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. Cancer incidence is increasing in Africa and is associated largely with lifestyle changes, resulting from increased urbanization. Ferlay et al 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, 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. Also, owing to the large burden of communicable and other non-communicable diseases in SSA, most resources are directed at controlling these diseases. Cancer research, especially molecular research, in SSA is often deprioritized against other pressing public health concerns.

The epidemiology of BC is complex and the causes are multifactorial, with genetic risk factors and the environment playing important roles in cancer development. Genetic risk factors contributing to the development of BC include rare pathogenic variants or many common variants that, in combination, increase the risk of developing BC. 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. The contribution of rare variants with moderate to high penetrance for BC risk has been reviewed recently by Nguyen and Thomas. 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. 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. 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. 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. 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. 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...
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. Of these, 16 were rare variant studies, and the remaining six investigated a few common variants in small sample sizes. 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: Burkina Faso, Cameroon, Democratic Republic of Congo, Ethiopia, Kenya, Nigeria, Rwanda, Senegal, South Africa, and Uganda.

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

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, Cameroon, Democratic Republic of Congo, Ethiopia, Kenya, Nigeria, Rwanda, Senegal, South Africa, and Uganda.
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 to sequence the exons of 25 genes for variants in 1,136 Nigerian women with BC and in 997 Nigerian female controls. 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 were significantly younger 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, 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.

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. 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 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. However, sequencing of BRCA1 and BRCA2

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

| Methodology                        | Country               | BC Cases | Controls | Variants Detected | 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.

*No. of pathogenic variants detected.*
In patients with BC in Burkina Faso identified only benign variants in these genes and a screen for germline variants in CHEK2 in Rwandan BC cases and controls was negative.

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 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 Nigerian origin reflects the much larger and more comprehensive variant studies that have been conducted in this population.

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 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 nucleotide polymorphism (SNP; Gln223Arg) in the leptin 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).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 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 Southern Nigeria 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).38 A study of the thalassemia S-transferase variant in the GSTT1 gene in 802 Ethiopian BC cases and controls reported an association of the Arg/Arg (G/G) with an increased risk of BC (OR = 1.44; 95% CI, 1.01 to 2.06; P = .04). A lack of association of a functional SNP in the GPX1 gene with BC was reported in the Rwandese population, but the sample sizes were very small.

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

| Gene  | Variant Effect | No. of Cases | Country  | Reference |
|-------|----------------|--------------|----------|-----------|
| BRCA1 | c.80+1G>A      | 2            | Nigeria  | 23        |
| BRCA1 | c.133_134del   | 5            | Nigeria  | 23        |
| BRCA1 | c.191G>A       | 3            | Nigeria  | 30        |
| BRCA1 | c.203T>G       | 4            | Nigeria  | 23        |
| BRCA1 | c.815_824dup   | 15           | Senegal  | 20        |
| BRCA1 | c.1504_1508del | 2            | Nigeria  | 30        |
| BRCA1 | c.1623dup      | 4            | Nigeria  | 30        |
| BRCA1 | c.3637_3638del | 2            | Nigeria  | 23        |
| BRCA1 | c.4122_4123del | 3            | Nigeria  | 30        |
| BRCA1 | c.2402_2412del | 2            | Nigeria  | 23        |
| BRCA1 | c.2808_2811del | 2            | Nigeria  | 23        |
| BRCA1 | c.2541_5242ins TA | 2 | Nigeria  | 23        |
| BRCA2 | c.1310_1313del | 3            | Nigeria  | 30        |
| BRCA2 | c.1796_1800del | 3            | Nigeria  | 23        |
| BRCA2 | c.2402_2412del | 2            | Nigeria  | 30        |
| BRCA2 | c.2808_2811del | 2            | Nigeria  | 23        |
| BRCA2 | c.2541_5242ins TA | 2 | Nigeria  | 23        |
| BRCA2 | c.3524T>G      | 3            | Nigeria  | 30        |
| BRCA1 | c.203T>G       | 4            | Nigeria  | 23        |
| BRCA1 | c.815_824dup   | 15           | Senegal  | 20        |
| BRCA1 | c.1504_1508del | 2            | Nigeria  | 30        |
| BRCA1 | c.1623dup      | 4            | Nigeria  | 30        |
| BRCA1 | c.3637_3638del | 2            | Nigeria  | 23        |
| BRCA1 | c.4122_4123del | 3            | Nigeria  | 30        |
| BRCA1 | c.2402_2412del | 2            | Nigeria  | 23        |
| BRCA1 | c.2808_2811del | 2            | Nigeria  | 23        |
| BRCA1 | c.2541_5242ins TA | 2 | Nigeria  | 23        |

In patients with BC in Burkina Faso identified only benign variants in these genes and a screen for germline variants in CHEK2 in Rwandan BC cases and controls was negative.29

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| BRCA1 | c.191G>A       | 3            | Nigeria  | 30        |
| BRCA1 | c.203T>G       | 4            | Nigeria  | 23        |
| BRCA1 | c.815_824dup   | 15           | Senegal  | 20        |
| BRCA1 | c.1504_1508del | 2            | Nigeria  | 30        |
| BRCA1 | c.1623dup      | 4            | Nigeria  | 30        |
| BRCA1 | c.3637_3638del | 2            | Nigeria  | 23        |
| BRCA1 | c.4122_4123del | 3            | Nigeria  | 30        |
| BRCA1 | c.2402_2412del | 2            | Nigeria  | 23        |
| BRCA1 | c.2808_2811del | 2            | Nigeria  | 23        |
| BRCA1 | c.2541_5242ins TA | 2 | Nigeria  | 23        |
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.

| Gene | Methodology | Variant | Country       | BC Cases | Controls | ORs (95% CI) | 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 | 39        |
| TP53 | Allele-specific PCR | p.Pro72Arg | Rwanda        | 40       | 39       | Not reported | 40        |

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

*ORs and 95% CIs for strongest results.

*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. The strategy of, for example, Zheng et al., 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., 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. 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 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. 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.53 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, 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. 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. 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.\(^{64}\) 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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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018

2. Lukong KE, Ogunbolude Y, Kamdem JP: Breast cancer in Africa: Prevalence, treatment options, herbal medicines, and socioeconomic determinants. Breast Cancer Res Treat 166:351-365, 2017

3. Ferlay J, Colombet M, Soerjomataram I, et al: Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 144:1941-1953, 2019

4. Christopher PW, Weiderpass E, Bernard WS: World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France, International Agency for Research on Cancer, 2020, pp 1-630

5. Cumber SN, Nchang' N, Tsoka-Gwegaeni JM: Breast cancer among women in sub-Saharan Africa: Prevalence and a situational analysis. South Afr J Gynaecol Oncol 9:35-37, 2017

6. Roth GA, Abate D, Abate KH, et al: Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 392:1736-1788, 2018

7. Gouda HN, Charlson F, Sorsdahl K, et al: Burden of non-communicable diseases in sub-Saharan Africa, 1990–2017: Results from the Global Burden of Disease, 2017. Lancet Glob Heal 7:e1375-e1387, 2019

8. Ngoma T, Ngoma M: Cancer control in Africa: Is cancer research a luxury or necessity? Ecamericahealthscience 13:947, 2019

9. Momemniovahed Z, Salehiniya H: Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer Targets Ther 11:151-164, 2019

10. Doring L, Carvalho S, Allen J, et al: Breast cancer risk genes—Association analysis in more than 113,000 women. N Engl J Med 384:428-439, 2021

11. Maxwell KN, Nathanson KL: Common breast cancer risk variants in the post-COGS era: A comprehensive review. Breast Cancer Res 15:212, 2013

12. Nguyen JV, Thomas MH: Beyond BRCA: Review of hereditary syndromes predisposing to breast cancer. J Breast Imaging 1:84-91, 2019

13. Weeks DE, Lathrop GM: Polygenic disease: Methods for mapping complex disease traits. Trends Genet 11:513-519, 1995

14. Lilyquist J, Ruddy KJ, Vachon CM, et al: BRCA1, BRCA2 and PALB2 mutations and CHEK2 c.1100delC in different South African ethnic groups. J Breast Cancer Genetics 10:120-127, 2012

15. Arksey H, O’Malley L: Scoping studies: Towards a methodological framework. Int J Soc Res Methodol Theor Pract 8:19-32, 2005

16. Huo D, Feng Y, Haddad S, et al: Genome-wide association studies in women of African ancestry identify 3q26.21 as a novel susceptibility locus for oestrogen receptor negative breast cancer. Hum Mol Genet 25:dw305, 2016

17. Arkesy H, O’Malley L: Scoping studies: Towards a methodological framework. Int J Soc Res Methodol Theor Pract 8:19-32, 2005

18. Munn Z, Peters MDJ, Stern C, et al: Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 18:1-7, 2018

19. Torrey-Sawe R, van der Merwe N, Mining SK, et al: Pioneering informed consent for return of research results to breast cancer patients facing barriers to implementation of genomic medicine: The Kenyan BRCA1/2 testing experience using whole exome sequencing. Front Genet 11:513-519, 1995

20. Ndiiaye R, Diop JPD, Bourdon-Huguenin V, et al: Evidence for an ancient BRCA1/2 deleterious mutation (c.1949_1950delTA) in a woman of Senegalese descent with triple-negative early-onset breast cancer. Oncol Lett 10:120-127, 2020

21. Adeedokun B, Zheng Y, Ndom P, et al: Prevalence of inherited mutations in breast cancer predisposition genes among women in Uganda and Cameroon. Cancer Epidemiol Biomarkers Prev 29:380-394, 2020

22. Sagna T, Bonora E, Ouedraogo MNL, et al: Identification of BRCA1/2 p.Ser1613gly, p.Pro871leu, p.Lys1183arg, p.Glu1038gly, p.Ser1140gly, p.Ala2466val, p.His2440arg variants in women under 45 years old with breast nodules suspected of having breast cancer in Burkina Faso. Genom Med 5:1-6, 2020

23. Zheng Y, Walsh T, Gulsuner S, et al: Inherited breast cancer in Nigerian women. J Clin Oncol 36:2820-2825, 2018

24. Francis FZ, Wainstein T, De Leeneer K, et al: BRCA1, BRCA2 and PALB2 mutations and CHEK2 c.1100delC in different South African ethnic groups diagnosed with premenopausal and/or triple negative breast cancer. BMC Cancer 15:912, 2015

25. Mvila GL, Postema S, Marchal G, et al: From the set-up of a screening program of breast cancer patients to the identification of the first BRCA1/2 mutation in the DR Congo. BMC Public Health 14:1-10, 2014

26. Diez O, Pelegrín A, Gadea N, et al: Novel BRCA1 deleterious mutation (c.1949_1950delTA) in a woman of Senegalese descent with triple-negative early-onset breast cancer. Oncol Lett 2:1287-1289, 2011

27. Zoue AA, Staoui M, Bambara HA, et al: BRCA1 c.68_69delAG (exon2), c.181T>G (exon5), c.798_799delTT and 943ins10 (exon11) mutations in Burkina Faso. J Public Health Africa 9:11-15, 2018

28. Zhang J, Fackenthal JD, Zheng Y, et al: Recurrent BRCA1 and BRCA2 mutations in breast cancer patients of African ancestry. Breast Cancer Res Treat 134:889-894, 2012

29. Habyarimana T, Attaleb M, Mugenzi P, et al: CHEK2 germ line mutations are lacking among familial and sporadic breast cancer patients in Rwanda. Asian Pac J Cancer Prev 19:375-379, 2018

30. Fackenthal JD, Zhang J, Zhang B, et al: High prevalence of BRCA1 and BRCA2 mutations in unselected Nigerian breast cancer patients. Int J Cancer 131:1114-1123, 2012

No other potential conflicts of interest were reported.
31. van der Merwe N, Hamel N, Schneider S-RR, et al: A founder BRCA2 mutation in non-Afrikaner breast cancer patients of the Western Cape of South Africa. Clin Genet 81:179-184, 2012
32. Zhang B, Fackenthal JD, Niu Q, et al: Evidence for an ancient BRCA1 mutation in breast cancer patients of Yonguban ancestry. Fam Cancer 8:15-22, 2009
33. Gao Q, Adetamowo CA, Fackenthal J, et al: Protein truncating BRCA1 and BRCA2 mutations in African women with pre-menopausal breast cancer. Hum Genet 107:192-194, 2000
34. Diop JPD, Diallo RN, Bourdon-Huguenin V, et al: Novel BRCA2 pathogenic variant c.5219 T>G; p.(Leu1740Ter) in a consanguineous Senegalese family with hereditary breast cancer. BMC Med Genet 20:1-7, 2019
35. Okobia MN, Bunker CH, Garte SJ, et al: Leptin receptor Gin223Arg polymorphism and breast cancer risk in Nigerian women: A case control study. BMC Cancer 8:1-8, 2008
36. Okobia MN, Bunker CH, Garte SJ, et al: Cytochrome P450 1B1 Val432Leu polymorphism and breast cancer risk in Nigerian women: A case control study. Infect Agent Cancer 4:1-8, 2009
37. Kiendrebeogo IT, Zoure AA, Sorgho PA, et al: Glutathione S-transferase M1 (GSTM1) and T1 (GSTT1) variants and breast cancer risk in Burkina Faso. Biomol Concepts 10:175-183, 2019
38. Ahmed JH, Makonnen E, Fotoohi A, et al: Vitamin D status and association of VDR genetic polymorphism to risk of breast cancer in Ethiopia. Nutrients 11:1-14, 2019
39. Habaryrimana T, Bakri Y, Mugenzi P, et al: Association between glutathione peroxidase 1 codon 198 variant and the occurrence of breast cancer in Rwanda. Mol Genet Genomic Med 6:268-275, 2018
40. Habaryrimana T, Attaele M, Mugenzi P, et al: Association of p53 codon 72 polymorphism with breast cancer in a Rwandese population. Pathobiology 85:186-191, 2018
41. Shirts BH, Casadei S, Jacobson AL, et al: Improving performance of multigene panels for genomic analysis of cancer predisposition. Genet Med 18:974-981, 2016
42. Kuchenbaecker KB, Hopper JL, Barnes DR, et al: Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 317:2402-2416, 2017
43. Shahid T, Soroka J, Kong EH, et al: Structure and mechanism of action of the BRCA2 breast cancer tumor suppressor. Nat Struct Mol Biol 21:962-968, 2014
44. Deng C, Brodie S: Roles of BRCA1 and its interacting proteins. Bioessays 22:728-737, 2000
45. Tarsounas M, Sung P: The antitumorigenic roles of BRCA1–BARD1 in DNA repair and replication. Nat Rev Mol Cell Biol 21:284-299, 2020
46. Sirugo G, Williams SM, Tishkoff SA: The missing diversity in human genetic studies. Cell 177:26-31, 2019
47. Ahmed M, Rahman N: ATM and breast cancer susceptibility. Oncogene 25:5906-5911, 2006
48. Fang Y, Rhei SK, Huo D, et al: Characterizing genetic susceptibility to breast cancer in women of African ancestry. Cancer Epidemiol Biomarkers Prev 26:1016-1026, 2017
49. Chang BL, Spangler E, Gallagher S, et al: Validation of genome-wide prostate cancer associations in men of African descent. Cancer Epidemiol Biomarkers Prev 20:23-32, 2011
50. Shriner D, Adeyemo A, Berry NP, et al: Transferability and fine-mapping of genome-wide associated loci for adult height across human populations. PLoS One 4:e8398, 2009
51. Chen WC, Bye H, Matejic M, et al: Association of genetic variants in CHEK2 with oesophageal squamous cell carcinoma in the South African Black population. Carcinogenesis 40:513-520, 2019
52. Choudhury A, Aron S, Botigué LR, et al: High-depth African genomes inform human migration and health. Nature 586:741-748, 2020
53. Yadav S, Couch FJ: Germline genetic testing for breast cancer risk: The past, present, and future. Am Soc Clin Oncol Ed Book 39:61-74, 2019
54. Duncan LE, Ostacher M, Ballon J: How Genome-Wide Association Studies (GWAS) made traditional candidate gene studies obsolete. Neuropsychopharmacology 44:1518-1523, 2019
55. Pacella-Norman R, Urban MI, Stitas F, et al: Risk factors for oesophageal, lung, oral and laryngeal cancers in black South Africans. Br J Cancer 86:1751-1756, 2002
56. ERICA-SA. http://www.mrc.ac.za/intramural-research-units/evolving-risk-factors-cancers-african-populations-ERICA-sA
### 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 | Field: Title/Abstract                  |
| #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 (mai) OR (mauritania) OR (mozambique) OR (nigeria) 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 (south african) OR (sub saharan africa), Field: Title/Abstract | Field: Title/Abstract                  |

The entire search looked like this: (((((((((((((((((((((((((((((africaTitle/Abstract)) OR (africanTitle/Abstract)) OR (angolaTitle/Abstract)) OR (beninTitle/Abstract)) OR (botswanaTitle/Abstract)) OR (burkina fasoTitle/Abstract)) OR (burundiTitle/Abstract)) OR (cameroonTitle/Abstract)) OR (central african republicTitle/Abstract)) OR (chadTitle/Abstract)) OR (comorosTitle/Abstract)) OR (congoTitle/Abstract)) OR (democratic republic of congoTitle/Abstract)) OR (DRCTitle/Abstract)) OR (djiboutiTitle/Abstract)) OR (equatorial guineaTitle/Abstract)) OR (eritreaTitle/Abstract)) OR (ethiopiaTitle/Abstract)) OR (gabonTitle/Abstract)) OR (gambiaTitle/Abstract)) OR (ghanaTitle/Abstract)) OR (guineaTitle/Abstract)) OR (bissauTitle/Abstract)) OR (ivory coastTitle/Abstract)) OR (kenyaTitle/Abstract)) OR (lesothoTitle/Abstract)) OR (liberiaTitle/Abstract)) OR (malawiTitle/Abstract)) OR (maiTitle/Abstract)) OR (mauritaniaTitle/Abstract)) OR (mozambiqueTitle/Abstract)) OR (nigeriaTitle/Abstract)) OR (nigerTitle/Abstract)) OR (rwandaTitle/Abstract)) OR (senegalTitle/Abstract)) OR (sierra leoneTitle/Abstract)) OR (somaliaTitle/Abstract)) OR (south africanTitle/Abstract)) OR (sudanTitle/Abstract)) OR (swazilandTitle/Abstract)) OR (tanzaniaTitle/Abstract)) OR (togoTitle/Abstract)) OR (ugandaTitle/Abstract)) OR (zaireTitle/Abstract)) OR (zambiaTitle/Abstract)) OR (zimbabweTitle/Abstract)) OR (central africaTitle/Abstract)) OR (west africaTitle/Abstract)) OR (east africaTitle/Abstract)) OR (south africanTitle/Abstract)) OR (sub saharan africaTitle/Abstract)) AND (((((((((((((breast cancerTitle/Abstract)) AND (variantTitle/Abstract)) AND (warfarinTitle/Abstract)) AND (variantTitle/Abstract)) AND (breast cancerTitle/Abstract)) AND (mutationTitle/Abstract)) AND (breast cancerTitle/Abstract)) AND (mutationsTitle/Abstract)) AND (breast cancerTitle/Abstract)) AND (germlineTitle/Abstract)) OR (breast cancerTitle/Abstract)) AND (hereditaryTitle/Abstract)) OR (breast cancerTitle/Abstract)) AND (inheritedTitle/Abstract)) OR (breast cancerTitle/Abstract)) AND (geneticTitle/Abstract)) OR (breast cancerTitle/Abstract)) AND (geneticsTitle/Abstract)) OR (breast cancerTitle/Abstract)) AND (GWASTitle/Abstract)) OR (breast cancerTitle/Abstract)) AND (genome wideTitle/Abstract)) OR (breast cancerTitle/Abstract)) AND (associationTitle/Abstract))

Abbreviation: GWAS, genome-wide association study.