BREAST CANCER

Genetic Susceptibility to Breast Cancer in Sub-Saharan African Populations

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INTRODUCTION

Breast cancer (BC) is the most common cancer among African women and is the second most common cause of cancer deaths in Africa as estimated by GLOBOCAN 2018.[1] Cancer incidence is increasing in Africa[1] and is associated largely with lifestyle changes, resulting from increased urbanization.[2] Ferlay et al[3] predicted a 49% increase in BC incidence across Africa between 2018 and 2040, an increase faster than any other region in the world. The International Association of Cancer Registries cancer incidence report includes data for only 20 of 46 sub-Saharan African (SSA) countries,[4] and it is likely that the incidence of BC is under-reported owing to lack of infrastructure for cancer diagnosis in resource-constrained countries in SSA.[5] Also, owing to the large burden of communicable and other non-communicable diseases in SSA, most resources are directed at controlling these diseases.[6,7] Cancer research, especially molecular research, in SSA is often deprioritized against other pressing public health concerns.[8]

The epidemiology of BC is complex and the causes are multifactorial, with genetic risk factors and the environment playing important roles in cancer development.[9] Genetic risk factors contributing to the development of BC include rare pathogenic variants[10] or many common variants that, in combination, increase the risk of developing BC.[11] Familial or hereditary BC is associated with rare variants, which significantly increase the risk of developing BC and occur in genes such as *BRCA1*, *BRCA2*, *PTEN*, *FGFR2*, *CHEK2*, *TP53*, *PALB2*, *ATM*, and *XRCC2*. Hereditary BC accounts for only 5%-7% of all cases of BC.[2] The contribution of rare variants with moderate to high penetrance for BC risk has been reviewed recently by Nguyen and Thomas.[12] The other category is BC that occurs in the general population without evidence of a significant family history and results from a combination of genetic and environmental risk factors. The genetic risk is conferred by the presence of multiple genetic variants such as single-nucleotide polymorphisms (SNPs), which are relatively common in the population being studied, with allele frequencies of 1% or more.

Each variant individually confers only a small increase in risk of disease, but the presence of many such variants together significantly increases the risk of developing BC.[11,13] The contribution of common variants to BC risk has been investigated through the use of genome-wide association studies (GWASs), with at least 172 known genetic loci associated at genome-wide significance with the risk of BC.[14]

A majority of studies into the molecular etiology of BC have been performed in non-African populations, although there is substantial emerging literature on the genetics of BC in African-American populations.[15,16] However, published data on resident Black African populations from continental Africa are much more limited. This scoping review aims to summarize genetic studies on BC risk that have been conducted in resident Black SSA populations and to identify potential gaps in knowledge and research opportunities.

METHODS

The research question for this review was, *what knowledge exists on the association of germline genetic variants with familial or sporadic breast cancer in Black populations resident in sub-Saharan Africa?* This review follows the framework for scoping studies according to Arksey and O'Malley.[17] We chose to carry out a scoping review rather than a systematic review on the basis of the criteria described in the study by Munn et al.[18] A scoping review is more appropriate since there is a limited body of evidence in SSA, and our purpose was to scope the available evidence on BC genetics in SSA and to identify gaps in knowledge and limitations in methodologic approaches.

PubMed and SCOPUS were used to search the literature, and only original research articles written in English were included. All studies published on or before April 1, 2020, were included. Review articles were excluded. Only studies including data from SSA populations were included. A comprehensive combination of keywords was used to identify genetic studies on participants resident in SSA countries (Appendix Table A1).

The selection of appropriate studies was carried out according to the following criteria: original research articles that studied inherited variants associated with

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Both rare and common genetic variants contribute to the risk of breast cancer (BC). Much is known about the genetics of BC in populations of European origin. Our objective was to review studies of genetic susceptibility to BC in the populations of sub-Saharan Africa to identify knowledge gaps and propose study designs to address these.

Knowledge Generated

A total of 22 studies were identified in 10 of 46 countries in sub-Saharan Africa. Rare variants predicted to be pathogenic were detected most commonly in the *BRCA1*, *BRCA2*, and *PALB2* genes. There were few studies of common genetic variants, none of which provided strong evidence for association with BC risk.

Relevance

Knowledge of genetic factors contributing to BC risk has important implications for patients and their families both for genetic counseling and for potential access to new therapies, which improve survival and reduce side effects.

BC in resident SSA populations. Screening of titles and abstracts for all papers was done independently by the lead authors (M.H. and W.C.C.), and papers were included on the basis of consensus agreements between them. If there was uncertainty on deciding whether a study was relevant, the full article was read to make a final decision. Studies of South African women of European, Indian, or mixed ancestry were excluded. If the abstract or full text to a study could not be accessed, it was excluded from this study. The following information was extracted: PMID, year of study, population, sample size, key findings (variants and genes), the predicted pathogenicity of variants, methodology, and a brief summary of the study. Rare variants were considered of interest if predicted to be deleterious by variant effect predictor tools and/or significantly enriched in BC cases compared with controls.

RESULTS

Using the comprehensive list of keywords to search, PubMed identified a total of 1,029 articles (Fig 1). Scanning the titles and the abstracts led to exclusion of 1,002 studies as they were not BC genetic studies, did not include samples from SSA, or were reviews, leaving 27 that met the broad inclusion criteria. A further four studies were excluded after full-text evaluation as they were conducted in African-American populations, and our aim was specifically to review studies of BC genetics in SSA populations. One study was removed as it only investigated tumor DNA. The search in SCOPUS did not yield any additional eligible articles.

The remaining 22 papers were included and assessed in this review.[19-40] Of these, 16 were rare variant studies,[19-34] and the remaining six investigated a few common variants in small sample sizes.[35-40] The studies used protein truncation tests, variant-specific polymerase chain reaction assays, sequencing of genes, exons, or coding regions, or gene panel sequencing to identify variants. There were no GWASs among the 22 papers. The studies in this review included populations from 10 of the 46 SSA countries:

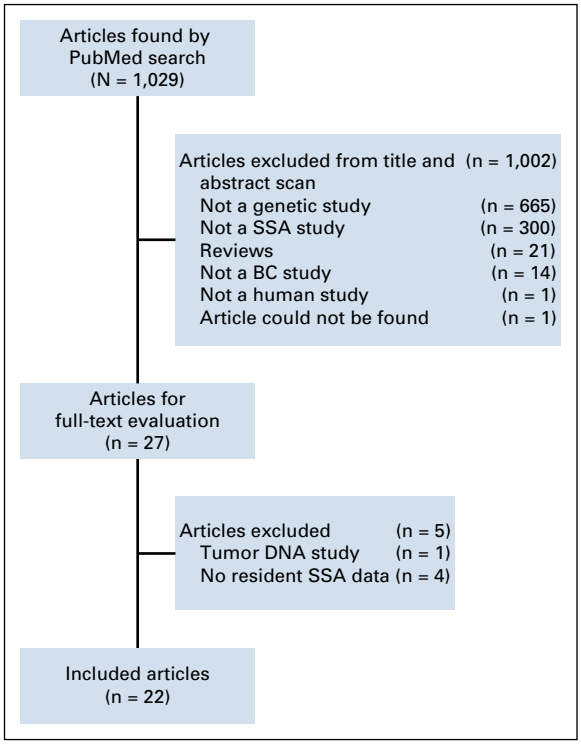

FIG 1. Process of selection of papers. The selection criteria were germline genetic studies focusing on BC and carried out in an SSA population(s). BC, breast cancer; SSA, sub-Saharan African.

Burkina Faso,[22,27,37] Cameroon,[21] Democratic Republic of Congo,[25] Ethiopia,[38] Kenya,[19] Nigeria,[23,28,30,32,33,35,36] Rwanda,[29,39,40] Senegal,[20,26,34] South Africa,[24,31] and Uganda.[21]

The Contribution of Rare Variants to BC Risk in SSA

Among the 22 studies identified, 16 were rare variant studies, which involved the screening of exons of genes of interest for variants with moderate to high penetrance and low population frequencies. A summary of the rare variant studies including countries of origin of participants and

sample sizes is shown in Table 1. Probable pathogenic variants, which have been detected in two or more patients, are listed in Table 2. Some of the rare variant studies (6 of 16) genotyped only a few specific variants, which had been identified previously in other populations. In 14 of the 16 studies, variants were identified in one or more known BC susceptibility genes, with sample sizes ranging from 1 to 1,136 patients with BC. The largest and most comprehensive of these, which built on previous studies in the Nigerian population, used the BROCA gene panel[41] to sequence the exons of 25 genes for variants in 1,136 Nigerian women with BC and in 997 Nigerian female controls.[23] Variants predicted to be deleterious were detected in 16 genes, including *BRCA1*, *BRCA2*, *PALB2*, and *TP53*. Deleterious variants were detected in 14.7% of patients with BC and in 1.8% of controls. Carriers of mutations in *BRCA1* and *TP53* had a significantly younger age at diagnosis than noncarriers, and *BRCA1* mutation carriers were more likely to have TNBC. The majority of patients for whom tumor stage was available were stage III (41.8%) or stage IV (42.6%), but no association of tumor stage with mutation status was reported. Four other previous studies of *BRCA1* and *BRCA2* in Nigerian patients with BC are summarized in Table 1, and mutations detected are listed in Table 2.

A South African study sequenced *BRCA1*, *BRCA2*, and *PALB2* from several ancestral groups, which included 85 South African Black patients with BC,[24] and found pathogenic variants in *BRCA1*, *BRCA2*, and *PALB2* in this ethnic subset. The group of patients with triple-negative breast cancer had a higher mutation frequency than the group of patients diagnosed before age 50 years. In another South African study, which included 16 women of Xhosa ancestry with BC, the same deleterious variant in *BRCA2* (p.Ile1924ArgTer) was detected in four of 16 patients and is suggested to be a founder variant in both Black and mixed ancestry populations in the Western Cape Province.[31] A study of patients with BC from Cameroon and Uganda sequenced 12 known or candidate BC genes in 196 cases and 185 controls unselected for age at diagnosis or family history[21] and identified pathogenic or likely pathogenic variants in 15.8% of BC cases and 1.6% of controls. Their findings included two patients with a mutation in *ATM* and single patient with mutations in *BARD1*, *CDH1*, and *TP53*. One of three studies in Senegal identified a duplication of 10 nucleotides in the *BRCA1* gene, c.815_824dup10, in 15 index cases from families with hereditary BC.[20] This duplication was located on the same microsatellite haplotype in all cases, had previously been reported in BC cases from France, Spain, and the United States, particularly in people of African or Hispanic descent, and is thus a founder mutation likely to be of West African origin. Whole-exome sequencing of 13 patients with BC in Kenya[19] detected five variants of uncertain clinical significance in *BRCA1* and *BRCA2* and a pathogenic variant in *BRCA2*. A study in the Democratic Republic of Congo detected a pathogenic *BRCA1* variant in all three affected members of a BC family.[25] However, sequencing of *BRCA1* and *BRCA2*

TABLE 1. Studies of Rare Variants in BC Genes in SSA

Methodology	Country	BC Cases	Controls	Variants Detected[a]	Reference
Whole-exome sequencing	Kenya	13	0	1	19
BRCA1/BRCA2, Sanger sequencing	Senegal	27	90	1	20
CHEK2 sequencing	Rwanda	41	42	0	29
BRCA1/BRCA2 sequencing	Nigeria	434	0	29	30
Gene panel	South Africa (Xhosa)	16	0	1	31
Allele-specific PCR	Nigeria	365	117	1	32
SSCP and protein truncation test	Nigeria	70	0	3	33
BRCA2 exon sequencing	Senegal	33	96	1	34
Gene panel sequencing	Cameroon and Uganda	196	185	34	21
Sequencing of coding regions of genes	Burkina Faso	9	0	0	22
BROCA gene panel sequencing	Nigeria	1,136	611	106	23
Coding gene sequencing and MLPA	South Africa (Black)	85	0	6	24
BRCA1/BRCA2 sequencing	DRC	3	0	1	25
BRCA1 sequencing	Senegal	1	0	1	26
BRCA1 sequencing (exons 2, 5, and 11)	Burkina Faso	15	0	0	27
SNAPSHOT and sequencing	Nigeria	356	0	12	28

Abbreviations: BC, breast cancer; MLPA, multiplex ligation–dependent probe amplification; PCR, polymerase chain reaction; SSA, sub-Saharan African; SSCP; single strand conformation polymorphism.

[a]No. of pathogenic variants detected.

TABLE 2. Predicted Pathogenic Variants Detected in Two or More African Patients

Gene	Variant	Variant Effect	No. of Cases	Country	Reference
BRCA1	c.80+1G>A	Splice site	2	Nigeria	23
BRCA1	c.133_134del	p.Lys45IleTer	5	Nigeria	23
BRCA1	c.191G>A	p.Cys64Tyr	3	Nigeria	30
BRCA1			4	Nigeria	23
BRCA1	c.303T>G	p.Tyr101Ter	4	Nigeria	28
BRCA1			10	Nigeria	23
BRCA1	c.815_824dup	p.Thr276Ter	15	Senegal	20
BRCA1	c.838dup	p.Ala280GlyTer	3	Nigeria	23
BRCA1	c.1504_1508del	p.Leu502AlaTer	2	Nigeria	30
BRCA1			3	Nigeria	23
BRCA1	c.1623dup	p.Asn542GluTer	3	Nigeria	23
BRCA1			4	Nigeria	30
BRCA1	c.2192_2196del	p.Lys731ArgTer	2	Nigeria	23
BRCA1	c.2329del	p.Tyr777MetTer	4	Nigeria	23
BRCA1	c.2864C>A	p.Ser955Ter	3	Nigeria	23
BRCA1	c.3268C>T	p.Gln1090Ter	2	Nigeria	30
BRCA1			4	Nigeria	23
BRCA1			2	Nigeria	33
BRCA1	c.3637_3638del	p.Glu1213ArgTer	2	Nigeria	23
BRCA1	c.4122_4123del	p.Ser1374ArgTer	3	Nigeria	30
BRCA1			3	Nigeria	23
BRCA1	c.4240dup	p.Leu1414ProTer	2	Nigeria	30
BRCA1	c.4484G>T	p.Arg1495Met	3	Cameroon	21
BRCA1	c.4986+6T>C	Splice site	2	Cameroon	21
BRCA1	c.4992C>T	Splice site	2	Nigeria	23
BRCA1	c.5095C>T	p.Arg1699Trp	2	Nigeria	23
BRCA1	c.5177_5180del	p.Arg1726LysTer	2	Nigeria	23
BRCA1	c.5324T>G	p.Met1775Arg	3	Nigeria	30
BRCA1			7	Nigeria	23
BRCA2	c.93G>A	p.Trp31Ter	2	Nigeria	23
BRCA2	c.1310_1313del	p.Lys437IleTer	3	Nigeria	30
BRCA2			4	Nigeria	23
BRCA2	c.1796_1800del	p.Ser599Ter	3	Nigeria	23
BRCA2	c.2402_2412del	p.Asn801IleTer	2	Nigeria	30
BRCA2			3	Nigeria	23
BRCA2	c.2808_2811del	p.Ala938ProTer	2	Nigeria	23
BRCA2	c.5241_5242insTA	p.Ser1748Ter	2	Nigeria	23
BRCA2	c.5286T>G	p.Tyr1762Ter	2	Nigeria	23
BRCA2	c.5771_5774del	p.Ile1924ArgTer	4	South Africa (Black)	31
BRCA2	c.8351+2T>C	Splice site	3	Nigeria	23
BRCA2	c.8817_8820del	p.Lys2939AsnTer	2	Nigeria	30
BRCA2	c.9875C>T	p.Pro3292Leu	2	South Africa (Black)	24
BARD1	c.1396-1G>A	p.Tyr101Ter	2	Nigeria	23
ATM	c.7913G>A	p.Trp2638Ter	2	Cameroon	21
PALB2	c.2485C>T	p.Gln829Ter	2	Nigeria	23
RAD15C	c.186_187del	p.Gln62HisTer	2	Nigeria	23

in patients with BC in Burkina Faso identified only benign variants in these genes[22,27] and a screen for germline variants in *CHEK2* in Rwandan BC cases and controls was negative.[29]

In summary, a total of 36 predicted pathogenic variants were detected in two or more patients with BC. These variants, together with their country of origin, are listed in Table 2. Some *BRCA1* variants were detected in up to 15 patients, and, as noted above, there are suggestive founder pathogenic variants in the Senegalese and South African populations. Overall, pathogenic variants were detected in at least two patients in the *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, and *RAD51C* genes. The study by Zheng et al[23] in Nigeria suggests that variants in several other genes may also contribute to BC risk, but the mutations were too rare to draw firm conclusions on causality.

The number of predicted pathogenic variants found in each gene and the SSA country where the studies were conducted are summarized in Figure 2. The preponderance of variants of Nigerian origin reflects the much larger and more comprehensive variant studies that have been conducted in this population.[23]

The Contribution of Common Variants to BC Risk in SSA

Our search did not find any GWAS of BC performed exclusively in resident SSA populations. The genetic association studies carried out in SSA populations were candidate gene studies, which investigated a limited number of common variants previously associated with BC in other populations. These were genotyped in relatively small numbers of BC cases and controls and tested for association with BC and are summarized in Table 3. Okobia et al[36] genotyped a *CYP1B1* polymorphism Val432Leu (c.1294C>G) in BC cases and controls from Southern Nigeria and found association of the heterozygous Val/Leu genotype with BC (odds ratio [OR] = 1.59; 95% CI, 1.01 to 2.52). The same group genotyped the c.668A>G single-nucleotide polymorphism (SNP; Gln223Arg) in the leptin receptor gene (*LEPR*) and reported a suggestive association of the 223Arg allele with disease risk in premenopausal women (OR = 1.8; 95% CI, 1.0 to 3.2; $P = .07$).[35] A study of the glutathione S-transferase null variants in the *GSTM1* and *GSTT1* genes in cases and controls from Burkina Faso found no association of the *GSTM1 null* variant with BC, whereas the *GSTT1 null* allele was associated with an increase in BC risk (OR = 2.42; 95% CI, 1.17 to 5.02; $P = .01$).[37] Investigation of an initiation codon variant (Met1Arg, rs2228570) in the vitamin D receptor (*VDR*) gene in 392 Ethiopian BC cases and controls reported an association of the Arg/Arg (G/G) genotype with an increased risk of BC (OR = 1.44; 95% CI, 1.01 to 2.06; $P = .04$).[38] A lack of association of a functional SNP in the *GPX1* gene (p.Pro198Leu) and the *TP53* functional SNP (p.Pro72Arg) with BC was reported in the Rwandese population,[39,40] but the sample sizes were very small.

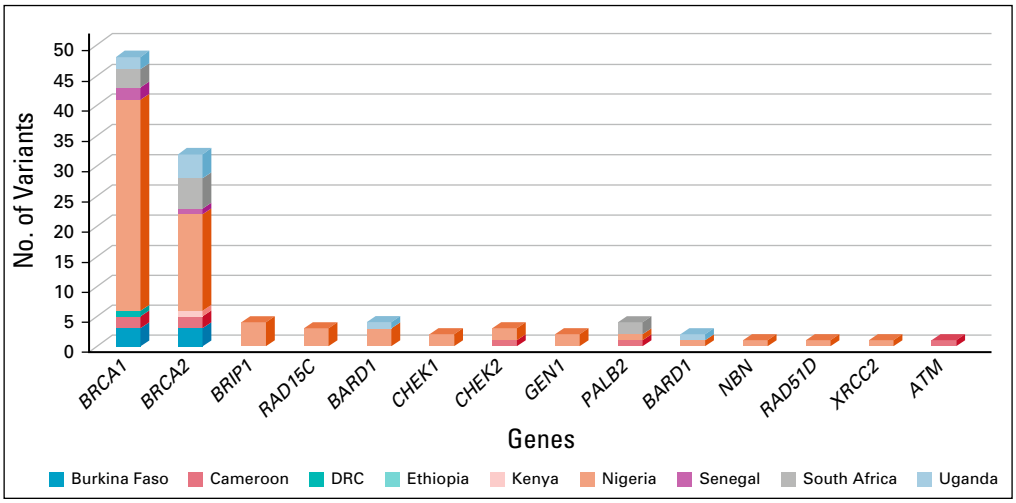

FIG 2. Variant distribution in genes and countries. This shows how many predicted pathogenic variants were identified in breast cancer susceptibility genes in each reported sub-Saharan African country. DRC, Democratic Republic of Congo.

DISCUSSION

Our initial PubMed and SCOPUS search yielded 1,029 articles from which 22 were selected for this review. These studies investigated the association of germline variants with BC in resident SSA populations. A large majority of studies focused on the detection and analysis of rare variants in known BC susceptibility genes in cases and, in some studies, also in controls. Our search did not find any GWAS for BC in resident African populations, but we did find a small number of association studies of candidate genes and common variants in cases and controls. Although the focus of our review was on sub-Saharan Africa, we discuss the findings below in the context of the extensive literature on BC genetics in African-American populations, which provide important insights relevant to continental Africa.

The studies included in this review either tested for specific variants known to be associated with BC risk in non-African populations or used DNA sequencing of the coding regions of known BC genes to explore the contributions of rare germline variants to the etiology of BC in their local populations. These germline variants are rare in the general population but have moderate to high penetrance, and thus, individuals with these variants are at substantially higher risk of developing BC compared with the general population.[42] Most of the studies focused on the key BC predisposition genes, *BRCA1* and *BRCA2*, which play important roles in DNA repair pathways.[43,44]

The variants of particular interest listed in Table 2 indicate that at least six genes, *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *BARD1*, and *RAD51C*, collectively make a significant contribution to BC risk in the African populations that were studied. The variants disrupt normal protein function either by early termination of mRNA translation by the introduction of stop codons or by missense variants, which may affect key functional elements of the protein.[45] However, we note that no functional assays were performed in any of the studies reviewed here and all potential functional effects were predicted in silico. There is also the problem of variants of unknown significance involving missense variants

TABLE 3. Association Studies of Common Variants in SSA BC

Gene	Methodology	Variant	Country	BC Cases	Controls	ORs (95% CI)[a]	Reference
LEPR	PCR-RFLP	p.Gln223Arg	Nigeria	209	209	1.8 (1.0 to 3.2)	35
CYP1B1	PCR-RFLP	p.Leu432Val	Nigeria	250	250	1.59 (1.0 to 2.52)	36
GSTT1	PCR	Deletion (null)	Burkina Faso	80	100	2.42 (1.17 to 5.02)	37
VDR	PCR-RFLP	p.Met51Thr	Ethiopia	392	193	1.44 (1.01 to 2.06)	38
GPX1	Exon sequencing	p.Pro198Leu	Rwanda	41	42	Not reported[b]	39
TP53	Allele-specific PCR	p.Pro72Arg	Rwanda	40	39	Not reported[b]	40

Abbreviations: BC, breast cancer; OR, odds ratio; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSA, sub-Saharan African.

[a]ORs and 95% CIs for strongest results.

[b]No association with BC overall. No ORs reported.

in known BC susceptibility genes that fail current predictive algorithms for pathogenicity, which will be amplified by inclusion of diverse and understudied African genomes.[46] The strategy of, for example, Zheng et al,[23] in which genes were sequenced in large numbers of cases and controls, is helpful in this regard, as it demonstrated a significant excess of many variants in cases vs controls, but the cost of sequencing large numbers of samples may be unaffordable for many African researchers. The contribution of other genes in which potentially pathogenic variants were found is not yet clear as the number of cases with variants in each of these genes was very small. However, for some of these genes, such as *ATM*, there is strong epidemiologic and molecular evidence of causality in other populations.[47] Another question of interest is whether specific pathogenic variants are found in more than one African country or ethnic group, such as is the case for European populations. There is currently insufficient evidence to resolve this question in African populations, but it could be addressed by larger-scale studies, such as the Nigerian study of Zheng et al,[23] being carried out in other African populations.

All the genetic association studies for common variants which we identified involved genotyping a small number of SNPs in one or two candidate genes and in small sample sizes. Some marginally significant associations were reported, but such studies would have very low power to detect the typically small effect sizes for individual variants in genetic susceptibility to disease in a complex trait. A further difficulty with candidate gene studies is that they do not provide the means for correction of population structure in the samples, which is an important requirement for a robust genetic association study.

Although the abovementioned studies are limited in scope and of low statistical power, recently, there have been several well-powered genetic studies in BC cases and controls of African ancestry, not resident in Africa. For example, a meta-analysis of two GWASs and a replication study in women of African ancestry identified 3q26.21 as a novel susceptibility locus for estrogen receptor (ER)–negative BC.[16] This study involved genotyping of more than 6,657 BC cases and 7,713 controls on a genome-wide SNP array. BC risk variants identified in other populations were tested for association in another large study of women of African ancestry[48] and at least 12 regions were identified, which showed evidence of association in this population. These findings suggest that there is at least partial transferability of BC risk loci between different populations and ethnicities. This phenomenon was also observed for other cancers such as prostate and esophageal cancers where some but not all risk loci were transferable across African, European, and Asian populations.[49-51] These studies suggest that the GWAS approach may be fruitful for studying the genetics of BC in resident African populations.

Whole-genome sequencing of many ethnolinguistic groups in Africa has confirmed the extraordinary degree of genomic diversity across the African continent.[52] A comprehensive analysis of the contribution of germline variants to BC risk in continental Africa will therefore require studies in a wide range of populations and regions. Another important consideration is the study design, which will depend on whether the aim is to identify rare variants of moderate to high penetrance in genes such as *BRCA1* and *BRCA2*, likely associated with familial cancers, or to identify variants with low penetrance, which collectively make a large contribution to BC risk in the general population.

To identify rare and novel germline variants of intermediate to high penetrance, DNA sequencing, rather than genotyping of known risk variants across the regions and populations of Africa, will be required since the limited data available suggest extensive diversity of BC risk variants across the African continent. The study design should also include an equivalent set of well-matched controls, which, together with algorithms for predicting functional effects in silico, will help to identify variants that are likely to be pathogenic. The sequencing strategy will depend on available financial and bioinformatic resources. Whole-exome sequencing would allow interrogation of the entire coding genome but is still relatively costly and requires bioinformatic skills to call, annotate, and interpret variants. Sequencing a panel of genes known to be involved in BC susceptibility, such as the BROCA panel,[41] would reduce costs and simplify the bioinformatic analysis but only investigate genes already implicated in other populations. The probability of detecting pathogenic variants in such genes would be increased by enriching the BC samples for younger patients and those with a family history of BC, as these are groups in which such variants are most likely to be identified. Finally, a substantial sample size will be needed to obtain a robust assessment of the contribution of these rare variants to BC risk in local populations. An exemplar that includes these desirable features is the study by Zheng et al[23] in the Nigerian population. Larger sample sizes would also allow tests of whether germline mutations were associated with clinical features such as hormone receptor status, tumor stage, and survival. A large study of germline mutations in African-American women, for example, showed a twofold higher incidence of pathogenic mutations in ER-negative BC compared with ER-positive BC.[15] Detection of germline mutations in genes such as *BRCA1* and *BRCA2* has important implications for clinical care such as the risk of further cancers in the patient, genetic counseling to other family members, and potential access to new classes of drugs such as poly (ADP-ribose) polymerase inhibitors, which can improve survival and reduce side effects in mutation carriers.[53]

Regarding the detection of common risk variants for BC, small sample sizes such as those reported to date in SSA populations do not have the power to detect associations of

common variants with small effects. A shortcoming of most candidate gene studies is that a limited number of variants are genotyped, which do not capture the full genetic diversity of the gene and genome.[54] Also, genotyping a small number of variants does not allow correction for the population structure, which is particularly important in populations with a high degree of genetic diversity and substructure. This requires either a genome-wide study or at least a genotyping array containing thousands of common variants to detect and control for population structure. The route to significant discoveries of common BC risk variants in African populations is to carry out GWAS using SNP arrays, which are designed to capture a substantial component of African genetic diversity, and by genotyping thousands of cases and controls to achieve the statistical power required to detect variants with modest effect sizes. We are currently carrying out a GWAS using the H3Africa array on more than 2,700 BC cases and 1,100 controls from the Johannesburg Cancer Study[55] in the Black South African population as part of the ERICA-SA study,[56] which aims to identify evolving risk factors for cancer in African populations.

A major difficulty regarding the desirable study designs outlined above is the resource-intensive nature of molecular cancer research such as next-generation sequencing and genome-wide genotyping in terms of funding and appropriately skilled personnel, both of which are relatively scarce in Africa. Significant progress in improving our understanding of the genetics of BC in Africa will require a substantial investment from governments or other sources to generate the grant income and training programs needed to achieve this goal.

In conclusion, although some studies on the genetics of BC have been carried out in populations of African origin, few comprehensive large-scale studies have included populations resident in SSA. This scoping review has identified that more extensive studies of the contribution of both rare and common variants to BC risk are needed in a broader range of African countries. The knowledge gap creates an opportunity for African researchers to gain new insights into the molecular epidemiology of BC on the African continent.

Both rare and common genetic variants contribute to the risk of BC. A wealth of information exists on genes and variants associated with BC risk in populations of European origin, but knowledge of the genetics of BC susceptibility in SSA is limited. Our scoping review found relevant published data from only 10 of 46 SSA countries, and most studies focused on detection of rare variants in known BC susceptibility genes such as *BRCA1* and *BRCA2*. Few studies looked for association of common variants with BC in the general population, and these had neither the statistical power nor the scope to identify common risk variants for BC or to correct for population structure differences. No GWASs for BC have been performed in resident SSA populations. Thus, there is limited information on the contribution of variants to BC in most SSA countries. More extensive screening of BC gene panels for high-penetrance variants is needed in SSA, and GWASs of large case-control samples are required to identify common variants contributing to BC risk in SSA populations. This knowledge gap represents important and exciting opportunities for African cancer research.

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DISCLAIMER

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Keywords and Combinations of Keywords Used to Search the Literature Using PubMed

Search No.	Keywords	Fields Searched
#1	breast cancer and variant	Field: Title/Abstract
#2	breast cancer and variants	Field: Title/Abstract
#3	breast cancer and mutation	Field: Title/Abstract
#4	breast cancer and mutations	Field: Title/Abstract
#5	breast cancer and germline	Field: Title/Abstract
#6	breast cancer and hereditary	Field: Title/Abstract
#7	breast cancer and inherited	Field: Title/Abstract
#8	breast cancer and genetic	Field: Title/Abstract
#9	breast cancer and genetics	Field: Title/Abstract
#10	breast cancer and genomic	Field: Title/Abstract
#11	breast cancer and genomics	Field: Title/Abstract
#12	breast cancer and genome-wide	Field: Title/Abstract
#13	breast cancer and GWAS	Field: Title/Abstract
#14	breast cancer and associated	Field: Title/Abstract
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	
#16	(africa) OR (african) OR (angola) OR (benin) OR (botswana) OR (burkina faso) OR (burundi) OR (cameroon) OR (central african republic) OR (chad) OR (comoros) OR (congo) OR (democratic republic of congo) OR (DRC) OR (djibouti) OR (equatorial guinea) OR (eritrea) OR (ethiopia) OR (gabon) OR (gambia) OR (ghana) OR (guinea) OR (bissau) OR (ivory coast) OR (kenya) OR (lesotho) OR (liberia) OR (malawi) OR (mali) OR (mauritania) OR (mozambique) OR (namibia) OR (niger) OR (nigeria) OR (rwanda) OR (senegal) OR (sierra leone) OR (somalia) OR (south africa) OR (sudan) OR (swaziland) OR (tanzania) OR (togo) OR (uganda) OR (zaire) OR (zambia) OR (zimbabwe) OR (central africa) OR (west africa) OR (east africa) OR (southern africa) OR (sub saharan africa), Field: Title/Abstract	
#17	#15 AND #16	

The entire search looked like this: ((africa[Title/Abstract]) OR (african[Title/Abstract])) OR (angola[Title/Abstract])) OR (benin[Title/Abstract])) OR (botswana[Title/Abstract])) OR (burkina faso[Title/Abstract])) OR (burundi[Title/Abstract])) OR (cameroon[Title/Abstract])) OR (central african republic[Title/Abstract])) OR (chad[Title/Abstract])) OR (comoros[Title/Abstract])) OR (congo[Title/Abstract])) OR (democratic republic of congo[Title/Abstract])) OR (DRC[Title/Abstract])) OR (djibouti[Title/Abstract])) OR (equatorial guinea[Title/Abstract])) OR (eritrea[Title/Abstract])) OR (ethiopia[Title/Abstract])) OR (gabon[Title/Abstract])) OR (gambia[Title/Abstract])) OR (ghana[Title/Abstract])) OR (guinea[Title/Abstract])) OR (bissau[Title/Abstract])) OR (ivory coast[Title/Abstract])) OR (kenya[Title/Abstract])) OR (lesotho[Title/Abstract])) OR (liberia[Title/Abstract])) OR (malawi[Title/Abstract])) OR (mali[Title/Abstract])) OR (mauritania[Title/Abstract])) OR (mozambique[Title/Abstract])) OR (namibia[Title/Abstract])) OR (niger[Title/Abstract])) OR (nigeria[Title/Abstract])) OR (rwanda[Title/Abstract])) OR (senegal[Title/Abstract])) OR (sierra leone[Title/Abstract])) OR (somalia[Title/Abstract])) OR (south africa[Title/Abstract])) OR (sudan[Title/Abstract])) OR (swaziland[Title/Abstract])) OR (tanzania[Title/Abstract])) OR (togo[Title/Abstract])) OR (uganda[Title/Abstract])) OR (zaire[Title/Abstract])) OR (zambia[Title/Abstract])) OR (zimbabwe[Title/Abstract])) OR (central africa[Title/Abstract])) OR (west africa[Title/Abstract])) OR (east africa[Title/Abstract])) OR (southern africa[Title/Abstract])) OR (sub saharan africa[Title/Abstract])) AND ((((((((((((breast cancer[Title/Abstract]) AND (variant[Title/Abstract])) OR ((breast cancer[Title/Abstract]) AND (variants[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (mutation[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (mutations[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (germline[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (hereditary[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (inherited[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (genetic[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (genetics[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (GWAS[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (genome wide[Title/Abstract]))) OR ((breast cancer[Title/Abstract]) AND (association[Title/Abstract])))

Abbreviation: GWAS, genome-wide association study.