Minireview

Breast cancer in sub-Saharan Africa: The current state and uncertain future

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Impact statement

Breast cancer is a major global health challenge and more so in sub-Saharan Africa. However, the quality and quantity of data generated in extant Africans, which is the most genetically diverse population, hinders estimation of the actual disease burden. This review collates and presents the most current available information on breast cancer burden in sub-Saharan Africa. It provides evidence on the paucity of epidemiological and genetic data from across the subregion. It further strengthens the need for population-specific research, most importantly in sub-Saharan Africa, through coherent depiction of evidence on the inherently diverse genetic variations, risk factors, and breast cancer presentation in the African population.

Abstract

Breast cancer is the commonest cause of global cancer-related deaths in women and a public health burden in sub-Saharan Africa (SSA). Although the disease incidence in SSA seems lower, mortality rates are disproportionately high in comparison to high-income countries. The global disease burden is growing, with SSA reporting the majority of cases; however, the dearth of information results in insufficient data which is barely representative of the actual disease burden in this population. Future incidence predictions assign the subregion with a majority of the cases and associated deaths. Breast cancer presents with racial and ethnic variations, and available evidence suggests geographical diversity and persistent risk factors that have barely been explored in SSA. Breast cancer is a complex genetic disease, but the genetic risk factors in the extant African population, which is the most genetically diverse population, is scant and of low quality. This review focuses on the burden, prevalence, detection, treatment, survival, biology, as well as risk factors, and reinforces the need for breast cancer-associated risk factor investigation and population-specific studies in SSA.

Keywords: Breast cancer, burden, sub-Saharan Africa, risk factors, population-specific research, genetic diversity

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Introduction

Breast cancer is a global menace that afflicts mostly women and a public health burden in sub-Saharan Africa (SSA)[1] (Figure 1). The quality and quantity of data from low- and middle-income countries (LIC and MIC) on the Global Cancer Observatory (GLOBOCAN) project resource used widely in estimating global cancer mortality and incidence globally are generally low.[2] Additionally, deficits in statistics on prevalence are particularly apparent in SSA.[3] However, breast cancer mortality and incidence rates in SSA are on the rise in comparison to developed countries.[4] By 2050, the prevalence is projected to double in SSA.[5] Available data on the disease is scant and, where available, are mostly of epidemiological or clinical nature.[3] Notably, the majority of countries in SSA lack cancer registries; hence, the true disease burden remains elusive. Only 20 (43.4%) of the 46 World Health Organization (WHO) member states in SSA have active cancer registries spanning a wide range of completeness and coverage[6] (Table 1). They are largely limited to specific sub-national populations, poorly funded, and probably not population-specific, hence do not meet active data collation standards. Therefore, breast cancer will most likely be a neglected healthcare issue in SSA, as governments in these countries focus on other healthcare priorities, particularly communicable diseases. SSA countries generally allocate insufficient GDP expenditure to health care, as such limited health infrastructure, staffing, and low sensitization rates contribute to the dearth of reliable data.[3] More so, 27 out of the world's 28 poorest countries are in SSA, making up approximately 50% of SSA.[7] Reports indicate an increase in Gross National Income (GNI) based on purchasing-power-parity per capita of SSA countries, which somehow indicates

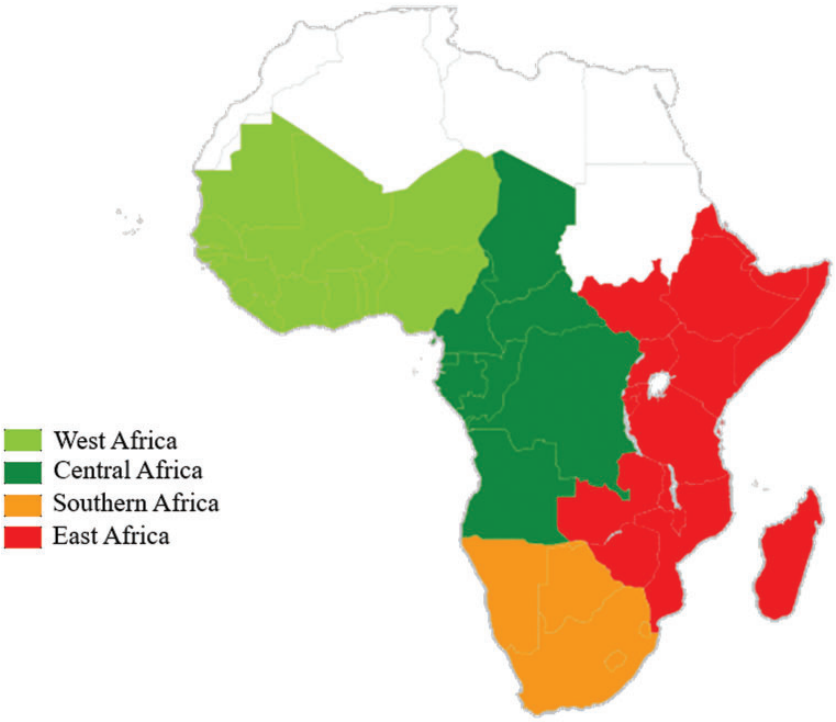

Figure 1. Sub-Saharan Africa. **West Africa**: Mauritania, Senegal, Gambia Guinea-Bissau, Guinea, Sierra Leone, Liberia, Côte d'Ivoire, Ghana, Togo, Benin, Burkina Faso, Nigeria, Niger, Mali, and Cabo Verde; **Central Africa**: Cameroon, Central African Republic, Chad, Democratic Republic of the Congo, Equatorial Guinea, Gabon, and Sao Tomé and Principe; **Southern Africa**: South Africa, Lesotho, Namibia, Swaziland, and Botswana; **East Africa**: Tanzania, Kenya, Uganda, Rwanda, Burundi, South Sudan, Mozambique, Madagascar, Malawi, Zambia. Zimbabwe, Mauritius, Comoros, Djibouti, Ethiopia, Eritrea, Seychelles, Somaliland, Somalia, and Réunion. The figure was drawn using geographic heatmap in excel. (A color version of this figure is available in the online journal.)

poverty alleviation and elevation to middle-income status. Nonetheless, SSA is estimated to report 9 out of every 10 individuals living in extreme poverty by 2030.[8] This may further support the projected future breast cancer incidence and associated mortalities. Breast cancer control in SSA requires a concerted approach and should include population-based studies, early detection, prevention, and effective palliative care and treatment[3] (recommendations summarized in Table 2).

Burden and diagnosis

Breast cancer is the global leader of cancer-related deaths in women and impacts approximately 2.1 million women yearly.[9] About 627,000 breast cancer-related deaths were recorded in 2018, with the majority from SSA,[9] representing about 15% of all cancer-related deaths. According to the 2020 GLOBOCAN data, 186,598 breast cancer cases were reported in Africa with 85,787 related deaths. While the disease burden seems relatively lower in SSA, survival is staggeringly low, with disproportionately high mortality rates (Figure 2).[10] The global breast cancer incidence has increased by 20% since 2008, making it the most commonly diagnosed cancer in women in Africa (Figure 3).[11] The incidence increased from 1.2 to 2.4 million cases between 2005 and 2015, with population growth and aging contributing 13 and 15%, respectively.[12]

In 2012, 56.8% of the 1.7 million women diagnosed with breast cancer were from low-income countries, and the majority of the 522,000 related deaths were recorded in SSA. Against this backdrop, over 19.3 and 21.7 million women are estimated to suffer from breast cancer by 2025 and 2030, respectively, again with the majority from SSA.[3,12] A systemic review and meta-analysis reported an incidence of 22.4 per 100,000 women in SSA, which is comparable to North Africa, with 24.0 per 100,000 women.[13] Incidence rates have increased considerably between 2000 and 2015 across both registries.[13]

Indications of marked geographic diversity and persistent local risk factors in populations at different economic transition phases could give more insight into the geographic variability of cancer incidence and mortality. The disproportionate breast cancer-associated mortality in SSA has been partly attributed to epidemiological transitioning hinged on an aging population, improved infectious disease control, and increased urbanization- and development-associated risk factors for non-communicable diseases.[14] The highest breast cancer prevalence rates in 2017 were reported in West, East, and North Africa.[3] Central Africa recorded an incidence to mortality ratio of 0.55 in comparison to 0.16 in the US and attributed primarily to ignorance of the disease manifestations and other related challenges.[4] A related report updating breast cancer incidence in Africa indicated an increase throughout Africa and projected to double by 2050.[4] The current cumulative breast cancer incidence per 100,000 women in Southern (46.2), Western (37.3), Eastern (29.9), and Central Africa (27.9) has associated mortality rates estimated at 15.6, 17.8, 15.4, and 15.8, respectively.[15] Contrary to the incidence trend, Southern Africa, which had the

Table 1. List of cancer registries in SSA and the population characteristics.

Countries (no. of registries)	Name of registries	2020 population	Yearly change (%)	Median age
Benin (1)	Cotonou Cancer Registry	12,123,200	2.73	19
Botswana (1)	Botswana National Cancer Registry	2,351,627	2.08	24
Congo (1)	Registre des cancers de Brazzaville	89,561,403	2.56	19
Cote D'Ivoire (1)	Registre des Cancers d'Abidjan	26,114,963	2.57	19
Ethiopia (1)	Addis Ababa City Cancer Registry	114,963,588	2.57	19
Eswatini (1)	Eswatini National Cancer Registry	1,160,164	1.05	21
Gambia (1)	Gambia Cancer Registry	2,416,668	2.94	18
Ghana (1)	Kumasi Cancer Registry	31,072,940	2.15	22
Guinea (1)	Registre de Cancer de Guinée	13,137,795	2.83	18
Kenya (2)	Eldoret Cancer Registry Nairobi Cancer Registry	53,771,296	2.28	20
Malawi (1)	Malawi Cancer Registry	19,129,952	2.69	18
Mali (1)	Registre des cancers du Mali	20,250,833	3.02	16
Mauritius (1)	Mauritius National Cancer Registry	1,271,768	0.17	37
Mozambique (2)	Registro de Cancro de Beira Maputo Cancer Registry	31,255,435	2.93	18
Namibia (1)	Namibian Cancer Registry	2,540,905	1.86	22
Niger (1)	Registre des Cancers du Niger	24,206,644	3.84	15
Nigeria (5)	Abuja Cancer Registry Calabar Cancer registry Ekiti Cancer Registry Ibadan Cancer Registry Nigerian National system of Cancer Registries	206,139,589	2.58	18
Reunion (1)	Registre des cancers de la Réunion	895,312	0.72	36
Rwanda (1)	Rwanda Cancer Registry	12,952,218	2.58	20
Seychelles (1)	Seychelles National Cancer registry	98,347	0.62	34
South Africa (3)	South African Children's Cancer study Group (SACCSG) South Africa Eastern Cape Province Cancer Registry National Cancer Registry of South Africa (NCR-SA)	59,308,690	1.28	28
Tanzania (3)	Dodoma Cancer Registry Kilimanjaro Cancer Registry (KCMC) Mwanza Cancer Registry	59,734,218	2.98	18
Uganda (2)	Gulu Cancer Registry Kampala Cancer Registry	45,741,007	3.32	17
Zambia (1)	Zambia National Cancer Registry	18,383,955	2.93	18
Zimbabwe (1)	Zimbabwe National Cancer Registry (Harare & Bulawayo	14,862,924	1.48	19

Table 2. Recommendations to address breast cancer research and care challenges in SSA.

Outstanding challenges	Recommendations
Misrepresentation of the actual disease burden.	• In-depth epidemiological studies to define the disease landscape and risk assessment. Generating and sustaining regional cancer registries of sufficient coverage and completeness, with sustained commitment from respective governments.
Underrepresented SSA ancestry individuals in clinically important data repositories.	• Building local capacity in genomic research, data generation, and indexing of the most genetically diverse population to enable imputation into global data repositories. Including more SSA participants in worldwide genomic research projects aimed at classifying pathogenic and genetic risk factors. Decentralizing genomic initiatives like the African Genomic Medicine training Initiative, into distinct areas with core mandates such as working exclusively on breast cancer.
Unvalidated breast cancer biomarkers for SSA populations.	• Population-specific studies focused on demystifying and defining the population stratifications via subregion-specific genomic profiling. Subregion-specific transcriptome profiling to establish and understand the subtle ethnic contributions to the disease biology and presentations. Generation of population-specific research model systems (e.g. cell lines) for the validation of candidate risk factors. • Fostering population-specific pharmacogenomic studies.
Unwilling participation in research.	Focus on training in research communications to enhance public engagement, education and awareness creation.

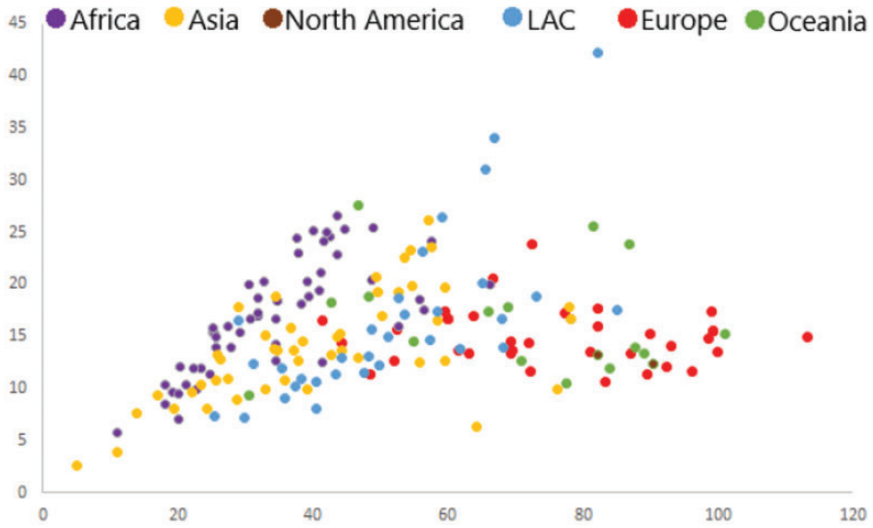

Figure 2. The 2018 global breast cancer Mortality versus Incidence in women. Incidence in the African countries (purple dots) seems low; however, mortalities are relatively high. Europe reports the highest incidence and LAC, the highest mortality. The Republic of Gambia recorded the lowest incidence and mortality (6.9, 4) and Mauritius, the highest (69.6, 21.8) in Africa. This graph was generated using excel and data from the GLOBOCAN (http://gco.iarc.fr/) interactive observatory, and includes data from all the 54 African countries. ASR (W): age-standardized rate (World); LAC (Latin America and the Caribbean). (A color version of this figure is available in the online journal.)

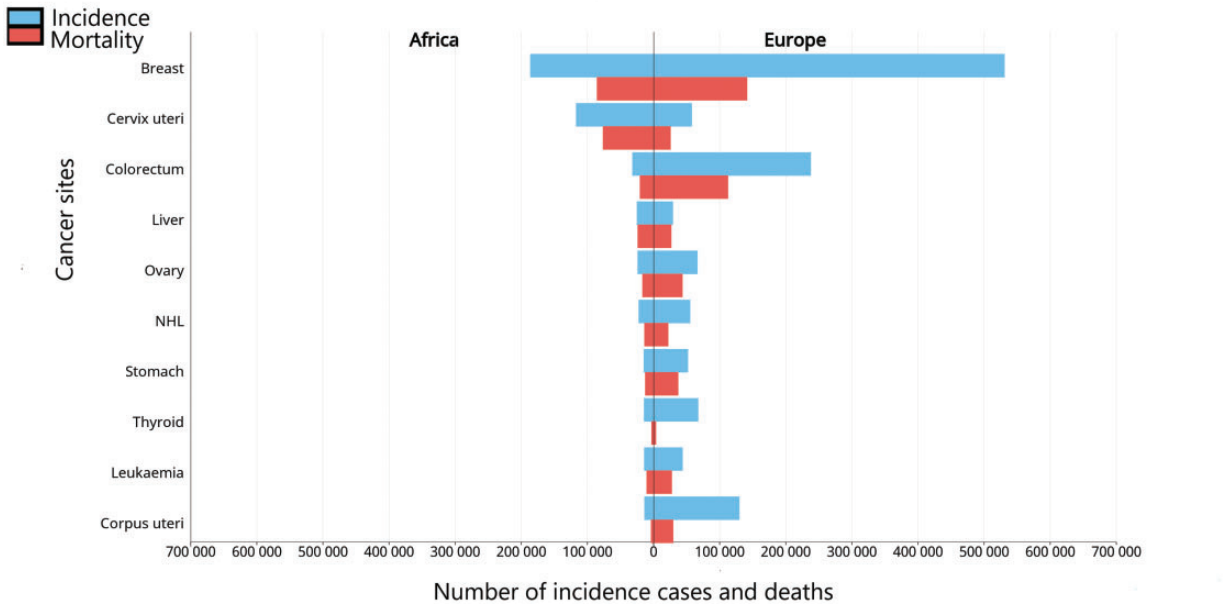

Figure 3. The estimated number of new cancer cases in females in 2020. Breast cancer was the most diagnosed cancer and cause of cancer-related death in females in 2020. Africa reported 531,086 (74.3/100,000) new cases. Africa recorded a mortality of 85,787 (19.4/100,000), compared to Europe with 141,765 (14.8/100,000). In comparison to Europe, the associated deaths recorded in Africa seems disproportionate to the incidence reported. This data was generated using the GLOBOCAN 2020 data and interactive observatory. NHL: non-hodgkin lymphoma. (A color version of this figure is available in the online journal.)

highest incidence, did not report the highest mortality. This may largely be due to underreported data and challenges in implementing robust screening programs.[4] It could also be a reflection of better healthcare facilities and treatment services in Southern Africa.

The cornerstone of breast cancer control is early detection.[16] Early diagnostic strategies aim to reduce barriers to care and/or improve access to effective diagnostic services and provide timely access to cancer treatment.

Detection

Certain cultural beliefs and breast cancer treatment-related stigma hinder health-seeking and early diagnosis in SSA.[17] In some regions, the disease has been ascribed to supernatural forces, thereby diminishing a sense of personal control over the outcomes. The idea of "beauty" in other countries involves a "whole" woman; hence, needing a mastectomy may evoke a sense of worthlessness, which impedes early health-seeking.[18] Ignorance of the disease, unavailability of tests, and inaccessibility of treatment and detection

facilities bedevil screening and early detection in SSA.[19] Guidelines for breast cancer screening differ mostly depending on age at which screening begins (45 vs. 50 years) and intervals (1 vs. 2 years) between screens. Prognosing women with breast cancer in SSA is also impaired by shortage of trained personnel, noncompliance, and poor drug supplies.[19] The majority of late detections has been recorded in South Africa, Cameroon, the Central African Republic, Malawi, and Tanzania.[20] This does not suggest early detection in other countries, but a lack of comprehensive data to make substantive conclusions. The younger age at diagnosis in SSA has been widely attributed to the younger population age (Table 1) structure in the region, but this is not conclusive.[10]

Factors affecting treatment and survival

Treatment

Breast cancer treatments generally depend on the disease type, and stage, and current options include surgery, chemotherapy, or hormonal, biological, and radiation therapies.[21] In SSA, options for advanced stages are limited and coupled with a scarcity of chemotherapy and radiotherapy facilities, most women undergo mastectomy.[18] About two-thirds of SSA countries lack radiotherapy facilities,[22] while those available meet only approximately 18% of the projected need.[23] Furthermore, tumor marker histological classification and identification facilities are limited in SSA, as are hormonal therapies and other targeted treatments.[23] Patients with human epidermal growth factor receptor 2-positive ($HER2^+$) breast cancer exhibit poor survival rates, especially in the absence of targeted therapies, which is the case in most SSA countries. Breast cancer management is often deterred by treatment- and travel-related costs, particularly for those not living close to the medical centres.[18] Most women resort to other alternatives such as the use of herbs, visiting prayer camps and native doctors, which impede treatment and consequently translate to poor prognoses.[24] Another pivotal breast cancer treatment challenge in SSA is the scarcity of trained health professionals in cancer care and diagnosis. Additionally, medical oncologists, well-equipped and reliable pathology laboratories, and pathologists are rare, especially in the poorest countries.[25] As seen in Figure 4, the majority of SSA countries are poor.[26]

Survival

The five-year breast cancer survival rate in SSA is less than 40% compared to 86% in the USA.[20] The low survival rate borders on factors including low awareness, late detection and treatment, poor prognosis, unavailability of treatment facilities and advanced therapies, high cost, and lack of prevalence documentation. Breast examination and early detection practices are low and contribute to late-stage diagnoses.[1] There is a notable delay between symptom onset and seeking healthcare in SSA. Most countries in SSA have not implemented and sustained screening programs owing to logistical, sociocultural, and financial constraints.[1] Breast cancer molecular subtypes also affect the survival rates. Breast cancer is population-specific, and the different prevalence rates of subtypes suggest heterogeneity in oncogenesis and partly explain the differing survival outcomes observed among ethnicities.[27] Survival outcomes in HICs have been improved by targeted therapies, which are hardly accessible to women in poor countries.[27] Further, survival has been enhanced by advances in population-specific genetic research, which has led to the development of molecular diagnostics for risk assessment. This has redefined the quality of treatments available in HICs. This is lacking in the African population, and a key determinant of the survival rates observed.

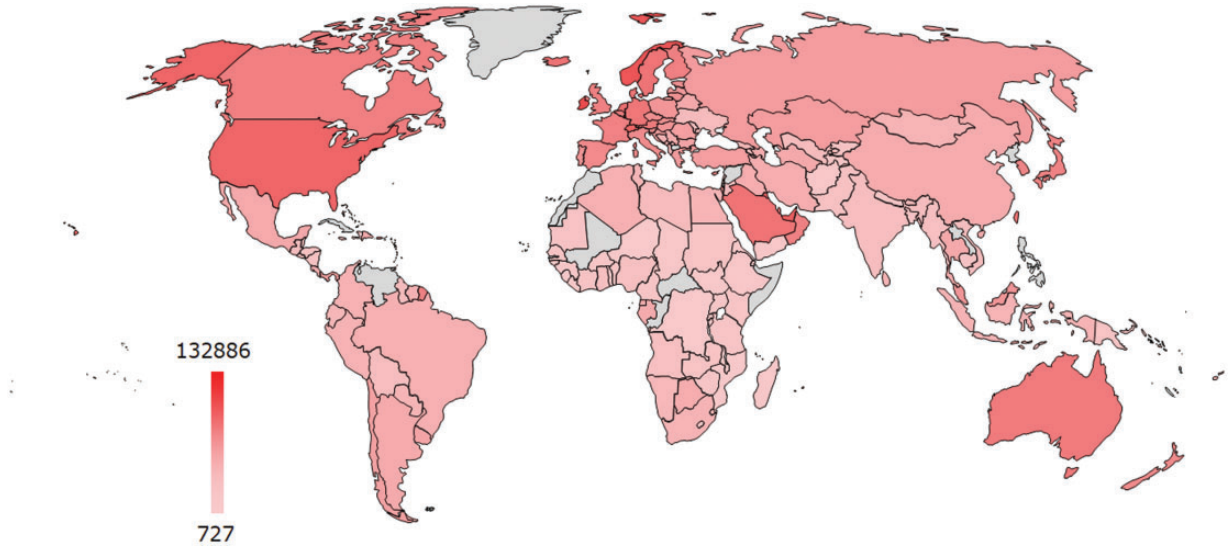

Figure 4. The 2019 World Bank global landscape of poor countries as per GNI-PPP ($). The African countries ranged from $727 (Burundi) to $19,057 (Gabon), however, out of the four low-income countries, three (Burundi, Central Africa Republic and Democratic republic of Congo) are in SSA. The heatmap was generated using power-user in excel and countries investigated by the African Strategies for Advancing Pathology Group Members.[26] Countries in grey did not have data at the time of generation. USD (US dollar); GNI-PPP (Gross National Income based on purchasing-power-parity). (A color version of this figure is available in the online journal.)

Clinical features and molecular subtypes in SSA

In SSA, about 80% of breast cancers are diagnosed at late stages (stages III or IV) compared with 15% in HICs.[22] The high late-stage disease presentation rate in SSA has been attributed to low awareness and detection in patients and the absence of diagnosis facilities and limited early detection programs.[28] Reports show that stages III and IV constituted 77% of breast cancer patients at the Mulago Hospital in Uganda;[29] 77% at the Butaro Cancer Centre of Excellence in Rwanda;[30] 78% at the Angolan Institute of Cancer Control;[31] and 87.7% at the Komfo Anokye Teaching Hospital in Ghana.[32] This is compounded by the breast cancer histological subtypes. A prevalence study on the molecular subtypes reported 34% triple-negative breast cancer (TNBC), 38% Luminal A, 22% $HER2^+$, and 5% Luminal B in Uganda.[27] High-grade (grade 3) tumors made up 68% and late stage, 75% of the presentations; invasive ductal carcinoma was the predominant histological type recorded in the same population. TNBC is aggressive, recurs and metastasizes more often than the other subtypes,[33] and disproportionately affects women of African descent, with worse clinical outcomes compared to women of European ancestry.[34,35] Studies have associated a high frequency of TNBC, particularly in women of West African ancestry.[36] An estimated TNBC incidence ranging between 20.8 and 46.4% was reported in African-American women in the United States.[37] This seems consistent with the 2–3-fold TNBC over-representation (34%) reported in SSA; both rates are relatively high in comparison with Caucasians, where prevalence is 12–17% or less, with TNBC and $HER2^+$ tumors together constituting about 60% of the molecular subtypes and the majority of women aged 50 years and younger.[33,38] The estrogen receptor-negative (ER^-) subtypes, including TNBC and some $HER2^+$, have been associated with higher proliferative capacity and grade.[27] $HER2^+$ and TNBC subtypes have the most unfavorable treatment outcomes. Mediators of the relatively high $HER2^+$ and TNBC proportions are not fully understood. Genetic differences, including unidentified founder mutations in breast cancer, have been suggested to partly account for the disparities.[39,40] Exploring the mutation patterns and other genetic risk factors of breast cancer is an imperative.[41]

Women with breast cancer in SSA are reportedly younger with peak incidence a decade earlier (50.2 years) in comparison with African Americans and White Americans with peak incidences of 60.8 and 62.4 years, respectively.[10,42] Current reports in SSA show an increasing number of diagnosed cases between the ages of 35 and 49 years, with most presenting with advanced late-stage disease.[28] This was corroborated by a systematic review of population- and hospital-based breast cancer registries,[13] which revealed a mean age range between 30.6 and 60.8 years, with over 33 and 81% of the African population aged 30–49 and 30–59 years, respectively. Although inconclusive, these data suggest a high breast cancer incidence in the younger age groups in Africa. There are limited treatment options with advanced disease, which translates into poor prognosis.

Breast cancer risk factors and genetics

Risk factors

Studies show that most breast cancer risk factors in SSA are similar to those in HIC (age, race, genetic mutation, reproductive history, familial susceptibility, personal breast cancer history or any other non-breast cancer, lifestyle choices, etc.).[21,22] Data on risk factors unique to SSA, including environmental exposures and infections, are limited and not conclusive.[23]

Pathogens like viruses, which have been implicated in about a fifth of all cancers, may be major risk factors in breast cancer in SSA.[43–45] The human papillomavirus (HPV) and human immunodeficiency virus (HIV) have been associated with breast cancer in SSA.[43] Reports indicate that chronic infectious diseases, specifically lifelong exposure to malaria, lead to loss of cell-mediated immunity and promote viral carcinogenesis, which has been observed in HPV-associated cervical cancer.[46] SSA is a malaria-endemic region,[47] and the association between insecticide exposure and hormone receptor-positive breast cancers is still debated.[1]

Contraceptive use is another implicated breast cancer risk factor. The Collaborative group in hormonal factors in breast cancer analyzed data from 54 epidemiological studies using 53,297 breast cancer and 100,239 non-cancer patients and reported a 24% increase in relative risk in women currently using contraceptives and 7% in women who have ever used, compared to women who have never used them.[48] A population-based cross-sectional study in SSA reported an average contraceptive use of 17%, which is relatively low; however, the prevalence varied substantially across the individual countries.[49] This conclusion was drawn from data on contraceptive use from Demographic and Health Surveys (DHS) from 17 out of the 48 SSA countries. All SSA regions were not adequately covered; thus, the actual contraceptive use may probably be underreported. The relationship between contraceptive use and breast cancer cases reported has been observational; thus, inferences indicating their use as a risk factor are not enough to account for the incidence of breast cancer. More so, other factors, including duration of use and age of start of use, had no significant effect on the general risk, once recency of use has been established. Interestingly, no pronounced variation in recency of use has been reported between women of different backgrounds (ethnicity and race), reproductive histories, and breast cancer risks.[48]

Breast-associated conditions including lobular carcinoma *in situ* and atypical ductal hyperplasia have been correlated with an increased risk of breast cancer.[50] Diabetes mellitus has been proposed to increase the risk of breast cancer.[50] Reproductive factors including early menarche and menopausal status have been acclaimed breast cancer risk factors; however, no association was found between these risk factors and breast cancer in Senegalese women.[51] Some breast cancers have been attributed to post-menopausal body mass index (Figure 5) globally. Possibly, many more risk factors are unexplored; hence there is an urgent need to exhaustively investigate breast

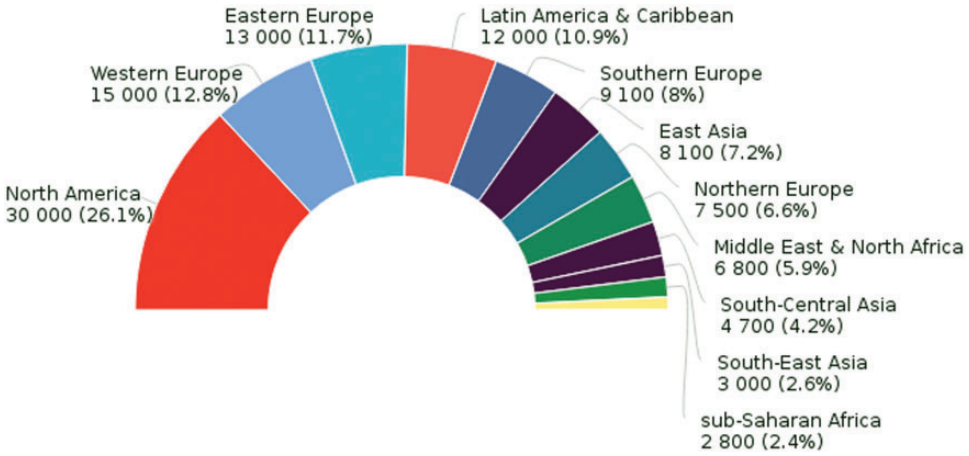

Figure 5. The predicted proportion of the 2012 global postmenopausal breast cancer cases among women attributable to body mass index (BMI). This prediction hinges on the assumption that the average population-level BMI remained constant since 1982. Per this record, SSA recorded the lowest attributable cases, probably due to underreporting. Data was obtained from GLOBOCAN 2012, Graph production: IARC World Health Organization. (A color version of this figure is available in the online journal.)

cancer-associated risk factors in SSA. More so, data on risk factors in SSA are evidently old, mostly from 2012, and according to data available on GLOBOCAN, very few countries have made progress in investigating them.

Family history or susceptibility is an important breast cancer-predisposing factor.[52] Early age at diagnosis and a positive breast cancer history may be suggestive of familial predispositions, which have not been thoroughly investigated in the SSA population.[51] Women with a familial breast cancer history with one or two first-degree premenopausal breast cancer relatives are at a 3.3-fold and 3.6-fold greater risk of developing breast cancer, respectively, compared to women without a family history.[53] Approximately 13–19% of diagnosed breast cancer patients had an affected first-degree relative.[54] This includes individuals carrying breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) gene mutations. Other significant driver mutations include those in tumor protein P53 (*TP53*), phosphatase and tensin homolog (*PTEN)*, and serine/threonine kinase 11 (*STK11)*, which have also been implicated in Li-Fraumeni syndrome, Cowden syndrome, and Peutz–Jeghers syndrome, respectively.[55]

Genetics

Breast cancer is heterogeneous and complex, with ethnic and racial variations in both histology and tumor behavior.[56] While 10–15% of cases have a familial predisposition, approximately 90% are sporadic and associated with somatic mutations acquired during an individual's lifetime.[55,57] Genetic data in SSA are scant,[58] and efforts to establish the genetic diversity in SSA peaked with the African Genome Variation Project involving 1481 individuals from the region.[59] However, data on the genetic profile of breast cancer is still lacking as not enough people are captured by such studies to represent the regional and subregional diversities.

Extant African populations have significantly higher genetic diversity in comparison to other populations, and this reflects in over 2000 distinct languages and ethnic groups.[60] Adaptations to climate-change, strong pathogen burden, and diet have contributed critically to shaping genomic diversity in the African population.[61] Additionally, the intrinsic "within continent" variations owing to population structure, isolation, and back migration of the Eurasian populations into Africa have contributed significantly to the genetic diversity.[62,63] Comprehensive genetic characterization of these migrations on the extant populations threw some light on the strong diversities between some geographically neighboring populations.[61]

Owing to the genetic diversity, African populations are expected to have the highest levels of sequence diversity.[60,64] Approximately 25% of hereditary cases are mediated by mutations in any of the few identified highly penetrant, but rare genes (*PTEN*, *BRCA1*, *TP53*, *BRCA2*, *CDH1*, and *STK11*) and these confer an 80% lifetime risk of breast cancer.[65] Causality has been established between early-onset breast cancer and germline mutations in *BRCA1* and *BRCA2*[66,67] in African-American women,[66–68] but the contribution of these genes to the disease in extant African women remains uncertain.[69–71]

Diverse *BRCA1* and *BRCA2* mutation and sequence variation spectra unique to Africans have been reported.[72] A global *BRCA2* sequence diversity study detected 42% of the sequence variants exclusively in Africa, although chromosomes of African origin constituted only 13% of the 332 chromosomes screened.[72] Additionally, 2–3% of breast cancer cases are attributed to mutations in rare, moderately penetrant genes including *BRIP1*, *CHEK2*, *PALB2*, and *ATM*.[65] Corroborating this is the observation of *PALB* deleterious mutations accounting for up to 2% of early-onset breast cancer cases in white South Africans.[73] The known familial breast cancer genes account for only about 20% of reported cases,[74] implying that most familial susceptibility genes are unknown. Genetic studies have indicated considerable linkage disequilibrium structure differences and extensive population substructure between African and Caucasian populations.[75] The African-American population is the closest population of reference

for the extant African population; however, they are an admixed population estimated to be approximately 80% West African and 20% European.[76] Inferences from this population are not entirely representative of the situation in the extant African population. Africans possess several genetic adaptations, which have evolved in response to exposure to infectious diseases, diverse climates, and diets. These may have influenced breast cancer manifestation in the African population.[77]

Breast cancer research

Breast cancer studies encompass genetic and epidemiological research. Well-powered research probing the genetic breast cancer predispositions includes genome-wide association studies (GWAS) and whole genome, exome, and transcriptome profiling studies. These have been particularly instrumental in defining the scope of clinical breast cancer management, from screening, through diagnosis, to treatment in HICs.[78] Such progress has fostered development of molecular diagnostic tools, employing genetics, and expression profiles of the American, European, and Asian populations in breast cancer risk assessment. Despite the knowledge on the unique genetic variations in ethnic groups and races, about 96% of subjects included in GWAS are of European ancestry.[79] The paucity of such research in Africa impairs full understanding of the disease presentation and progression.[78] Initiatives, including the Human Heredity and Health (H3) Network, are facilitating genetic research in Africa; however, not much has been done on breast cancer. Breast cancer research also involves the use of several models, including paraffin-embedded samples, xenografts, primary tumors, and human and animal cell lines.[80,81] Primary- or metastatic breast cancer-derived *in vitro* permanent cell lines are important experimental systems for investigating the biological and genetic alterations associated with cancer initiation and progression.[82] Cell lines are unlimited, self-replicating, and facilitate comparative studies in breast cancer research.[83] They are exceptional systems for studying cellular pathways and investigating genes critically involved in tumorigenesis.[84,85] However, genetic background of cell lines can significantly affect experimental results.[86] The most commonly used human breast cancer cell lines are of Caucasian origin.[87] A high degree of heterogeneity in terms of subtypes, disease progression, etc., has been observed in different ethnic groups.[86] Furthermore, studies show that expression levels of certain genes peculiar to specific populations differ between cell lines of different ethnicities, and these may cause significant discrepancies in the results obtained.[88] The indigeneity, admixture, and ethnicity of the few existing black cell lines are still debated,[89] and their use in indigenous African populations is questionable.[90] These cell lines may be used in experimental studies in the African population, irrespective of their ethnic origin; however, they are more likely to give results that could vary vastly from the natural populations. To optimize results in breast cancer studies performed in SSA, it is important to use cell lines that represent this divergent population. Nevertheless, a detailed characterization of the existing black cell lines is fundamental to their application in African populations. This will be an eye-opener on the need to develop purely African breast cell lines that will largely serve the African population. Establishing real population-specific case systems will help to determine cell lines that will best model the diversity.

Conclusions

The extant African population is the most diverse population in terms of genetics and environmental exposures. Future projections indicate that breast cancer will undoubtedly burden economies globally, and the SSA region will be dealt with the greatest blow. Considering the dearth of knowledge and data in SSA, understanding breast cancer presentation in this population requires an in-depth evaluation of the risk factors, including environmental and genetic, with a conscious attempt at a population-specific data generation and risk assessment. This will throw more light on the landscape of breast cancer, including its development, presentation, and outcomes, thereby allowing for the development of novel therapies. In furtherance, the high level of unshared genetic variation among the populations reinforces the need for large-scale genetic profiling across Africa.

AUTHORS' CONTRIBUTIONS

All the authors have read and approved the final manuscript. CAA drafted the manuscript, and LP and GAA critically reviewed the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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