4). Currently, the molecular link between disparities

and TNBC is poorly defined. Emerging areas of research include obesity, tissue inflammation and the role of disparities in altering phosphoprotein signalling (FIG. 2) and genomic instability (FIG. 3).

### Obesity and tissue inflammation

The Carolina Breast Cancer Study demonstrated that high body mass index and high waist/hip ratio increased the risk of the basal subset of TNBC in premenopausal African-American women<sup>3</sup>. Several studies, including a recent meta-analysis, have shown that obesity is a general risk factor for TNBC in premenopausal women<sup>71–73</sup>. Because there is a higher incidence of obesity in African-American women and obesity predicts poor survival, it is hypothesized that obesity is a potential driver of aggressive TNBC biology in African-American women. There are many potential biological mechanisms by which obesity might increase the incidence of aggressive subtypes of TNBC in African and African-American women (FIG. 2). Obese women have tissue inflammation associated with increased circulating levels of insulin and inflammatory cytokines, including interleukin-6 (IL-6), IL-8, tumour necrosis factor (TNF) and leptin. IL-6 and IL-8 activate signal transducer and activator of transcription 3 (STAT3)–nuclear factor- $\kappa$ B (NF- $\kappa$ B) and EZH2 signalling, and predict poor prognosis in women with TNBC<sup>74,75</sup>.

### Pregnancy, involution and inflammation

Approximately 21% of African-American women breastfeed in comparison to 37% of European-American women<sup>76</sup>. A lack of breastfeeding increases the risk of women developing TNBC<sup>76–78</sup>. After lactation, or parturition in the absence of nursing, the mammary gland undergoes involution<sup>79</sup>. Using mice, Schedin and colleagues have shown that breast tissue involution following lactation results in tissue inflammation and activation of cyclooxygenase 2 (COX2; also known as prostaglandin G/H synthase 2), and wound-healing programmes that promote the deposition of high-risk crosslinked, fibrillar collagen<sup>79</sup>. Aligned fibrillar collagen predicts poor survival in European-American women with invasive breast cancer<sup>80</sup>. Further studies are needed to better understand the molecular link between pregnancy, parity and TNBC in African-American and African women.

### Summary and future directions

Less than 20–25% of African-American women with TNBC have a germline *BRCA1* mutation. Future challenges include defining the molecular signalling pathways that promote TNBC in women of African descent. It will be important to distinguish whether women of African descent have an increased incidence of TNBC subtypes that have a poor prognosis or whether there are unique biological factors that promote aggressive biology.

Studies of African women provide evidence that TNBC is a disease of young women of African descent and suggest that environmental and/or genetic factors may influence the age of onset and subtype frequency in different populations. Defining the molecular link between environmental exposures, disparities and TNBC in African-American and African women is a complex undertaking. Key areas include the identification of windows of vulnerability (such as environmental exposures *in utero*, during puberty and during



pregnancy), the role of obesity in promoting aggressive TNBC biology and the determination of whether environmental disparities, such as unsafe neighbourhoods, stress and toxic-waste dumping, play a part in aggressive biology.

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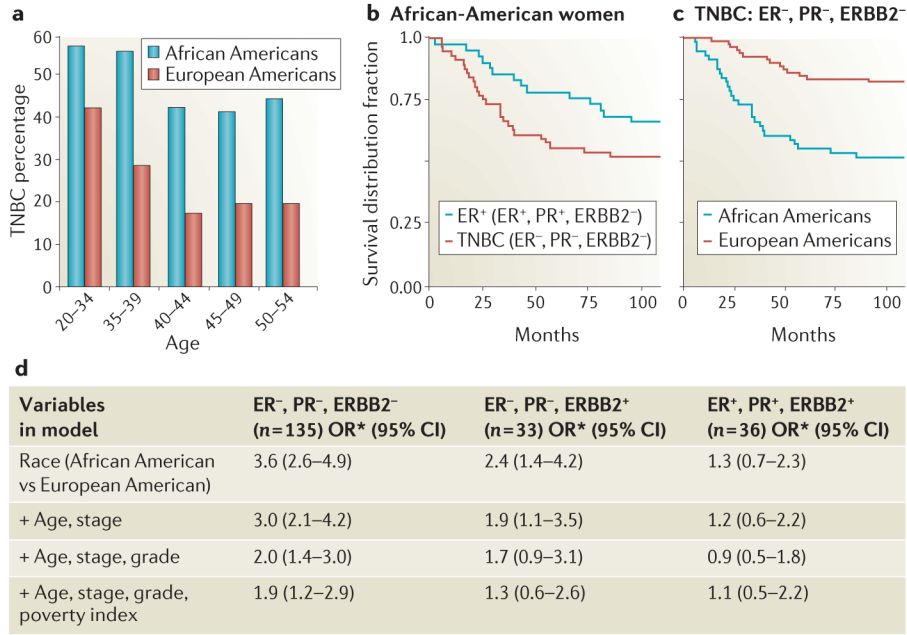
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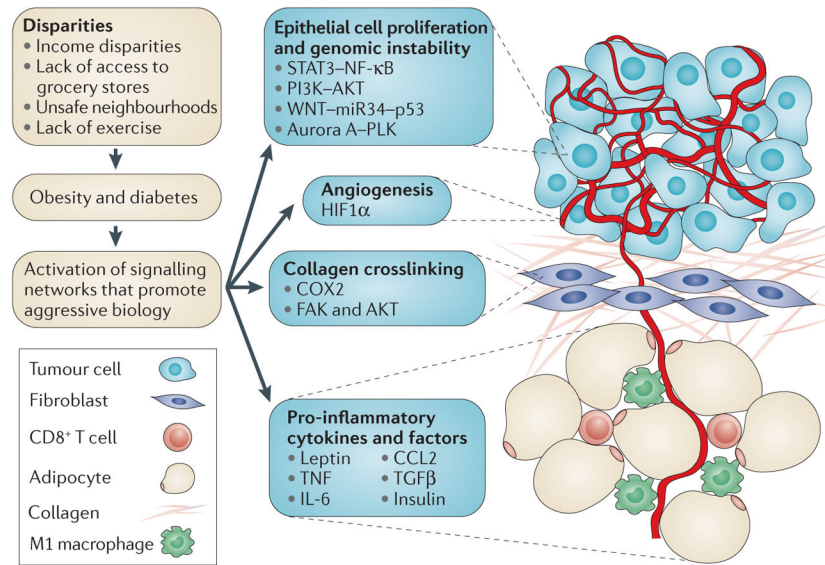
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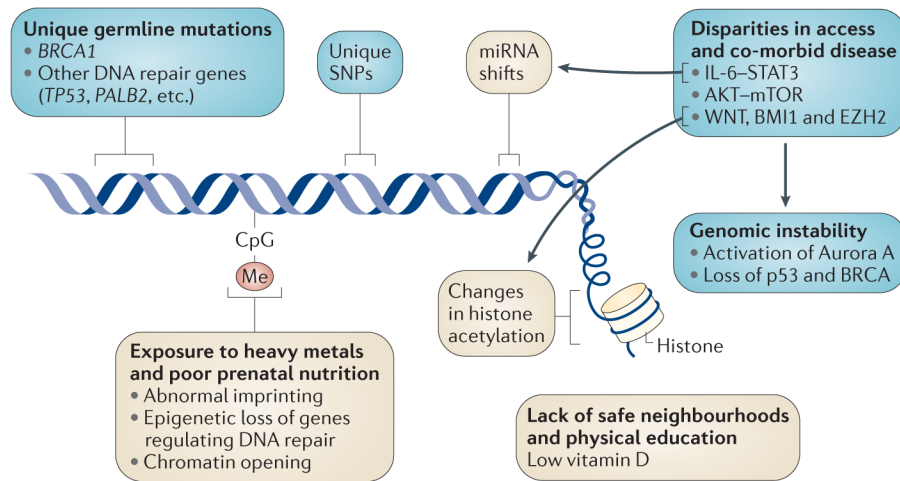


**Figure 1. TNBC in African-American compared with European-American women**  
**a** | Age-related incidence of triple-negative breast cancer (TNBC) by race, shown as a percentage of overall breast cancer incidence. **b** | Survival of African-American women based on breast cancer subtype (oestrogen receptor (ER)<sup>+</sup>, progesterone receptor (PR)<sup>+</sup>, ERBB2<sup>-</sup> versus ER<sup>-</sup>, PR<sup>-</sup>, ERBB2<sup>-</sup>). **c** | TNBC survival rate based on race. **d** | Adjusted odds ratios (ORs) for race (African Americans compared with European Americans) in the Atlanta study<sup>4</sup>. Data for parts **a–d** are derived from Lund *et al.*<sup>4</sup> with kind permission from Springer Science and Business Media. CI, confidence interval.



**Figure 2. Proposed model of how disparities might drive signalling pathways associated with aggressive biology in TNBC**

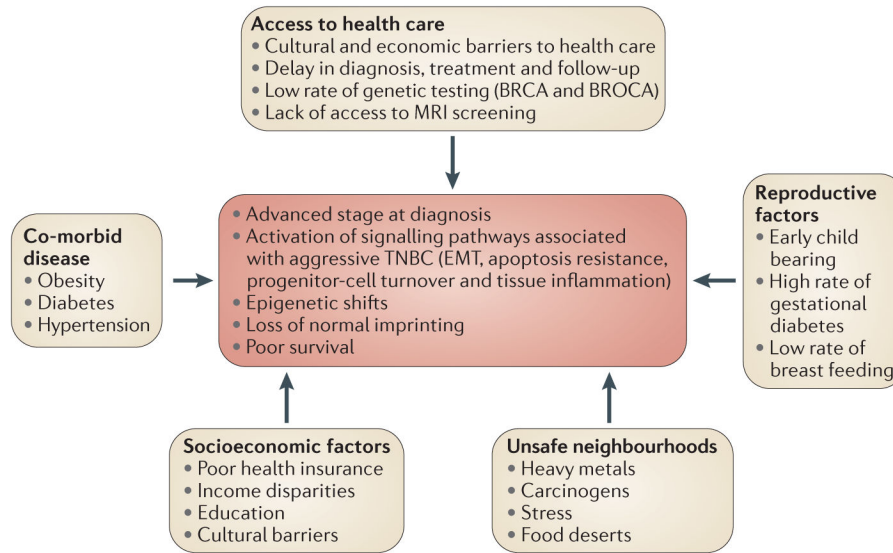
Disparities in income, lack of access to fresh vegetables and healthy food, unsafe neighbourhoods, and lack of exercise can promote co-morbid diseases such as obesity and diabetes, which in turn may drive phosphoprotein signalling pathways associated with aggressive biology in triple-negative breast cancer (TNBC). Obesity and diabetes result in increased levels of circulating insulin and tissue cytokines, such as interleukin-6 (IL-6), tumour necrosis factor (TNF), leptin, chemokine (C-C motif) ligand 2 (CCL2) and transforming growth factor-β (TGFβ), which activate signalling networks that are known to promote epithelial cell proliferation and genomic instability, including PI3K–AKT, signal transducer and activator of transcription 3 (STAT3)–nuclear factor-κB (NF-κB), WNT–microRNA 34 (miR34)–p53, and Aurora A–polo-like kinase (PLK)<sup>52,57–59,62</sup>. Obesity and accompanying tissue inflammation increases tissue factors, such as hypoxia-inducible factor 1α (HIF1α), that promote angiogenesis and contribute to aggressive biology. Recent studies provide evidence that chronic tissue inflammation and cyclooxygenase 2 (COX2) activation promote changes in collagen structure that result in the activation of focal adhesion kinase (FAK) and AKT network signalling<sup>79,81</sup>.



**Figure 3. Proposed model of genetic and epigenetic mechanisms that link unique DNA sequences and disparities with genomic instability, loss of BRCA1 function and aggressive TNBC biology in women of African descent**

Over 60% of Ashkenazi Jewish women with triple-negative breast cancer (TNBC) have a mutation in *BRCA1*. By contrast, less than 20–25% of African-American women with TNBC have a germline DNA mutation. Although many sequence variations of *BRCA1* have been found in women of African descent, only a small number of the mutations are protein truncating<sup>37–42</sup>, and these protein-truncating mutations occur in women of African origin at a lower rate than is observed in women of European descent<sup>37</sup>. On-going studies are testing for germline mutations in other genes that regulate BRCA1-associated DNA repair (for example, partner and localizer of BRCA2 (*PALB2*)) and/or signalling pathways that promote epigenetic loss of BRCA1 function. As the Black Women’s Health Study matures, it is anticipated that genome-wide association studies focusing on women of African ancestry will provide important insights into the genetic basis of TNBC in African-American women. Active areas of research aim to link disparities in access, environmental exposures, neighbourhood safety and obesity with epigenetic mechanisms that promote genomic instability. These emerging areas of research have important potential to identify important epigenetic mechanisms that link disparities with genomic instability. For example, emerging data indicate that low vitamin D levels may affect DNA repair<sup>82</sup>. African-American women have low vitamin D levels owing to increased skin pigmentation<sup>83,84</sup>; lack of safe neighbourhoods further contributes to low vitamin D levels<sup>85</sup>. Blue boxes: strong mechanistic evidence exists in TNBC, but specifically linking this evidence with TNBC in women of African descent is a work in progress. Tan boxes: areas of on-going investigation for which published data are currently weak or lacking. EZH2, enhancer of zeste homologue 2; IL-6, interleukin-6; miRNA, microRNA; SNP, single-nucleotide polymorphism; STAT3, signal transducer and activator of transcription 3.





**Figure 4. Proposed model depicting the intersection of disparities and aggressive biology in African-American women with TNBC**

Lack of access to health care and cultural barriers result in delays in diagnosis, delays in treatment, lack of completion of therapy and lack of follow-up for screening tests and treatment, culminating in women presenting with breast cancer at an advanced stage and having poor survival rates. Income inequality results in unequal health insurance and lack of access to genetic testing and state-of-the-art screening for triple-negative breast cancer (TNBC), such as breast magnetic resonance imaging (MRI). Co-morbid diseases such as obesity, diabetes and hypertension complicate therapy and can result in treatment delays. Obesity increases tissue inflammation and the production of tissue cytokines and growth factors that promote aggressive cancer biology. Signalling networks activated by insulin, such as AKT–mTOR, are associated with aggressive cancer biology. Unsafe neighbourhoods and an unequal burden of environmental exposures contribute to stress, lack of access to healthy food (food deserts, which in turn promotes obesity), lack of exercise and exposure to carcinogens and heavy metals (such as cadmium, lead and arsenic) that are thought to promote abnormal imprinting and epigenetic changes<sup>86–89</sup>, which in turn may promote aggressive biology. EMT, epithelial–mesenchymal transition.

**Table 1**

Incidence of TNBC in population-based studies of black women of African and European origins

Geographical location	TNBC incidence	Mean age at diagnosis	Study	Refs
Ghana	82% (37/45)	48.0 +/- 6.4 years	Population-based; consecutive; Komfo Anokye Hospital, Kumasi, Ghana; Jan 2007–Dec 2008	17
Soweto, South Africa	20.4 (209/1,092)	55.3 +/- 14.3 years	Population-based; consecutive; Soweto; 2006–2012	21
North Carolina, USA	39% AA (52/196); 16% EA (48/300)	46 years (basal subtype); 52 years (luminal A subtype)	Population-based; case-control; North Carolina Central Cancer registry; Mar 1993–Dec 1996	3
Philadelphia, Pennsylvania, USA	20.8% AA (59/283); 10.4% EA (203/2,230)	Not stated	Population-based; SEER registry; 1990–2000	15
Boston, Massachusetts, USA	30% AA (52/177); 19% EA (13/148)	No difference in age	Population-based; consecutive; Boston University Hospital, Massachusetts; Mar 1998–Nov 2006	16
Georgia, USA	46.4% AA (56/116); 21.8% EA (79/360)	AA women were a younger age at diagnosis	Population-based; consecutive; 1990–1992	4
Michigan, USA	26.4% AA (107/405); 16.0% EA (122/763)	60.8 +/- 13.7 years (AA); 62.4 +/- 13.7 years (EA)	Population-based; consecutive; Henry Ford Hospital; Jan 2001–Dec 2007	17

AA, African American; EA, European American; SEER, Surveillance, Epidemiology, and End Results; TNBC, triple-negative breast cancer.