ANNUAL REVIEWS

Annual Review of Genomics and Human Genetics

Breast Cancer: Genetic Risk Assessment, Diagnostics, and Therapeutics in African Populations

Achille V.C. Manirakiza,[1,2,3] Leon Mutesa,[3] Christopher G. Mathew,[4,5] and Olufunmilayo I. Olopade[1,6]

[1]Center for Clinical Cancer Genetics and Global Health, University of Chicago, Chicago, Illinois, USA; email: folopade@medicine.bsd.uchicago.edu

[2]Oncology Unit, Department of Medicine, King Faisal Hospital Rwanda, Kigali, Rwanda

[3]Centre for Human Genetics, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda

[4]Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[5]Department of Medical and Molecular Genetics, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom

[6]Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, Illinois, USA

Annu. Rev. Genom. Hum. Genet. 2025. 26:245–59

First published as a Review in Advance on April 28, 2025

The *Annual Review of Genomics and Human Genetics* is online at genom.annualreviews.org

https://doi.org/10.1146/annurev-genom-111522-013953

Keywords

breast cancer, genetic risk, cancer genomics, African populations

Abstract

Breast cancer is a major public health burden that disproportionately affects women of African descent. Substantial progress has been made in understanding the genetic and biological drivers of breast cancer worldwide. However, this knowledge is unevenly distributed among all women with breast cancer, particularly those of African descent. The highlights of nearly three decades of research among women of African descent point mainly to a young age at diagnosis, aggressive disease, and distinct biomarkers, as well as a clear geographical distribution of disease subtypes and genetic variants. Despite this growing wealth of information, the African population's access to genetic care and understanding of inherited risk and disease biology remain limited. This review summarizes the state of knowledge on genetic risk in African populations with breast cancer, evaluates the strengths

and limitations of the methodological approaches used, and suggests innovative strategies to ensure equitable participation in cancer genetic and genomic research. We discuss genotype–phenotype correlations and the inherited risk of breast cancer, including both rare and common genetic variants. We also address the role of somatic drivers of breast cancer, disease biomarkers, treatment targets, and pharmacogenomics in this population. Finally, we provide recommendations to enable future progress in diagnosis and treatment.

1. INTRODUCTION

Although it has been 30 years since the discovery of the major breast cancer risk genes *BRCA1* and *BRCA2* (59, 100), and substantial gains have been made in the management of individuals at high risk of breast cancer, women of African descent remain underrepresented in breast cancer genetics research worldwide. Several disparities characterize this population. First, breast cancer has an estimated overall five-year survival of 40% in countries in sub-Saharan Africa (53). Second, Black women present with breast cancer at a younger age and have more aggressive disease than women from other ancestries (47, 76, 92). And third, access to timely treatment is limited (97). These variations are considered to result from a blend of socioeconomic and biological factors that are unique to Africans on the continent and in the diaspora. For example, the basal-like breast cancer subtype, which is associated with aggressive disease and poor outcomes, is particularly common among Black women (8, 47, 65, 72, 76, 92) and has few and expensive treatment options compared with treatments for other disease subtypes. Genetic cancer risk assessment (GCRA) services, consisting of collecting and interpreting multiple factors contributing to cancer development (12), are lacking for the majority of women of African descent, a challenge that is compounded by limited knowledge of the full scope of the genetic and molecular determinants of breast cancer.

The high levels of genetic diversity in African populations have been described in previous studies (25, 50). Distinctive findings from breast cancer–specific germline and somatic mutations and the African genomic work done in the last few decades make a compelling case for further leveraging existing and novel individualized solutions. Indeed, the high rates of inherited breast cancer, the finding of new polymorphisms contributing to breast cancer risk, the tumors' molecular characteristics, the adaptive selection of tropical zones, and other factors (15, 73, 93, 102) provide a way to leapfrog to high-risk precision management.

GCRA research among African populations has highlighted limited access to testing services, a high rate of uncertain and inconclusive results, and the lack of newer tools for risk prediction and biomarker discovery (2, 68, 86, 87, 96). Additionally, the participation of individuals of African descent in cancer genetic and molecular research has focused primarily on African Americans and women from the West African regions, reflecting the transatlantic slave trade and its origins. However, conflict-driven migration patterns are diversifying the African diaspora, which should lead to a greater engagement of African regions in research on breast cancer and its multiple drivers in African populations.

The goals of this review are to summarize the state of research on GCRA for breast cancer, critically appraise the methodology used in current genetic studies, and propose innovative and inclusive approaches based on the characteristic features of women of African descent with breast cancer. The review focuses on breast cancer genetics among women of African descent in view of its high incidence and mortality in African populations and the substantial research progress in this area.

2. ACCESS TO GENETIC CANCER RISK ASSESSMENT SERVICES

Genetic counseling capacity and access for African populations are extremely limited. In sub-Saharan Africa, only South Africa has documented clinical genetic counseling service and training programs, and little of this expertise makes its way to other African countries (1). Compared with programs that address broader issues related to other genetic conditions, programs for treating inheritable cancers encounter larger obstacles in the healthcare infrastructure for their longitudinal follow-up and management needs (4, 35, 86, 87). In these regions of the world, genetic testing is done primarily as part of research programs, with little or no follow-up plans for either the carriers or their families (2, 6, 11, 103, 104). Furthermore, populations of African descent are less likely to participate in GCRA services where genetic counseling is available (e.g., in the United States) or adhere to disclosure recommendations (9, 23, 38, 58, 60, 75, 80, 90, 101). A wealth of literature has demonstrated that culturally sensitive models are more effective for African Americans than traditional methods of genetic care delivery (38, 45, 70, 74). In underserved regions of sub-Saharan Africa, upcoming programs should seek to uphold guidelines-compliant task-shifting models and empower women to make informed genetic testing decisions, in addition to using innovative familial approaches.

Studies probing the willingness to participate in GCRA clinics show great interest in participation but a rather lower financial commitment to pay for the services, underscoring competing life priorities. In two countries, participants were only willing to pay up to $50 for GCRA services (7, 57). Investigating affordable yet informative and quality strategies to disseminate genetic services will be necessary to advance our understanding of breast cancer risk in individuals of African descent.

3. GERMLINE CONTRIBUTORS TO BREAST CANCER RISK

3.1. Germline Variants

BRCA1 and *BRCA2* are the genes with the most common germline variants causative of breast cancer in women of African descent, with a conferred risk that is similar to that in women of European descent (11, 22, 65, 72, 104). Women of African descent from different regions of the African continent and the world have varying prevalences of pathogenic variants in these genes, mirroring the known regional genetic differentiation, admixture, and major human movements a few centuries ago (2, 6, 21, 36, 49, 56, 79, 96, 104). Pathogenic variants in *BRCA1* are relatively the most prevalent variants in West African populations with breast cancer, and comparable rates are observed among African Americans and Caribbean populations, with rates decreasing further west based on population admixture (11, 37, 72, 104). Case–control studies in West Africa have shown relative risk (odds ratio) estimates ranging from 13.1 to 23.4 ($p < 0.001$) (11, 104). By contrast, pathogenic variants in *BRCA2* are found mainly in East Africa, which is populated by individuals known to have identifiable traits in North African populations (6, 16, 21, 43, 44, 83, 95). In congruence with these findings, several similar variants are shared between these two parts of the African continent. The two regions have known human movements originating from the Middle East, South Asia, and southern Europe, which is explained by the nature of the genetic admixture and linguistic particularities in these regions (25, 73, 93). Larger studies are needed to further investigate these observations.

The remaining breast cancer risk in African populations is most commonly conferred by other DNA damage repair pathway genes, namely *ATM* and *PALB2*, in varying and not regionally distributed patterns, followed by *TP53* (2, 3, 6, 11, 37, 44, 62, 71, 95, 104). **Figure 1** details the most common prevalence ranges of breast cancer causative gene variants where they have been studied in regions with high concentrations of populations of African descent.

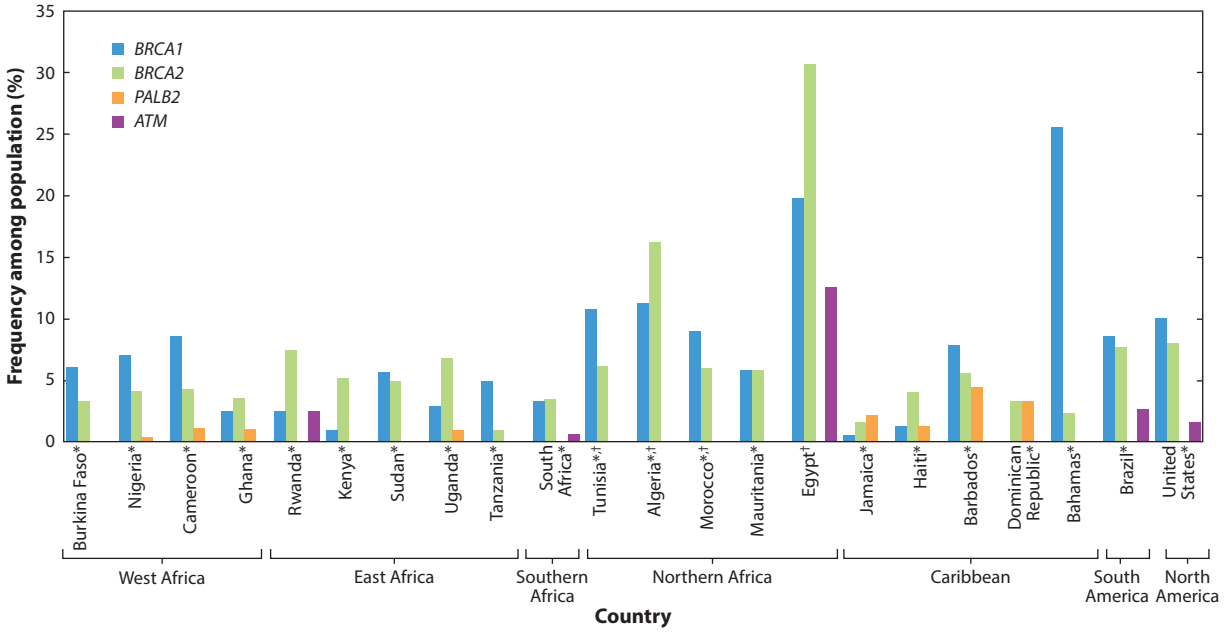

Figure 1

Frequency of pathogenic germline variants among women of African descent. Asterisks denote that studies were conducted among individuals unselected for family history; crosses denote that they were conducted among individuals selected for family history.

The size and scope of germline genetic studies in African populations vary from small studies of high-risk families to large case–control studies, leading to a range of findings spanning from founder mutations in smaller, regional groups of populations to estimation of gene penetrance and cancer risk in women of African descent. Both approaches have merits to not only advance African genome research but also further define cancer risk in underreported populations (2, 11, 20, 21, 85). The two methodologies could be bridged by population-based studies starting with guideline-identified high-risk individuals with breast cancer coupled with rigorous follow-up methods for carriers and their families through cascade testing.

Various approaches have been used to investigate the germline characteristics causative of breast cancer among women of African descent. The most common have been whole-genome/whole-exome sequencing and/or specific gene (e.g., *BRCA1/2*) sequencing (2). Both types of tests are expensive and difficult to sustain. Additionally, the complexity of ensuring the reproducibility of findings in low-resource settings means that researchers need standardized and affordable means of testing. Multigene panel testing, consisting of evaluating multiple genes with known predetermined variations and risk, is now considered a gold standard in familial and population-based genetic testing studies (101). Small to medium-sized multigene panels that include two to five of the most common, recurrent, and actionable gene variants for each region would be one way to introduce and advance cancer genetic care for underserved populations of African descent.

The application of large multigene panels in underrepresented populations would not only detect potentially deleterious variants with little knowledge of causal effects but also increase the detection of variants of uncertain significance (VUSs) in high-risk populations (8). VUSs are variants in the coding regions of genes that may or may not affect disease risk and warrant active investigation. Their increased rate in populations of African descent underscores the dismal representation and characterization of germline genetic variants in these populations. In

Tunisia, close to 30% of individuals and families with strong phenotypes and inconclusive results were reclassified as carriers of deleterious DNA repair variants following gene panel testing and functional analyses (21). In South Africa, the use of an expanded gene panel led to a large increase in the prevalence of VUSs in populations of African descent, which was substantially mitigated by using African genomic data to reclassify VUSs based on African allele frequencies (69). Adopting standardized functional classification methods, as investigated by various consortia (26, 91), would support the identification of unsolved families of women of African descent.

There is a dearth of literature linking genotypes of breast cancers among women of African descent with the corresponding phenotypes. African Americans are known to have higher rates of *BRCA1* mutations in exon 11 (19). There is a clear geographical distribution of disease subtypes correlating with the differences and similarities of germline variants between regions, as described above. An important example of this is triple-negative breast cancer (TNBC), in which receptors for the hormones estrogen and progesterone and the protein human epidermal growth factor receptor 2 (HER2) are lacking, which limits the treatment options for this subtype. Women from North Africa have less TNBC, lower proliferative indexes, and similar rates of the luminal breast cancer disease subtype compared with women from southern Europe (27). In a comparative study of women from different African regions, East African women were more likely to have a hormone receptor–positive breast cancer subtype than West African women, who had high rates of TNBC (51). Similarly, a recent meta-analysis highlighted a TNBC frequency of 42.3% in West Africa compared with 18–28% in the northern, eastern, central, and southern regions of Africa (67). Further investigations are needed to corroborate these findings and specifically to explore the molecular variations of breast cancer subtypes between regions.

Unique environmental exposure influences breast cancer disease behavior among women of African descent. An identified element of adaptive selection associated with TNBC in African women includes natural protection against the *Plasmodium vivax* strain conferred on individuals living in regions where malaria is highly endemic, covering populations from Sierra Leone to South Africa (31, 73, 99). Further, a single-nucleotide variant in the coding area of the *DARC/ACKR1* (Duffy antigene receptor for chemokines/atypical chemokine receptor 1) gene has been found at an elevated frequency in TNBC tumors of women of African descent (63).

3.2. Breast Cancer Risk Conferred by Common Genetic Variants

The relationships between specific genetic variants and their phenotypic outcomes among individuals of shared ancestry have been thoroughly studied in genome-wide association studies (GWASs) in populations of European descent. These GWASs have led to a much deeper understanding of the contribution of common, low-penetrance variants to breast cancer risk, with more than 200 such loci identified (50), and have improved the understanding of breast cancer risk. The contributors, mainly single-nucleotide polymorphisms (SNPs), have been used to develop polygenic risk score (PRS) testing for breast cancer and many other disorders. However, this is an area that lacks thorough investigation for women of African descent, although it is used routinely in high-risk clinics in high-income countries. Validation studies for these tests have been undertaken and have observed varying levels of performance among Black women relative to disease subtype (32).

Researchers have discovered many new risk loci over the past decade and continue to expand the understanding of risk diversity and refinement for individuals of African descent, but the findings are limited to a smaller patient population. Some of the initial studies conducted on African American women identified two risk loci associated with TNBC risk on chromosome 3p26 (rs7610073 and rs10510333) in the intron and upstream of the *GRM7* gene, respectively (24). Other established loci that are strongly associated with TNBC have been discovered in women of African American descent on *TERT-CLPTM1L* (5p15, rs10069690) (41), *TNFSF10*

(3q26.21, rs13074711) (46), *KCNK2* (1q41, rs67931591) (5), *ANKLE1/ABHD8* (19p13, rs2363956) (48), and *SIN3A* (15q24.2, rs60381548), the last of which also contributes to overall breast cancer risk (5). Variants in *FGFR2* are strongly associated with hormone receptor–positive breast cancer disease and favorable prognosis and have been found in North African populations and African Americans (17, 88, 94) but were not associated with breast cancer in the Black South African population (30). Another important SNP that has a strong correlation with hormone receptor–positive breast cancer among individuals of African descent is located on 2q35 (rs12998806), on the *DIRC3-AS1* gene (48). A recent GWAS of more than 18,000 cases and 22,000 controls of African descent identified 12 independent loci associated with breast cancer risk and constructed an African PRS that outperformed a PRS developed from women of African descent (50). **Table 1** provides a detailed account of each locus and its known disease subtype associations.

Table 1 Genetic loci with a significant association with breast cancer risk for different disease subtypes in women of African descent with breast cancer

Disease subtype	Locus	Gene	SNP
Hormone receptor positive	2q14.2	*AC073257.2*	rs940672 (50)
	2q14.2	*INHBB*	rs6750813 (50)
	2p21	*CALM2*	rs13032512 (40) rs114416221 (40)
	2q35	*DIRC3-AS1*	rs12998806 (48) rs13387042 (48)
	2q35	*IGFBP5*	rs2372943 (48)
	3p24	*SLC4A7*	rs4973768 (48)
		NEK10	rs2370946 (48)
	4q24	*ARHGEF38*	rs61751053 (50)
	5p12	*LINC02224*	rs4415082 (48) rs10941679 (48)
	5q11.2	*MAP3K1*	rs889312 (78)
	6q25.1–25.2	*ESR1* (*c6orf97*)	rs35240111 (50) rs9397435 (48)
	10q26.13	*FGFR2*	rs2981578 (78) rs2981579 (17) rs2981582 (17) rs10736303 (94) rs1219648 (94) rs17542768 (50)
	11q22.1	*PGR*	rs11571215 (40) rs590688 (40) rs10895054 (40)
	14q13.3	*SLC25A21*	rs4575439 (50)
		PAX9	rs73258644 (34)
	15q24	*CYP1B1*	rs10012 (40)
	16q12	*TOX3/TNRC9*	rs3104793 (48) rs8051542 (99)
	16q23	*CDYL2*	rs9940301 (34)
	18q11.2	*TTC39C*	rs10853615 (50)
	18q12.1	*FAM59A/GAREM1*	rs16963205 (50)
	Xp21.2	*NROB1*	rs138860909 (40)

(*Continued*)

Table 1 (*Continued*)

Disease subtype	Locus	Gene	SNP
Hormone receptor negative/TNBC	1q32.1	*MDM4*	rs4245739 (50)
	1q41	*KCNK2*	rs67931591 (5)
	2q14.2	*RP11-19E11.1*	rs76664032 (50)
	2q35	*TNP1*	rs13000023 (63)
	3q26.21	*TNFSF10*	rs13074711 (46)
	3p26	*GRM7*	rs10510333 (24) rs7610073 (24)
	5p15	*TERT-CLPTM1L*	rs10069690 (41)
	6q14	*TENT5A*	rs17530068 (89)
	19p13.11	*ANKLE1/ABHD8*	rs12974508 (50) rs2363956 (48) rs56069439 (50) rs61494113 (50) rs67397200 (50)
		BABAM1	rs8170 (72)
	20q11.21	*BCL2L1*	rs22843378 (89)
Overall breast cancer risk	1p13.3	*DRAM2*	rs17024628 (5)
	4q24	*ARHGEF3*	rs6175105350 (5)
	5q31.3	*IRF1*	rs2522057 (5)
	14q31	*GALC/LINC02330*	rs4322600 (24)
	15q24.1	*SCAMP2*	rs1869959 (5)
	15q24.2	*SIN3A*	rs60381548 (5)
	15q26.3	*TPPP3*	rs181337095 (5)
	16q12.2	*FTO*	rs17817449 (34)

Abbreviations: SNP, single-nucleotide polymorphism; TNBC, triple-negative breast cancer.

The available GWASs to identify new loci in individuals of African descent with breast cancer have been limited to African Americans, some populations in the Caribbean, and populations in West and North Africa. Given the population diversity, weak linkage disequilibrium, region-specific adaptive selection, and potential discovery of novel SNPs, there are remaining questions related to the inheritability of the reported SNPs, their reproducibility in other regions, and other contributing SNPs in African populations.

The importance of exploring SNPs is found in their combined use to develop PRSs, leading to further precision in cancer risk prediction. However, large-scale GWASs in multiple African populations are needed to develop reliable PRSs in Africa based on risk variants that are relevant in African populations. Subsequent management based on high scores on polygenic risk calculations is still under investigation but could offer screening and prevention solutions for high-risk individuals.

4. SOMATIC DRIVERS OF BREAST CANCER RISK

In the last few decades, molecular studies of breast cancer have strongly associated TNBC with women of African ancestry. In summary, breast cancer among individuals of African descent is characterized by a young age and aggressive disease at diagnosis and is likely to be the basal-like 1 or 2 subtype in Nigerian patients (14). The breast tumors in this population usually have a high tumor mutation burden, increased genomic instability, kataegis (localized hypermutation), and a high rate of copy number alterations and are typically associated with *GATA3* and *TP53* somatic

Table 2 Summary of somatic findings among women of African descent with breast cancer

Type	Finding
Tumor signatures	S9 (impaired homologous recombination repair) S13 (APOBEC C > G) S2 (APOBEC C > T) S1 (aging)
Immune signatures	$CD8^+$ T cell exhaustion Predominance of tumor-infiltrating lymphocytes
Molecular nature	High tumor burden and genomic instability (kataegis) High copy number alterations
Common biomarkers[a]	Vascular endothelial growth factor Programmed death-ligand 1
Mutations	*GATA3* *TP53*

[a]For an exhaustive list, see Reference 29.

mutations. The discovery of different types of mutation signatures that have resulted from various mutational processes has provided new insights into the development of cancer (13). This approach has been used to show that breast tumors from West African populations have an impaired homologous recombination repair pathway (mutation signature S9) (14, 52, 61, 77, 98). Other tumor mutation signatures found in breast tumors of African women include S13 (APOBEC C > G), S2 (APOBEC C > T), and S1 (aging) (77, 98). Some of these signatures (APOBEC3 and impaired homologous recombination repair) are associated with hypermutation, a high mutational burden, and an overall poor prognosis (13, 81). Further, unique gene expression combinations that were dysregulated in samples from women of African descent contribute to poor treatment outcomes. For example, downregulation of *ESR1* (encoding the estrogen receptor α protein), *PGR* (encoding the progesterone receptor protein), and *AR* (encoding the androgen receptor protein) (39) has been found more often in women of African descent than in women of European descent and further contributes to an increased mortality from a lack of therapeutic targets.

Breast cancer in women of African descent has strong environmental and immune system crosstalk, hypothesized to be a result of centuries-long exposure to infectious pathogens and a prolonged immune response (25). Tumors from women of African origin have shown an abundant memory and activated immune response when compared with tumors from women of European descent. Breast tumors from women of African descent have an elevated number of tumor-infiltrating lymphocytes, seen with $CD8^+$ T cell exhaustion (18, 102). **Table 2** summarizes the somatic findings made among women of African descent.

These features place women of African descent at a critical confluence of health disparities and opportunities for precision medicine. A high disease grade and high tumor mutation burden are associated with a better chemotherapy and immunotherapy response, respectively (54, 66). Davis et al. (29) summarized potential therapeutic targets that have been identified in breast tumors from women of African origin. In addition to these targets, vascular endothelial growth factor (VEGF) and programmed death-ligand 1 (PD-L1) have been found to be highly upregulated among African women with TNBC (18, 42, 102). However, gaps in access to and distribution of clinical trials worsen breast cancer mortality among women of African origin (82).

5. PRECISION MEDICINE

Molecular research in breast cancer has found multiple targets for effective and personalized cancer treatment. However, disparities in access to cancer management exist among women of African

descent with breast cancer. Diagnostic capacity with imaging, pathology, and biomarker testing for breast cancer is lacking for most women in sub-Saharan Africa (10). Some notable progress is the availability of essential targeted therapy for HER2-positive disease (97). This imbalance of healthcare resources is highlighted by the paucity of cancer care plans in most African countries (33).

The pharmacogenomic characteristics of women of African descent with breast cancer provide more room for precision medicine solutions. While the high grade of breast cancer could offer a favorable outcome with traditional cytotoxic chemotherapy, pharmacogenomic investigations have revealed genes and SNPs that could explain both the high toxicity profile and lower effectiveness of chemotherapy in individuals of African descent (64). A SNP found in the *CBR1* gene (rs20572), known to support anthracycline elimination, is less common in Africans, demonstrating a potential hematologic toxicity of the medication in this population (28). Furthermore, a CYP450 member (CYP2B6), which functions to eliminate cyclophosphamide, and a rate-limiting variant of the *DPYD* gene that metabolizes antimetabolites (e.g., 5-fluorouracil and capecitabine) are more common in individuals of African descent (84). Similar metabolism and functional findings have been made for targeted therapy medications (64). For a population known to have burdensome chemotherapy at late stages of disease presentation (55), leaner, targeted treatments would offer better treatment responses.

6. CONCLUSION

Considerable knowledge has been generated on breast cancer in individuals of African descent, but population-specific and interregional disparities exist in genetic research representation. The influence of genetic admixture is an essential consideration in molecular studies of individuals of African descent. Historical European and Asian flows into the African continent in recent centuries and the forced slave migration away from the continent contribute substantially to population

Table 3 Summary of recommendations to enable future progress

Category	Subcategory	Recommendation(s)
Access	Patient ascertainment	Use evidence-based ascertainment
	Genetic counseling	Develop visual and culturally sensitive tools
	Genetic testing	Test and implement affordable and scalable technologies
Germline panel testing and genome-wide assay studies	Pathogenic variants	Build population-specific genotype–phenotype databases to guide patient ascertainment
	Variants of uncertain significance	Create smaller, population-specific panels (based on the most common pathogenic variants seen in a population)
	Common genetic variants	Perform genome-wide association studies in different African populations Test and refine studies in multiple African populations and design population-specific risk predictive (polygenic risk score) tools
Somatic testing and biomarker investigations	Genetic admixture	Perform ancestry estimation using various methods (e.g., gene expression patterns) to avoid self-reported race/ancestry bias
	Sample purity	Use paired blood and sample biopsies Perform multiple biopsies on one or multiple disease sites to account for sample and disease heterogeneity
	Biomarker discovery	Perform population-diverse studies for disease investigation and biomarker quantification Expand biomarkers and include pharmacogenomics to account for drivers of disease response

heterogeneity (25, 73). Further, self-reported ancestry without ancestry analysis is a potential source of bias in the interpretation of findings and understanding of molecular features exclusive to African individuals. A key area for future research is to expand knowledge of the contribution of common genetic variants to breast cancer risk by conducting large-scale GWASs in populations from central, eastern, and southern Africa. Also, the molecular basis of breast tumor development across Africa is poorly understood and requires substantial investment in tumor DNA sequencing and characterization. **Table 3** provides a summary of recommendations to establish sustainable cancer genetics programs for African populations. Innovative and scalable solutions are needed to understand the burden and diversity of hereditary breast cancer disease in African populations. The search for effective biomarkers to facilitate the early detection of cancer is a top priority. The finding of unique tumor characteristics and biomarkers should be supported by a significant investment in drug discovery. This is currently hindered by the competing health system priorities in most African countries and a lack of resources. In view of the large increase in the incidence of breast cancer in Africa, campaigns to foster public and governmental awareness are needed to respond to this major developing healthcare challenge.

DISCLOSURE STATEMENT

O.I.O. is a cofounder of CancerIQ and serves as scientific advisor to Tempus.

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