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Breast cancer disparities in outcomes; unmasking biological determinants associated with racial and genetic diversity

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Abstract

Breast cancer (BC) remains a leading cause of death among women today, and mortality among African American women in the US remains 40% higher than that of their White counterparts, despite reporting a similar incidence of disease over recent years. Previous meta-analyses and studies of BC mortality highlight that tumor characteristics, rather than socio-economic factors, drive excess mortality among African American women with BC. This is further complicated by the heterogeneity of BC, where BC can more appropriately be defined as a collection of diseases rather than a single disease. Molecular phenotyping and gene expression profiling distinguish subtypes of BC, and these subtypes have distinct prognostic outcomes. Racial disparities transcend these subtype-specific outcomes, where African American women suffer higher mortality rates among all BC subtypes. The most striking differences are observed among the most aggressive molecular subtype, triple-negative BC (TNBC), where incidence and mortality are significantly higher among African American women compared to all other race/ethnicity groups. We and others have shown that this predisposition for triple-negative disease may be linked to shared west African ancestry, where the highest rates of TNBC are observed among west African nations, and these high frequencies follow into the African diaspora. Genetic and molecular characterization of breast tumors among subtypes and racial/ethnic groups have begun to identify targets with future therapeutic potential, but more work needs to be done to identify targeted treatment options for all women who suffer from BC.

Keywords

Breast cancer heterogeneity; Breast cancer disparities

Social versus biological determinants in BC disparities

Over the past decade, significant progress has been made in identifying the multifactorial risk factors of Breast Cancer (BC) incidence and survival outcomes, paving the way to better

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screening and treatment options. Over the past 5 years, overall cancer mortality has steadily decreased, and this trend is expected to continue [1]. Despite these successes, BC is the most frequently diagnosed cancer globally and the leading cause of cancer-related death among women [2, 3], accounting for 25% of cancer cases and 15% of cancer-related deaths [3]. In the US, BC remains the second leading cause of death among women [4], and over 275,000 new BC cases are expected this year, with over 42,000 deaths from BC [1]. Among these deaths lurks persistent racial/ethnic disparities in outcomes over the past 50 years, and similar disparity trends are also observed globally [5, 6]. Historically, BC incidence rates have been lower for African American (AA) women compared to White/European American (EA) women, though incidence rates have recently increased in AA collapsing this incidence gap [7] (Fig. 1a). Disparities in BC mortality initially emerged during the mid-1980s and remains 40% higher among AA woman compared to EA women today [4] (Fig. 1b). The emergence of disparities in survival directly coincided with the advent of targeted endocrine therapies [8], where AA women present with tumors types that do not respond to these therapies (Fig. 1c). Factors associated with differences in mortality also include AA women more frequently presenting with higher grade and later stage tumors [2–4, 9].

African American women suffer from disproportionately higher cancer mortality rates across all cancer types [10]. It is well-established that the consequences of lower socioeconomic status (SES), systemic racism and environmental exposures that affect wellness create barriers to equitable care [11–14]. Several of these factors, such as housing options [15, 16] are highly correlated with food insecurity [17, 18] and neighborhood deprivation [19], and are mediators of disparities in AA BC mortality compared to EA [20, 21]. The higher burden of interval disease (diagnosed between screening timepoints) can also be partially attributed to factors of health equity [22]. The resulting SES correlations with survival are ultimately an effect of bias in the health system [23], and include lack of effective options for clinical treatment and prohibited medical access and medical equity [24, 25], even in the context of progressive policies to address disparities [26]. Interestingly, despite suffering from similar socioeconomic barriers to access, Latina women with shared American Native (NA) ancestry have been found to have genetic factors that are protective in BC disease and outcomes [27–29]. Together, these data indicate that while SES-related barriers to access are associated with worse BC outcomes, they cannot completely explain the ongoing disparities in AA survival observed in clinic. In addition to factors linked to SES [11, 12], analyses that address other multifactorial variables that factor into disparities concluded that excess mortality is consistently found in AA patients, even after controlling for SES factors, and excess mortality can be connected to tumor characteristics instead [10, 30–33]. For example, among Hormone Receptor-positive (HR+) BC, which represent the highest proportion of cancers among all race/ethnic groups and have targeted therapies available, survival outcomes are significantly worse among AA women [4, 34–36] (Fig. 2). Hormone Receptor-negative (HR-) and TNBC disease is diagnosed higher rates among AA women [35], and increased prevalence of these biologically distinct and aggressive subtypes among premenopausal AA women, are a prime example of biased incidence of specific tumor characteristics [37, 38] (Fig. 2). Additionally, worse survival outcomes persist among AA women with HR-/TNBC compared to EA women, again after controlling for

SES factors [39]. These observations indicate that SES factors cannot be the only drivers of the disparities we observe in the clinical setting [10, 30–33].

BC is a molecularly heterogeneous disease comprised of multiple subtypes with distinct prognostic outcomes

This disparity in BC outcomes is further complicated by the complexity of the disease, as BC represents a collection of heterogeneous cancer types characterized by molecular and intrinsic phenotypes. These tumor phenotypes are found at disparate frequencies across different racial/ethnic groups and have distinct prognostic outcomes which inform the clinical management of disease for the patient. Molecular subtypes of BC are defined by the presence or absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) on the tumor cell surface by immunohistochemistry (IHC) staining and/or in situ hybridization. ER and PR positivity in tumors represent HR + tumors, HER2 positive tumors represent their own molecular subtype, and triple-negative breast tumors (TNBC) are defined by the absence of these receptors on the breast tumor cell surface. HR + and HER2 + tumors have targeted molecular treatments available and have better survival outcomes compared to TNBC tumors, which lack targeted treatments, are more aggressive, and have worse survival outcomes [4, 7, 40].

Genomic investigations of tumors have further defined the phenotypic differences of molecular subtypes, where distinct gene expression profiles were found across a broad range of breast tumors [41, 42]. These gene expression profiles were refined into a panel of 50 genes (PAM50), that could reproducibly classify tumors into intrinsic phenotypes [43]. Five intrinsic subtypes have been defined with the PAM50 classification, and they represent HRpositive cancers (Luminal A (LumA), Luminal B (LumB), HER2 enriched (HER2), Normal-like and Basal-like BCs (comprising TNBC tumors) (Fig. 3). The concordance of these molecular phenotypes with intrinsic subtypes has been investigated by multiple groups and cohorts, and meta-analyses of these studies show that there is agreement between these two methods [38, 44]. These intrinsic phenotypes have additional prognostic value to molecular subtypes, where risk of recurrence is lowest among LumA cancers, and relapse-free survival rates are lowest among HER2 + and basal-like tumors [42, 43, 45]. The prognostic value of the PAM50 intrinsic subtyping tool has been validated in longer follow up survival cohorts [46], indicating its value in the clinical setting.

Incidence, prevalence and survival outcomes of BC subtypes across racial/ethnic groups

HR + cancers typically represent the highest proportion of cancers among all race/ethnic groups, however 5-year survival outcomes are worse among AA women for these cancers when looking across multiple studies/cohorts [4, 34–36]. Genetic profiling of LumA (ER+ and/or PR+) tumors between AA and EA women has revealed a set of genes upregulated in AA tumors associated with poor prognostic outcomes [47], and a multi-gene score derived from expression values of these upregulated genes was associated with increased risk of

recurrence [48]. HER2+ cancers are diagnosed at a similar frequency between race groups [4]. Higher odds ratio for HER2+ cancers are also observed among AA women [35], and relative to LumA/ER+ tumors, were more often late stage and had lymph node involvement [34, 37].

The widening gap in BC mortality among AA women began in the late 1970s, when targeted treatments for HR + BC became available, and subsequently standard of care [8]. With the advent of these targeted therapies, overall BC mortality began to decrease due to effective treatment response, but subsequently unmasked diversity in tumor phenotypes, where this widening of the mortality gap can be attributed to disproportionately higher prevalence of HR-/TNBC tumors among AA women compared to all other racial/ethnic groups in the US [4, 34, 37]. AA women have a higher likelihood of developing basal-like/TNBC disease compared to other subtypes [35], and also suffer from worse survival outcomes compared to other racial/ethnic groups [4, 37, 49]. Prevalence of TNBC is particularly high among premenopausal AA women [38], where a bimodal distribution of TNBC across age groups of AA women is observed [37]. Among young AA women (<35yo), over 50% of BC cases were determined to be TNBC, with the second peak of TNBC prevalence occurring among AA women aged 51–60 [37]. Similar to reports for overall BC survival, worse survival outcomes persist among AA women with TNBC disease after controlling for SES factors [39].

West African Ancestry and TNBC disease—race/ancestry-informed disparities research

Epidemiology of TNBC disease

Epidemiological data show higher rates of TNBC in subpopulations of shared west African ancestry, in most nations that track African ancestry through self-reported race (SRR) [30, 50–52]. In the ICSBCS cohort, prevalence of TNBC cancers is highest among west African and AA women compared to East African and EA women [53–55]. After quantifying west African ancestry in the ICSBCS cohort, we found that the percentage of west African ancestry is higher among TNBC cases compared to non-TNBC cases [54], which is concordant with other independent cohorts [56]. Global investigations of BC status indicate similar trends, where Great Britain [57, 58] and Switzerland [59] also show association between TNBC prevalence and west African ancestry.

Through comprehensive literature search, we have compiled TNBC prevalence rates reported from countries globally (Fig. 4). Higher frequency of TNBC disease is found among Sub-Saharan African nations, and we additionally observe higher rates of TNBC disease across the African diaspora in ad-mixed populations (Fig. 4). Compared to global BC mortality reports, countries with higher TNBC prevalence also report higher overall BC mortality. Despite reporting lower incidence of BC disease, low- and middleincome countries suffer from higher mortality rates, and these disparate outcomes are largely attributed to observed later stage at presentation and limited access to treatment options [3]. The highest frequencies of TNBC correlate with the highest mortality from BC, and

likely indicates the poor prognoses from this aggressive molecular subtype, lacking effective and/or targeted therapies.

Genomic investigations of TNBC among individuals of African ancestry

In a case-series analysis comparing TNBC cases versus non-TNBC cases in an African ancestry enriched cohort, we found the Duffy-null allele to be significantly associated with TNBC risk among AA, after controlling for age and west African ancestry [54]. This suggests that TNBC in women of African descent, aside from just having African ancestry, may be influenced by the biological mechanisms that are related to DARC function [60]. We hypothesize that DARC is the driving factor for differences in TNBC mortality [39]. Intriguingly, we have observed that the underlying tumor biology of TNBC does differ among race groups, with higher prevalence of certain TNBC subtypes in women of African descent.

We have also identified differences in gene expression patterns among TNBC tumors that are associated with west African ancestry [61], where we have identified ~ 150 genes that are associated with west African ancestry across TNBC tumors. This differentially expressed gene signature indicated alteration in TP53, NFKB1 and AKT pathways, and we additionally identified west African ancestry associated upregulated genes that have targeted therapeutics currently in clinical trials. Approximately half of our gene list overlapped with SRR differentially expressing genes, indicating that by using quantified genetic ancestry, we are able to better account for differences in tumor gene expression due to genetic admixture of the samples, that was otherwise lost in our SRR analysis [61].

Gene expression profiling defines subtypes of TNBC

Similar to the PAM50 intrinsic subtyping approach, subtypes of TNBC have been defined using gene expression profiling, and the distribution of TNBC subtypes are different among AA and EA women [52, 61–63]. Lehmann et al. have identified four TNBC subtypes based on gene expression profiling: basal-like1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal androgen receptor (LAR) [64, 65]. AA TNBC tumors are reported to be more frequently BL1/2 TNBC subtypes, [52, 61–63], where EA are more M and LAR [62]. In a TNBC cohort where patients received neoadjuvant chemotherapy, BL1 tumors have reported higher rates of pathological complete response (pCR), while BL2 and LAR have lowest rates of pCR [66].

Androgen receptor (AR) expression has also been investigated in the context of TNBC disease, where TNBC tumors that lack AR expression are classified as quadruple-negative BC (QNBC) [52, 67]. Comparing race/ethnicity groups, AA TNBC tumors were found to be more frequently ARor QNBC than EA (87% versus 56%, respectively). QNBC is associated with younger age at diagnosis compared to TNBC [52, 67], and worse survival outcomes for AA QNBC patients [52].

Conclusions—race and ancestry in cancer disparities; a way forward

Genetic ancestry of the modern African diaspora is largely representative of west African descendants of enslaved Africans, through the forced migration over hundreds of years

and dozens of generations due to the Trans-Atlantic Slave Trade. In the US, while west African ancestry is predominant among individuals who self-identify as AA [68, 69], varying levels of geographic ancestry from African, European and Native American groups are unpredictable in each individual. This draws concern over the reproducibility and validity of 'race-specific' risk and warrants a more quantifiable approach that assesses genetic ancestry on an individual basis. In our own analyses, we have shifted our focus to study the specific impact of west African ancestry in BC tumor biology, within admixed populations. Specifically, an individual's quantified African ancestry is utilized as a continuous variable in our gene network analyses, allowing for the selection of differential expression that is directly associated with shared west African ancestry. We do not disregard an individual self-reported race/ethnicity (SRR), but rather leverage their specific genetic ancestry composition to determine differences in BC risk, or tumor gene expression profiles. Using this approach, we and others have shown that west African ancestry among AA women is significantly with TNBC disease [50, 51, 54, 70]. This trend is also observed as we look globally, as comparison studies in countries such as Great Britain [57, 58] and Switzerland [59] also show increase risk of TNBC disease among individuals with African ancestry.

However, it is not necessary to totally disregard an individual's self-reported race/ethnicity, but rather utilize aspects of identity and ancestry as is appropriate for the investigation. Specifically, with integrated clinical and demographic data annotations, we can leverage specific genetic ancestry composition with social determinants to interpret the effects leading to gene network changes. This perspective can allow us to discern how differences in BC risk, or tumor gene expression profiles are either related to heritable factors or social/cultural factors. Ultimately, we may be able to even pinpoint the impact of systemic racism on tumor biology as a function of social determinant impacts on tumor etiology and progression. Such progress could have profound impacts on health policy and disease prevention to improve disparities.

Recent agency-level public endeavors have drawn more focus on the importance of inclusion of diverse ancestry and ethnic populations in clinical trials and translational research. While we understand that BC is a heterogeneous disease, where both tumor characteristics and patient race/ethnicity play an important role in prognostic outcomes of a BC diagnosis, there is still a dearth of diversity in the data. We also understand that SES and the outcomes of racism have attributed to disparities in BC mortality, where mortality is persistently higher among AA women. Our extensive efforts to identify the underpinnings of higher TNBC incidence across the African diaspora has revealed a significant link to shared west African Ancestry. Specifically, while TNBC frequencies are highest among Sub Saharan African countries and remain higher across the African diaspora, additional efforts are needed to unravel the confounding genetic admixture in the contemporary descendants of the Trans-Atlantic Slave Trade, which is associated with increased risk of TNBC. However, naming unique etiologies of BC disparities, be it social or biological determinants, will not ameliorate these disparities. The key to changing the paradigm is discerning the modifiable social determinant factors, and the targetable biological determinant factors, and affecting them with concerted medical research efforts. And without a doubt, this requires the consistent participation of the marginalized communities.

Genetic investigations of TNBC that have focused on the impact of west African ancestry on tumor biology have identified gene signatures that may serve as therapeutic targets and have made clear a path for development of targeted therapies. While a significant amount of research has been conducted to address these BC disparities, it is imperative that as we conceive and conduct future BC studies, we plan for inclusion of diverse patient populations. This includes designing studies to fully characterize tumor heterogeneity across subtypes and racial/ethnic groups, and to additionally identify targets for treatment that are effective across all BC patients.

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Abbreviations

BC	Breast Cancer
EA	European American
AA	African American
SES	Socio-Economic Status
HR	Hormone Receptor
TNBC	Triple-Negative Breast Cancer
pCR	Pathologic Complete Response
QNBC	Quadruple-Negative Breast Cancer

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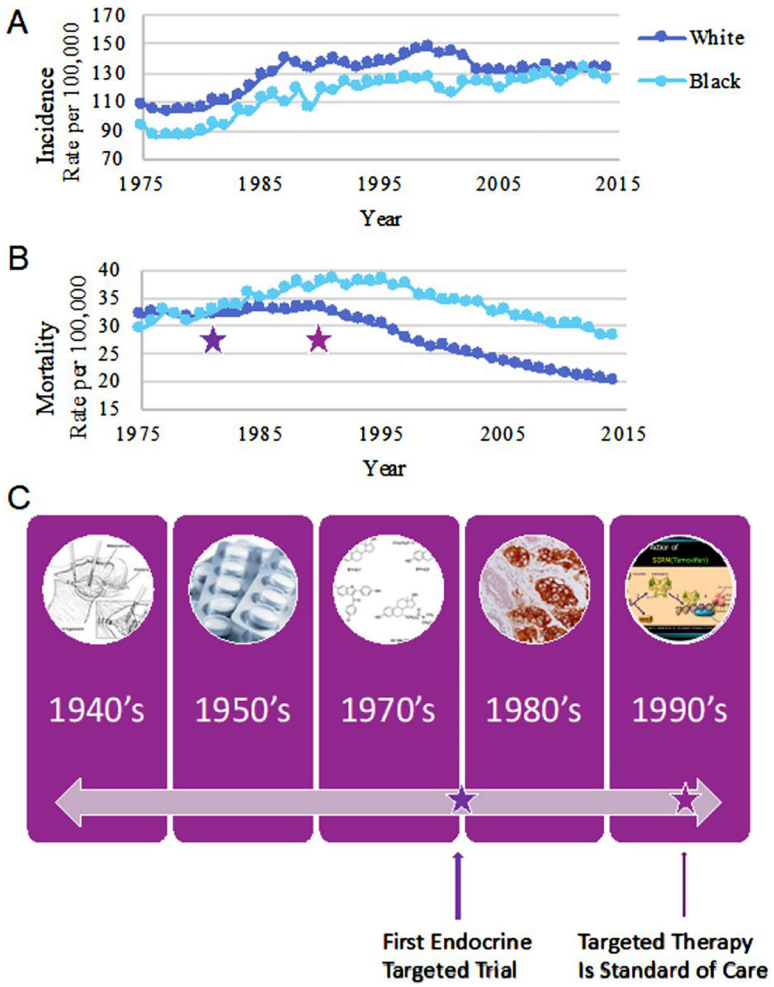

Fig. 1.

Emergence of BC diversity unmasked by advent of targeted endocrine therapy. BC incidence (**a**) and mortality (**b**) curves among females in the US from SEER data collected between 1975 and 2015. Incidence and mortality reported among White/European American women is shown in dark blue, and among Black/African American women is shown in light blue. Purple stars correspond with the timeline in panel C, highlighting the advent of targeted endocrine therapy in clinical trials (late 1970s/early 1980s, left), and its eventual use as standard of care beginning in the early to mid 1990s (right)

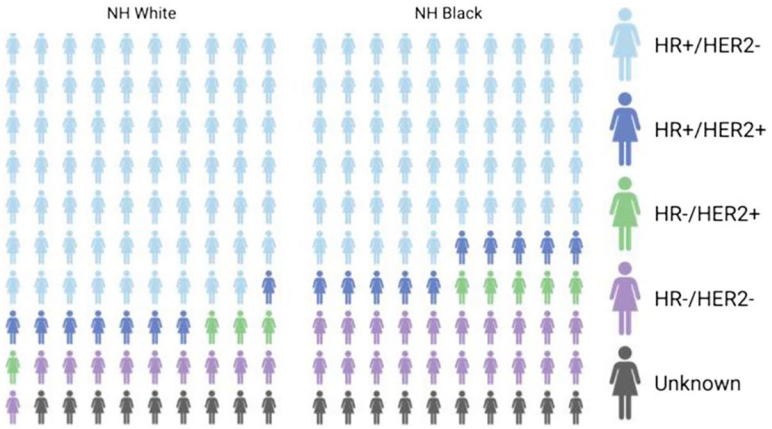

Fig. 2.

Distribution of BC subtypes have bias in prevalence between White and Black Americans. Distribution of BC subtypes among non-Hispanic White and non-Hispanic Black women in the US, 2012–2016. Data from SEER program and CDC National Program of Cancer Registries, frequencies reported from DeSantis et al. [4]

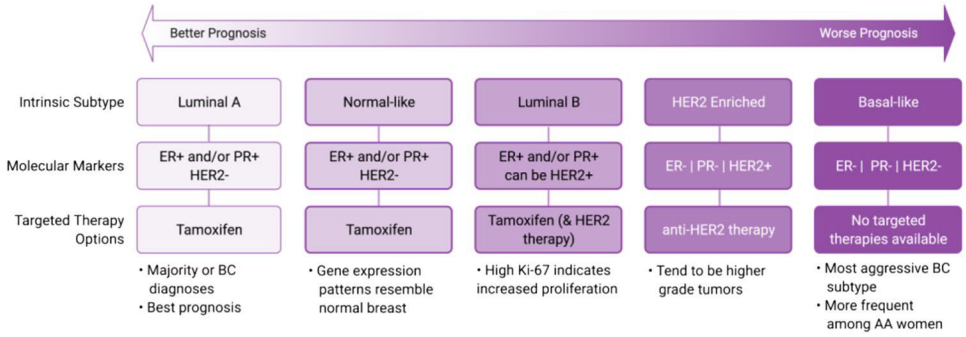

Fig. 3.

Relative prognosis and treatment options among BC subtypes. Adapted from Dai et al. [45]

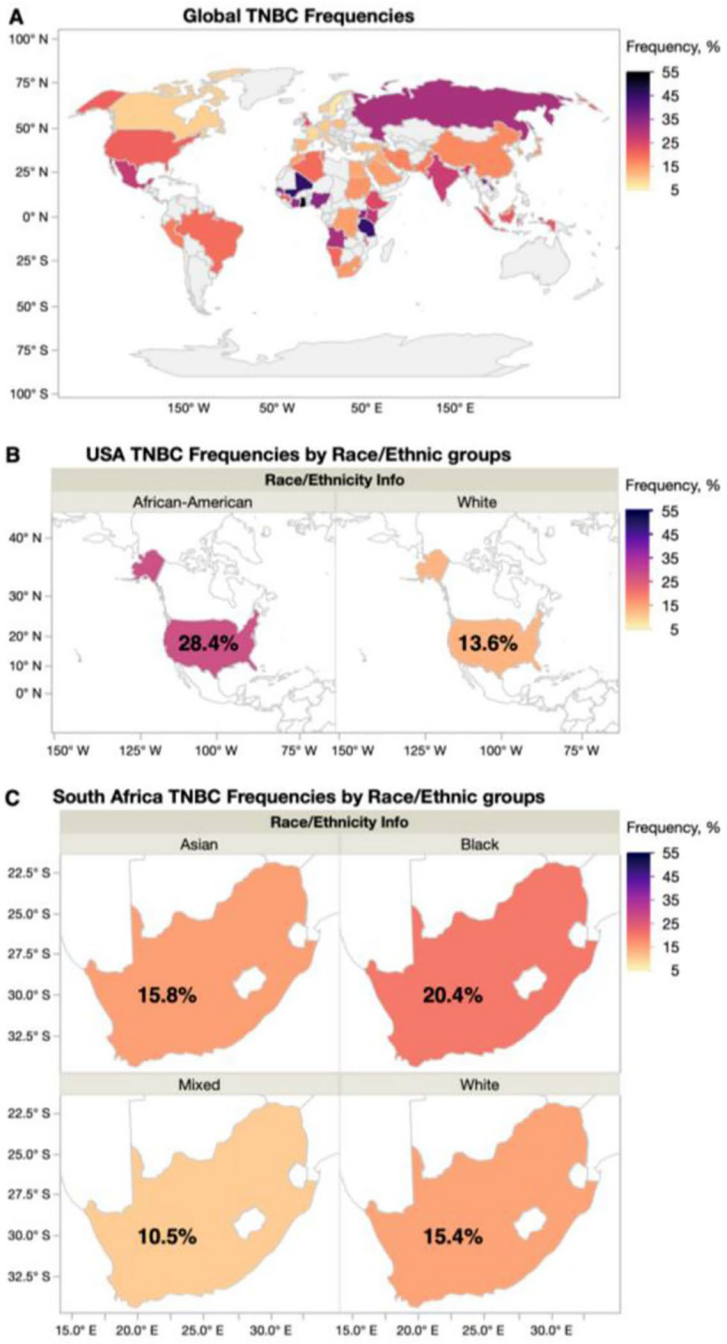

Fig. 4.

TNBC Frequencies globally and in ad-mixed populations. **a** Global TNBC frequencies reported from over 100 published studies. **b** Average TNBC frequency reported among African American and White BC patients in the USA. **c** Average TNBC frequency reported among Asian, Black, Mixed and White BC patients in South Africa