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BREAST CANCER DISPARITIES (LA NEWMAN, SECTION EDITOR)

Disparities in Genetic Testing and Care Among Black Women with Hereditary Breast Cancer

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Abstract

Purpose of Review Despite a steady improvement in breast cancer survival rates over the past several decades, mortality disparities remain among Black women, who have a 42% higher death rate compared to non-Hispanic white (NHW) women. Hereditary breast cancer (HBC) accounts for 5–10% of all breast cancer cases, the majority of which are due to the *BRCA1* and *BRCA2* (*BRCA*) genes. Despite the availability of *BRCA* testing for over 25 years, there remain disproportionately lower rates of genetic testing among Blacks compared to NHW due to a multitude of factors. The intent of this review is to discuss racial disparities focused on HBC across diverse populations and review the existing gaps to be addressed when delivering gene-based care.

Recent Findings The factors contributing to the racial survival disparity are undoubtedly complex and likely an interplay between tumor biology, genomics, patterns of care, and socioeconomic factors. Advances in genomic technologies that now allow for full characterization of germline DNA sequencing are integral in defining the complex and multifactorial cause of breast cancer and may help to explain the existing racial survival disparities.

Summary Identification of inherited cancer risk may lead to cancer prevention, early cancer detection, treatment guidance, and ultimately has great potential to improve outcomes. Consequently, advances in HBC diagnosis and treatment without widespread implementation have the potential to further widen the existing breast cancer mortality gap between Black and NHW women.

Keywords Hereditary breast cancer · BRCA · Genetic counseling · Genetic testing · Racial disparities · Breast cancer disparities

Introduction

Breast cancer is the most common cancer among women worldwide [1], with steady improvement in survival rates over the past several decades [2]. However, these increases have not been shared equally across populations with Black women having a 42% higher death rate compared to their non-Hispanic white (NHW) counterparts [3]. This difference is particularly pronounced among young Black women, who are more likely to develop and die of their breast cancer compared to their NHW counterparts [4–6] with a widening of this mortality disparity over the last few decades [7–9]. Factors contributing to racial survival disparities are complex and likely are an interplay between tumor biology, genomics, patterns of care, and socioeconomic factors [10]. Furthermore, Black women in both United States (US) and Africa are more likely to develop triple negative breast cancer (TNBC), an aggressive breast cancer subtype [11–21], which may contribute to the mortality disparity. Both early age of onset and the higher frequency of TNBC [22–25] are associated with higher risk for hereditary breast cancer (HBC), primarily due to pathogenic/likely pathogenic (P/LP) variants in *BRCA1* although also observed among those with *BRCA2* and *PALB2* P/LP variants [26–29]. The purpose of this article is to review our current understanding of racial disparities focused on HBC across diverse populations and review the existing gaps to be addressed when delivering gene-based care.

This article is part of the Topical Collection on *Breast Cancer Disparities*

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Hereditary Breast Cancer and Genetic Testing Considerations

HBC accounts for approximately 5–10% of all breast cancer cases, most commonly due to P/LP variants in the *BRCA1* and *BRCA2 (BRCA)* genes [30]. Prior studies suggest that the majority of HBC are attributed to the *BRCA* genes [31]; however, there are "non-*BRCA*" inherited breast cancer genes which include both high (e.g., *PALB2*, *TP53*, and *PTEN*) [32] and moderate (e.g., *ATM*, *CHEK2*) penetrance genes [33]. Emerging data from us and others suggest higher rates of *BRCA* mutations among Blacks across studies conducted in the US, the Caribbean, and western Sub-Saharan Africa [12, 34–39]. Black women also have a higher prevalence of variant of uncertain significance (VUS) results, which has increased in the era of multi-gene sequencing, with rates up to 44.5% compared to 23.7% among NHW women [36, 40••]. Most of our knowledge about HBC is defined in the context of European ancestry [2], due to low genetic testing rates among minority groups [30, 41, 42]. In fact, African Americans, Asian Americans, Latin Americans, and Native Americans are underrepresented in breast cancer genetic databases [30], making it difficult to estimate the actual prevalence of HBC across different racial/ethnic groups.

In addition to high and moderate penetrance genes, there have been an increasing number of "low penetrance" single-nucleotide polymorphisms (SNPs) identified within or outside of genes through genome-wide association studies (GWAS) that correlate with a < 2-fold risk of developing breast cancer [43, 44]. Algorithms through which multiple SNPs are combined have been developed to generate a polygenetic risk score (PRS). These scores are derived based on the sum of the SNPs on overall risk of breast cancer in combination with the frequency of that SNP in the population [43]. Current PRS are validated through large GWAS which are disproportionately composed of 79% European participants, who make up only 16% of the global population [45••]. Overrepresentation of European ancestry in GWAS has led to study bias when considering population differences in allele frequency and linkage disequilibrium structures [46]. Therefore, PRS are less applicable to Black patients, as the predictive value declines with genetic divergence [47]. Currently, PRS have the potential to improve risk assessment; however, further studies are needed to validate their clinical utility, management implications, and incorporation of results into clinical practice [48]. Given the limited representation of Blacks in GWAS in the context of significant variability of SNPs across racial/ethnic groups, the disparity in access to PRS among Blacks will only further perpetuate the racial disparity in access to PRS as clinical utility is established. Consequently, robust studies in diverse populations are needed to further characterize these differences and deploy these advances, such that existing disparities are not further exacerbated [3].

Disparities in the Delivery of Clinical Cancer Genetic Services (Fig. 1)

Identification of HBC

Identification of HBC susceptibility in individuals and their family members guides strategies to detect cancer early or prevent it all together. For example, female *BRCA* carriers have a 60–70% lifetime risk of developing breast cancer compared to 12% in the general population [30] and up to a 50% or greater risk of developing a second primary breast cancer [42, 49–52]. Strategies for early detection include high-risk breast screening inclusive of annual breast MRI, and cancer prevention options include risk-reducing mastectomy [53].

Despite the benefits of identifying HBC, it has been estimated that only 10% of adult women with P/LP *BRCA* variants in the US have had genetic testing [54]. Clinical *BRCA* testing became commercially available in the US in 1996; yet, disparities in the uptake and utilization of testing have varied across racial and socioeconomic groups [6, 55]. Per national practice guidelines, genetic testing is recommended for all women diagnosed with breast cancer at or below age 45, TNBC age ≤ 60 or those at high risk based on a combination of personal and/or family cancer history [53]. Black women are disproportionately diagnosed at younger ages and therefore are more likely to meet the criteria for genetic counseling and testing for HBC [6].

Access and Uptake of Genetics Services

Despite meeting the national guidelines for genetic testing referral, only 20% of high-risk breast cancer patients are referred for genetic testing [56], with lower testing rates reported among racial and ethnic minorities including Blacks [30, 41, 42, 57–59]. In our population-based sample of women ≤ 50 years old diagnosed with invasive breast cancer in Florida, 37% of Black women were referred for genetic counseling/testing compared to 85.7% of white women [41]. Contributing factors included provider referrals, with Blacks 16 times less likely to have genetic testing recommended by their provider compared to NHW [41]. Lower rates of provider discussions and recommendations for genetic testing among Blacks compared to NHW have also been demonstrated in other studies [60, 61]. These findings suggest that in addition to patient-level factors, provider-level and system-level factors also contribute to lower genetic testing rates among Blacks [41].

There are a multitude of factors which contribute to the underutilization of genetic testing services among Blacks, including lower awareness of testing, as well as support for obtaining genetic counseling and testing, particularly in resource-limited settings [62, 63]. Blacks have historically been considered to have an overall negative attitude toward

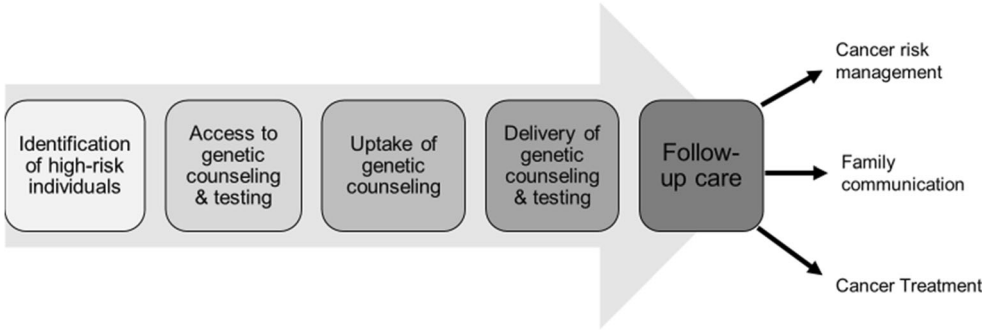

Fig. 1 Care delivery continuum of genetic services

genetic testing with possible concerns for racial discrimination [6]. However, more recent studies report that Black women were eager to receive genetic testing once they were made aware of the indications and implications [64–66].

Delivery of Genetic Counseling and Testing

The coupling of genetic testing for inherited cancer with pre- and post-test genetic counseling (GC) is endorsed by several national organizations [53, 67–69] and is a requirement for accreditation of breast centers of excellence [70]. The American Society of Clinical Oncology (ASCO) has provided guidance on standard elements to be discussed during the pre-test GC session since 1996 [71] and most recently updated in 2015 [68]. Given an upsurge of testing, in the context of a healthcare workforce with limited proficiency in genetics [72], many tests are performed without pre-test GC [73–75]. Yet, policies which mandate pre-test GC may disproportionately reduce testing rates among underserved populations [76, 77].

Delivery of Follow-up Care

The purpose of genetic testing is to provide information to individuals, with the goal of improving outcomes. Specifically, the identification of HBC may empower individuals and their families with options to detect cancers early or prevent them [78–80]. Women identified with a *BRCA* mutation may reduce their risk of developing breast cancer to through risk-reducing surgery [81, 82] or chemoprevention [83, 84] or detect cancer early through breast cancer screening [85–87]. However, our prior data among a population-based sample of *BRCA* carriers suggested that racial disparities may exist in the uptake of cancer risk management strategies [41]. Specifically, in our diverse cohort of young breast cancer survivors, although Black women with *BRCA* P/LP variants had significantly lower rates of risk-reducing mastectomy compared to NHW, this disparity became non-significant after accounting for those who received heightened screening and those who had not yet completed treatment. However, there were significantly lower rates of bilateral salpingo-oophorectomy among Blacks compared to NHW ($p = 0.008$), which remained significant even after controlling for age at enrollment, time since diagnosis, income, family history of breast and ovarian cancer, and private insurance at diagnosis [41]. Given that women with *BRCA* P/LP variants are at a substantially increased risk for ovarian cancer for which the only effective cancer risk management option is risk-reducing surgery, it remains critical to understand the reasons for this observed disparity.

In addition to the personal impact of identifying HBC, this information may be shared with at-risk family members to amplify the benefits of testing and subsequent care among those at high risk. Studies have shown lower rates of family disclosures among minorities [88], which is unfortunate given the implications for prevention and early detection in an already high-risk population.

Disparities in Treatment

Tremendous advances in the use of genetic testing have now expanded to guide eligibility for specific drugs based on genetic test results [89•]. In fact, PARP inhibitors are now FDA approved for use among women with germline P/LP *BRCA* variants with metastatic HER2 negative breast cancer, after they were shown to increase progression-free survival [89, 90]. However, the original clinical trial that resulted in FDA approval of a PARP inhibitor for breast cancer treatment based on germline *BRCA* positivity included 65.4% White, 32.4% Asian, and 2.4% women from other racial/ethnic groups [89•]. A subsequent PARP inhibitor trial among breast cancer patients with *BRCA* P/LP variants and locally advanced or metastatic disease which also led to FDA approval did not report on race distribution of participants at all [90]. The disparity in reporting race and the underrepresentation of minority groups in clinical trials is not unique to HBC and has been documented across all tumor types [91••]. In fact, Black women with breast cancer were reported to have the lowest clinical trial enrollment rate despite having the highest breast cancer-specific mortality rate across all racial/ethnic groups [91••]. In the era of precision oncology, as more targeted approaches to improve clinical outcomes emerge, there is an

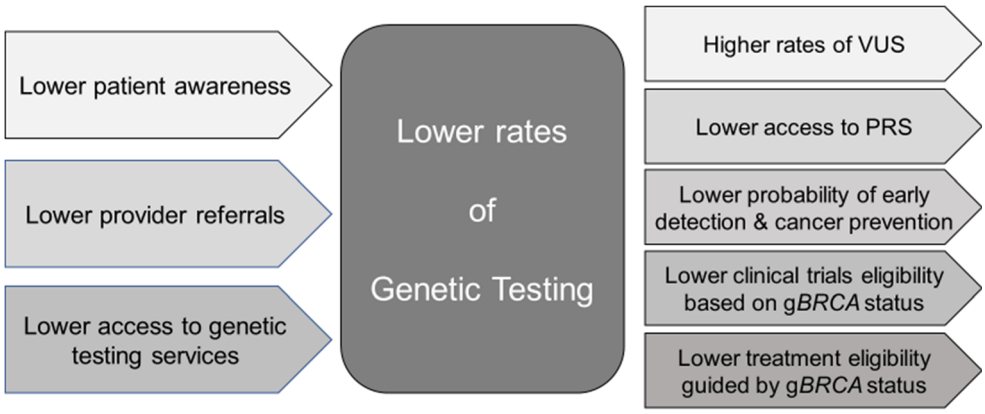

Fig. 2 Summary of contributing factors and impact genetic testing rates among Black women

urgent need to ensure that all women across the population with potential to benefit from these therapeutic advances are identified and offered enrollment in trials. Without the identification of women with germline *BRCA* mutations and widespread access to these effective therapies across all racial/ethnic groups, there is a potential to widen the existing breast cancer survival disparity.

Conclusion

Despite improved access to genetic services, racial disparities in genetic testing rates persist. The lack of both awareness and utilization of genetic services at both the patient and provider level contribute to existing racial disparities (Fig. 2). Indications for genetic counseling, testing, and discussions surrounding testing are often described as complicated and dynamic. A multi-level approach to increase awareness and utilization of genetic counseling and testing, through community outreach, as well as patient and provider education is paramount. Ultimately, advances in HBC diagnosis and treatment may further widen existing breast cancer survival disparities across racial/ethnic groups. Consequently, it remains imperative to enhance genetic testing opportunities across the entire population, to ensure that all populations have the opportunity to benefit from the tremendous diagnostic and therapeutic advances.

Compliance with Ethical Standards

Conflict of Interest Sonya Reid, Sydney Cadiz and Tuya Pal declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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