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Review and Meta-analysis

Demographic Pattern, Tumor Size and Stage of Breast Cancer in Africa: A Meta-analysis

Agodirin Olayide	Department of Surgery, University of Ilorin and University of Ilorin Teaching Hospital, Ilorin, Kwara state. Nigeria.
Aremu Isiaka	Department of Surgery, University of Ilorin Teaching Hospital
Rahman Ganiyu	Department of Surgery, University of Cape Coast and Cape Coast Teaching Hospital, Cape Coast. Ghana
Olatoke Samuel	Department of Surgery, University of Ilorin; Nigeria
Akande Halimat	Department of Radiology, University of Ilorin. Nigeria
Olaogun Julius	Department of Surgery, Ekiti State University. Nigeria
Romanoff Anyan	Breast Surgery, Dubin Breast Center, Icahn School of Medicine at the Mount Sinai Hospital New York, NY, USA

Purpose: Understanding the epidemiology of breast cancer (BC) in Africa, as well as regional variation is essential for planning future intervention. Our objective was to describe summary estimates of socio-demographic and clinical characteristics of BC in Africa, thus providing researchers and policymakers baseline data for planning diagnostic and treatment programs to improve BC outcomes in the future.
Method: We screened African publications on BC between 2010 and 2019 in PubMed, AJOL, Google, ScienceDirect, and ResearchGate to estimate the distribution of socio-demographic and clinical tumor characteristics. The meta-analysis used the random effect model.
Result: Eighty articles were eligible, including 33,199 total patients. Overall, 58% of patients were <50 years old. In East Africa, 38% (95% CI 31-45) were diagnosed before 40 years. Conversely, in Southern Africa, 37% were diagnosed after 60 years, with Caucasian-like age distribution. The overall prevalence of male BC was high (3%), with East Africa having the highest prevalence (5% (95% CI 5.0-6.0)). Only 2% (95% CI 1-2) of patients were diagnosed with carcinoma-in-situ. Invasive tumors were 7% stage I, 26% stage II, 50% stage III, and 17% stage IV. Seventy per-cent (95% CI 60-80) had clinical nodal involvement. The smallest tumors were in North Africa. The largest and most advanced tumors were in West Africa. Trend analysis showed decreasing age, an increasing population of unmarried BC patients, a relatively high proportion of uneducated BC patients, and a stable proportion of late-stage disease in the last decade.
Conclusion: Regional variation in the presentation of BC throughout Africa necessitates region/country-specific targets for improving BC control.

Introduction

According to 2018 global cancer statistics [1], breast cancer (BC) is one of the two most common adult cancers, accounting for nearly 25% of cancers in women worldwide. Africa has disproportionately high age-standardized mortality due to BC [2]. The World Health Organization (WHO) and other experts in the field [3] recommend early diagnosis combined with timely and effective treatment as cost-effective measures for improving BC outcomes in Africa. Understanding the epidemiology of BC in Africa, as well as regional variation, is essential for planning future interventions.

Prior researches have aggregated data to better understand BC in Africa, but there is a notable gap in the existing literature. Previous meta-analyses described BC incidence, stage at presentation [4], and biological characteristics in sub-Saharan Africa (SSA). However, none of the existing reviews

adequately summarize patient demographics, clinical pattern, or regional variation of BC. These factors are of significant prognostic value and are critical determinants of resource allocation that can allow for tailored screening, early detection, diagnostic and treatment programs to be adapted for specific local or regional contexts.

This meta-analysis aims to describe summary estimates of patient demographics, tumor size, and BC stage in Africa. A secondary aim is to compare the clinical pattern between African regions and countries. Our ultimate goal is to provide researchers and policymakers a baseline and region-specific targets for planning future interventions.

Method

This research aligned with the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations [5]. The needs assessment and preliminary literature review [in PubMed, African Journal Online (AJOL), Cochrane library, and Prospero reference ID CRD42020153269] confirmed no similar meta-analysis was ongoing or previously conducted. The full literature search was performed in PubMed.gov between November 10, 2019, and December 31, 2019, using an iterative process with the search term “breast cancer AND country name” for each African country and only as “breast cancer” in AJOL. Hand-search was done on Google, Google Scholar, ScienceDirect, PubMed central, ResearchGate, and Academia. Snow-balling search was in the reference list of original articles and already published review articles. We sent an exclusive request email to authors for full articles not available online or to clarify data.

Article screening and data extraction

Full-text screening used predetermined Population, Intervention, Control, Outcome, Time, Study design (PICOTS) criteria (Table 1).

Participants/Population	We included freely available publications of studies conducted in Africa and reporting on the total female breast cancer patients or both sexes or a representative sample. We excluded articles reporting on breast cancer patients’ subpopulations, such as early presentation alone, young women, older women, or treatment subgroups.
Intervention	Not applicable
Control	Not applicable
Outcomes	The outcomes were: patient demographics (including age, sex, marital status, educational status, and menopausal status), and locoregional characteristic (including the primary tumor size, lymph node status, combined tumor staging, proportion of invasive and in-situ tumors, and tumor laterality).
	The sex distribution was extracted in studies where the proportion of both sexes were reported. Age distribution was extracted in the range <40, 40-49, 50-59, and ≥60 years and in the binary distribution≤30 years/ >30 years, and <50 years /≥50 years. Marital status was extracted into three categories: married, unmarried (separated, divorced, or widowed), and single (never married). Education was extracted into three categories: none/primary, secondary, and tertiary. Tumor laterality was extracted from articles that reported both unilateral and bilateral disease.
	The proportion of invasive disease and carcinoma in-situ were extracted using articles that reported the two. The primary tumor size was based on the American Joint Committee on Cancer (AJCC) classification for the articles reporting in T1-4 fashion, and staging was based on articles where all four stages could be distinctly identified.
	Nodal status was extracted as the presence or absence of

	nodal metastasis using the clinical or pathologic description according to the American Joint Committee on Cancer (AJCC) clinical staging criteria version 6 or 7.
Time	Articles published between January 2010 and December 2019. Articles including data earlier than January 2000 were excluded.
Study design	Study design was not a strict exclusion criterion because demographic characteristics are expected to be fundamental elements in the reporting of any study. Language was also not an exclusion criterion. We included any original article with a sample size of at least 30 subjects providing at least one data point or observation according to the outcomes list above. We excluded review articles. Original articles involving more than one country were included if the observation (s) could be extracted separately for each country.

Table 1. PICOTS Article Screening Criteria.

Author AO performed the article title and abstract screening while AO and AI performed the full article review independently. The same authors also conducted data extraction. The authors discussed to resolve any disagreement.

Quality assessment

Five quality assessment variables were designed using domains in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [6]. The quality assessment classified the report into one of 5 levels, A-E, depending on the quality score, with A being the highest score of five and E being a score of one or zero. The quality score was not used in meta-analytical weighing.

Statistical analysis

The primary outcome was the summary estimate of each outcome variable defined in our PICOTS criteria. The meta-analytical procedure was conducted in MetaXL (www.epigear.com) add-in for Microsoft Excel. A random-effect model was implemented to obtain summary estimates using the double arcsine transformation to avoid overweighting studies with values close to 0 or 100%. I-squared [I2] values above 75% indicated high heterogeneity. Subgroup analysis was conducted based on the United Nations regional classification of African nations as Central Africa (CA), East Africa (EA), Northern Africa (NA), West Africa (WA), and Southern Africa (SNA). By-country analysis was also conducted to compare variables and explain the potential source of heterogeneity. We analyzed summary estimates of all variables where there were at least two observations for the continent, the region, or the country. The variables were analyzed as proportions of the total in each publication (n/N).

Tumor characteristics according to the clinical or pathologic AJCC, were analyzed separately. Results were presented in percentages with 95% confidence intervals (95% CI). The parent forest plots for all analyses are available in the supplementary file. Funding: No funding source.

Results

Full electronic search returned 5661 articles; 80 articles were eligible after the article selection process (Figure 1, Table 2).

Figure 1. Article Screening Flow Chart.

Author	Year	Country	UnitedNations Region	Race	Period	Location of hospital	Design	N	Study level age statistic. range/mean/ median
Adejumo, et al. [22]	2019	Nigeria	WA	NS	2015-2018	FMC Keffi	pros	199	NS/NS/NS
Adebamiji, et al. [23]	2016	Nigeria	WA	NS	2003-2007	University of Ilorin Teaching Hospital Oke Oyi	retro	203	21-99/49.2/ NS
Agbo, et al. [24]	2014	Nigeria	WA	NS	2007-2011	Usman Dan Fodio Teaching Hospital Sokoto	retro	816	NS/48.2/N S
Agodirin, et al. [25]	2018	Nigeria	WA	NS	2016-2018	Multicente r	survey	100	26-80/50.5/ NS
Akanbi, et al. [26]	2015	Nigeria	WA	NS	2012-2014	NS	cross-	120	NS
Akinkuolie, et al. [27]	2016	Nigeria	WA	NS	2007-2013	Wesley Guild Hospital Ilesha	cross	46	25-81/NS/ NS
Anyanwu, et al. [28]	2011	Nigeria	WA	NS	2004-2008	Nnamdi Azikwe University Teaching Hospital Nnewi	pros	275	18-80/45.2/ NS
Ayoade, et al. [29]	2015	Nigeria	WA	NS	2011-2014	Olabisi Onabanjo University Teaching Hospital Sagamu	survey	113	NS/47.8/N S
Balekouzou , et al. [12]	2016	Central African Republic	CA	NS	2003-2015	Tungji Med College & Bangui University	retro	174	16-90/ 45.83/ NS
Balekouzou , et al. [11]	2018	Central African Republic	CA	NS	2003-2015	National Lab in Bangui and General and Gyneco logic Service	retro	174	16-90/NS/4 5.5
Bambara, et al. [30]	2017	Burkina faso	WA	NS	2015-2016	Yaldago Ouedraogo Teaching Hospital	cross	80	28-80/48.2/ NS
Bennis, et al. [31]	2012	Morocco	NA	NS	2007-2010	Hazzan University Hospital Fez	retro	366	18-82/45/N S
Boder, et al. [32]	2010	Libya	NA	NS	2002-2006	African Oncology Institute	database	234	NS/46/NS
Brinton, et al. [33]	2017	Ghana	WA	NS	NS	Korle Bu Teaching Hospital & Komfo Anoyle	case	1184	18-74/NS/ NS

						Kumasi & Peace and Love Kumasi			
Burson, et al. [21]	2010	Tanzania	EA	NS	2007-2009	Ocean Road Cancer Institute dar es Salam	retro	488	NS/43.4/NS
Cubasch, et al. [34]	2018	South Africa	SNA	blk (542)nblk (55)	2009-2011	CHBAH breast Clinic	database	602	
Dagne, et al. [35]	2019	Ethiopia	EA	NS	2011-2012	Tikur Ambessa Specialized Hospital	retro	303	N/42.1/NS
Dauda, et al. [36]	2011	Nigeria	WA	NS	2000-2007	FMC Gombe	retro	172	21-80/43.9/NS
Dedey, et al. [37]	2016	Ghana	WA	NS	2013	National Center for Radiotherapy and Nuclear Medicine Korle Bu Teaching Hospital	survey	265	NS/51.1/NS
Deressa, et al. [16]	2019	Ethiopia	EA	NS	2016-2017	University of GondorHospital Cancer Center	cross	82	25-82/NS/45
Dickens, et al. [8]	2014	South Africa	SNA	blk (964)nblk (107)	2006-2016	CHBAH breast Clinic	retro	1071	NS/55.4/NS
Effi, et al. [38]	2017	Ivory Coast	WA	NS	2013-2015	Central Laboratory Abidjan	pros	302	24-84/48/NS
Engbang, et al. [14]	2015	Cameroon	CA	NS	2004-2013	Multicenter	retro	3044	13-95/46/NS
Eniojukan, et al. [39]	2015	Nigeria	WA	NS	2008-2012	University College HospitalIbadan	retro	583	NS/44.9/NS
Ermiah, et al. [40]	2012	Libya	NA	NS	2008-2009	National Oncology Institute Sabratha	survey	200	22-75/45.4/NS
Errahhali, et al. [41]	2017	Morocco	NA	NS	2005-2012	Hassan II regional oncology center	retro	2406	NS/48.7/NS
Fatiregun, et al. [42]	2016	Nigeria	WA	NS	NS	Lagos State University Teaching Hospital Ikeja	survey	200	NS/49.6/NS
Fessahaye, et al. [43]	2017	Eritrea	EA	NS	2013-2014	National Health Laboratory Ministry of Health	retro	144	19-91/51.5/NS

						Amara			
Fitzpatrick, et al. [44]	2018	Senegal	WA	NS	2001-2016	Dantec Hospital	retro	197	NS/47/NS
Gabremariam, et al. [45]	2019	Ethiopia	EA	NS	2017-2018	Multicenter	cross	441	NS/44.4/NS
Galukande, et al. [46]	2014	Uganda	EA	NS	2008-2011	Mulago Hospital Kampala	retro	201	22-87/46.5/45
Galukande, et al. [47]	2015	Uganda	EA	NS	2004-2012	National Institute Oncology Sabratha		200	22-75/NS/NS
Gross-frie, et al. [48]	2018	Mali	WA	NS	2016	University Hospital Bamako	survey	64	NS/45/NS
Hussein, et al. [49]	2013	Egypt	NA	NS	2006-2011	Mansoura University Oncology center	retro	263	NS/52/NS
Jedy-Agba, et al. [4]	2017	Nigeria	WA	NS	2014-2016	Multicenter	pros	316	24-86/45.4/NS
Joffe, et al. [50]	2018	South Africa	SNA	NS	2015-2016	Chris Hani Baragwanath Academic Hospital Hospital Soweto	survey	499	NS
Kene, et al. [51]	2010	Nigeria	WA	NS	2001-2005	ABUTH Zaria	retro	103	NS/44.5/NS
Khaial, et al. [52]	2015	Libya	NA	NS	2007-2008	Al-Jamhouria Hospital	pros	301	NS/49/NS
Kholer, et al.[53]	2015	Malawi	EA	NS	2011-2013	Kamuzu Central Hospital Lilongwe	retro	198	12-89/NS/34
Kone, et al. [54]	2019	Mali	WA	NS	2014-2016	Bamako Radiotherapy center	retro	134	18-88/47.1/N
Lopes, et al. [55]	2015	Angola	CA	NS	2006-2014	Angola Institute of Cancer Control Luanda	retro	1843	16-87/NS/47
Mabula, et al. [56]	2012	Tanzania	EA	NS	2002-2011	Bugando Medical Centre, Mwanza	retro	384	21-78/NS/NS
Medhin, et al. [57]		Eritrea	EA						
Mensah, et al. [58]	2016	Ghana	WA	NS	2002-2008	Korle Bu Teaching Hospital & National center for radiology and Nuclear medicine	pros	1022	20-92/47.9/NS
Miguel, et al. [59]	2017	Angola	CA	NS	2011-2014	Angola Institute of Cancer	pros	140	24-84/47/NS

						Control Luanda & clinica Sagrade esperanca			
Mokone-Fatunla, et al. [15]	2019	South Africa	SNA	blk (1461)others 25	2000-2016	Dr George Mukhari Academic Hospital	retro	1482	21-96/54.9/NS
Moodley, et al. [60]	2018	South Africa	SNA	NS	2015-2016	Breast Clinic WesternProvince	cross	201	NS/NS/54
Mousa, et al. [61]	2011	Egypt	NA	NS	2009-2010	Tanta Cancer CenterGharbiah Province	survey	163	NS
Muchuweti, et al. [19]	2017	Zimbabwe	EA	NS	2010-2013	Parirenyatwa Group of Hospital Harare	pros	73	NS
Murugan, et al. [9]	2014	South Africa	SNA	blk (964)	2006-2012	CHBAH Soweto	database	1071	N/55/N
Mechita, et al. [62]	2016	Morocco	NA	NS	2005-2008	National Institute of Oncology Rabat	database	626	NS/51.1/NS
Nasiru, et al.	2011	Nigeria	WA	NS	2006-2009	LASUTH Ikeja	pros	350	23- 104/48.9/55.4
Nguefack, et al.[13]	2012	Cameroon	CA	NS	2006-2009	Duala General Hosptial	pros	42	29-73/46/NS
Nwafor, et al. [63]	2012	Nigeria	WA	NS	2009-2013	MeCure Health Limited Lagos	retro	48	29-78/49.5/NS
O neil, et al. [64]	2017	Rwanda	EA	NS	2012-2013	Butaro Cancer Center of Excellence	retros	150	26-84/48.3/N
Oguntunde, et al. [20]	2016	Nigeria	WA	NS	2011-2016	University of Ilorin Teaching Hospital Oke Oyi	database	300	20-96/49.7/NS
Ohene-yeboah, et al. [65]	2012	Ghana	WA	NS	2004-2009	Komfo Anokye Teaching Hospital Kumasi	pros	330	N/49.1/N
Okoye, et al. [66]	2016	Nigeria	WA	NS	2012-2016	Multicentered	retro	334	23-95/50.3/N
Omoniyi-esan, et al. [67]	2015	Nigeria	WA	NS	2007-2012	OAUTHC Ile-Ife	retro	136	23-92/50.7/NS
Otieno, et al. [68]	2010	Kenya	EA	NS	2003-2006	Kenyatta National Hospital	Pros	166	17-88/47/NS
Otieno, et al. [69]	2010	Kenya	EA	NS	2000-2004	Kenyatta National Hospital	retro	389	17-99/44/NS
Pace, et al. [70]	2015	Rwanda	EA	NS	2012-2014	Butaro & RwnkwavuHosptial	survey	144	NS/NS/49

Popoola, et al. [71]	2013	Nigeria	WA	NS	NS	Lagos State University Teaching Hospital Ikeja	Pros	190	NS/32/NS
Popoola, et al. [18]	2012	Nigeria	WA	NS					
Quayson, et al. [72]	2014	Ghana	WA	NS	2000-2004	Korle Bu Teaching Hospital	retro	821	14-98/48/NS
Rahman, et al. [73]	2014	Nigeria	WA	NS	2003-2008	University of Ilorin Teaching Hospital Oke Oyi [68]	retro	82	29-75/48.9/NS
Rambau, et al. [74]	2014	Tanzania	EA	NS	NS	Bugando Medical Centre, Mwanza	retro	52	NS/49/NS
Rayne, et al. [75]	2017	South Africa	SNA	blk (85)nblk (170)	2011-2013	Johannesburg	survey	263	18-86/NS/52
Salih, et al. [76]	2016	Sudan	NA	NS	2014-2018	Bashaier University Hospital & Khartoum Center for Radiation and Isotopes	pros	63	22-91/46.8/NS
Sayed, et al. [77]	2018	Kenya	EA	NS	2012-2015	Multicenter	survey	846	NS/48/NS
Sengal, et al. [10]	2017	Sudan	NA	NS	2010-2015		retro	560	20-94/48.8/NS
Sengal, et al. [7]	2017	Eritrea	EA	NS	2011-2015	University of Gezira	retro	562	NS/NS/NS
Sengal, et al. [7]	2017	Sudan	NA	NS	2011-2015	Orotta School of Medicine and Dentistry Amaru	retro	116	NS/NS/NS
Ssemanda, et al. [78]	2018	Uganda	EA	NS	2005-2014	MaKCHS Lab Kampala	retro	599	NS/NS/NS
Stapleton, et al. [79]	2011	Egypt	NA	NS	2007-2008	National Cancer Institute of Cairo University & Tanta Cancer Center Nile Delta	cross	343	NS/NS/NS
Tazzite, et al. [80]	2013	Morocco	NA	NS	2009	Oncology Centre, Ibn Rochd University Hospital Casablanca	retro	570	NS/47.07/NS
Tesfamariam, et al.	2013	Eritrea	EA	NS	2007-2008	Multicenter	retro	82	26-80/48.4/NS

[81]									
Titiloye, et al. [82]	2013	Nigeria	WA		2004-2006		retro	89	
Traore, et al. [83]	2015	Guinea	WA	NS	2007-2012	Donka Chu Conakry	retro	278	20-85
Usman, et al.[84]	2019	Nigeria	WA	NS	2011-2015	Amino Kano Teaching Hospital Kano	retro	478	20-80/46.9/ N
Wondima -gagnehu, et al. [85]	2019	Ethiopia	EA	NS	2017-2018	Multicente red	cross	428	NS/40/NS

Table 2. List of Eligible Articles and Their Characteristics.

Result of article request; Four authors contacted for full-text responded [42, 86-88] yielding one eligible article. One [54] of 20 authors [7, 12, 31, 32, 36, 40, 49, 54, 60-62, 64, 74, 75, 77, 89-93] contacted for data on age distribution responded. Three authors [30, 39, 61] could not be reached to clarify data on age distribution, two could not be reached for data on educational status [39, 94], and one could not be reached for data on time to presentation [94]. Five authors contacted for data on stage distribution did not respond [48, 58, 60, 64, 70], and one could not be reached [95]. Three authors could not be reached to clarify data on tumor stage [30, 39, 61]. Two authors contacted for data on tumor size did not respond. One [37] of four authors contacted for data on marital status [37, 40, 70, 75] responded with usable data and one could not be reached [31, 74, 95]. Regional representation and summary of design; Twenty-four countries were represented from all five regions of Africa; CA-6, EA-19, NA-13, SNA-7, and WA-35. Three publications were in french [14, 62, 83]; all others were in English. Abbreviations, CA- Central Africa; EA- East Africa; WA-West Africa; NA- North Africa; WA-West Africa; SNA- Southern Africa; udy, retro- retrospective study' survey- questionnaire-based survey

Each article contributed data for one country except Sengal et al. [7], which provided data for Sudan and Eritrea in one article. Two articles from South Africa [8, 9], Sudan [7, 10], and Central African Republic [11, 12] shared the same population of subjects but provided different data points (Table 2). Attempts to clarify incomplete or obscured data via email communications with authors yielded variable results as detailed in Table 2 footnote.

Twenty-three countries from all five regions of Africa contributed articles. WA contributed the largest number of articles (35 articles), followed by EA-19, NA-13, SNA-7, and CA 6. Nigeria contributed 23 articles, the largest from a single country (Figure 2).

Figure 2. Map of Africa Showing the Distribution of Study Subjects from each Country. The deeper blue shading represents a higher contribution, and lighter blue shading represents a lower contribution. The gray shadings represent no contribution.

There were 33,199 subjects in total. The minimum number of subjects in a study was 42 [13], and the maximum was 3044 [14]. The maximum number of subjects from one country was 5425, contributed by Nigeria (Figure 2). The majority of studies (n=39) were in the B quality assessment category; the study rationale was well stated in 84%, the design was adequate in 85%, and the participants were adequately stated in all studies. The study outcomes were adequately described in 77%, but the ease of data extraction was present in only 36% (Supplementary File). There was marked heterogeneity (>75%) in the overall summary estimates of the continent- wide analysis. The heterogeneity was significantly reduced or eliminated in most by-region and by-country analyses (Supplementary File).

Sex distribution

Twenty-five articles, including 11,476 subjects, contributed to the analysis of sex distribution. Ninety-seven per-cent (95% CI 97-98, I2 77%) of patients were female and 3% (95% CI 2.0-4.0%, I2 77) were male. EA had prevalence of male BC at 5% (95% CI 2.0-476%), more than double the prevalence in WA (2% (95% CI 2.0-2.0, I2-80%). Regional analysis was not feasible for NA, CA and SNA. By-country analysis showed a similar distribution of 2-3% in Nigeria, Tanzania, Eritrea, and Ghana. Single studies reported 2% male prevalence in Cameroon [14] and South Africa [15]. A single study from Ethiopia recorded male BC prevalence of 18% [16]. Subgroup analysis showed a rising trend in male BC incidence in the last ten years compared to the decade before. (Supplementary file).

Age distribution

Thirty-three articles (14,545 subjects) contributed to age distribution analysis. Overall, more than half of patients (58%) were diagnosed before the age of 50. Twenty-eight per-cent of patients (95% CI 24-31) were diagnosed before the age of 40, and 6.0% (95% CI 5.0-8.0, I2=90%) were diagnosed at 30 years or younger. The youngest patients were in EA, where 8% (95%CI 6.0-11, I2=82%) were diagnosed under the age of 30, 38% (95% CI 31-45, I2=85%) were diagnosed under the age of 40, and 64% were diagnosed before the age of 50. Conversely, in SNA, over 60% were diagnosed at the age of 50 or above, and 37% (95% CI 35-39, I2=0%) were diagnosed at the age of 60 or above. The age distribution analysis was possible for NA only in the 50-year cutoff, showing that the majority were also younger than 50 years (58%, (95% CI 44-72, I2=94%). (Figure 3, Supplementary file)

Figure 3. Age of Breast Cancer Patients in Africa.

By-country analysis showed Ethiopia had the youngest patients with 10% (95% CI 8.0-13, I2=63%) being younger than 30 years and 73% (95% CI 61-80, I2=87%) younger than 50 years (Figure 3 and Supplementary File). Temporal analysis revealed declining age of BC patients over time. Sixty per-cent of patients from 2010-2019 were less than 50 years of age, compared to 55% in 2000-2010 period. Eight per-cent of patients were less than 30 years of age from 2010-2019 compared to 4% in the 2000-2010 period (Figure 2, Supplementary file). Overall, 57% (95% CI 54-61, I2 87%) of patients were premenopausal. This was similar throughout regions with available data (56-60%). By-country analysis showed that Ghana had the highest prevalence of premenopausal patients (64% (95 % CI 42-83, I2=92%)) (Supplementary file).

Educational and marital status

Eleven publications (3747 subjects) contributed to the marital status analysis. Overall, 61% were married and 39% were unmarried, including 20% single. One study from CA [12] reported the highest proportion (74%) of unmarried singles; sensitivity analysis excluding this study saw the proportion of singles overall drop to 15%. The regional distribution of single patients was 11% EA, 14% WA, and 24% SNA. The largest unmarried population was in South Africa (57%) while the smallest was in Nigeria (27%). The temporal trend showed a slight increase in unmarried women diagnosed with BC in the last decade (41%) compared to the period between 2000-2010 (35%) (Table 3). Twelve articles (3,103 subjects) contributed to the educational status analysis. Thirty-eight per-cent of patients had none or primary education, 36% completed secondary education, and 26% completed tertiary education overall. The proportion of patients with secondary or tertiary level education was highest in SNA (75%) than EA (62%) and WA (62%). The proportion of patients with secondary or tertiary level education in the last decade (64%) was slightly higher than the overall analysis (62%) (Table 3). Subgroup analysis for 2000-2010 was not feasible. However, a single study from Nigeria in the 2000-2010 period recorded 52% secondary and tertiary education [17], another study from Nigeria with data between 2010 and 2012 recorded 66%, [18], and a

separate study in Uganda including data between 2010 and 2013 [19] recorded 62%. (Supplementary file).

Laterality

Eight articles (2,947 subjects) contributed to the analysis of BC laterality in the continent. Most patients (97%) had unilateral BC, compared to 3% (95% CI 2.0-6.0 I2=80%) who had bilateral BC. The highest prevalence of bilateral BC was in Nigeria, 8% (95% CI 6.0-12) [20] and Tanzania (6%, 95%CI 4-8) [21]. A slightly higher proportion (51% (95% CI 46-55) were left-sided tumors (Table 3).

Sex	Female % (95 % CI)	Male % (95 % CI)		I-squared (%)
Africa Overall	97 (96-98)	3 (2-4)		77
By-region				
EA	96 (93-97)	5 (3-7)		76
WA	98 (96-99)	2 (1-4)		80
By-country				
Eritrea	96 (93-96)	4 (2-7)		23
Ghana	98 (97-99)	2 (1-3)		23
Nigeria	97 (96-99)	3 (1-4)		85
Tanzania	97 (95-98)	3 (2-5)		16
Educational Status	None/Primary % (95 % CI)	Secondary % (95 % CI)	Tertiary % (95 % CI)	
Africa Overall	38 (29-47)	36 (28-41)	26 (19-34)	95
Africa (2011-2019)	35 (25-46)	39 (27-49)	26 (17-36)	90
By-region				
EA	36 (19-56)	38 (18-56)	26 (9-43)	57
SNA	25 (21-29)	48 (43-53)	27 (23-31)	0
WA	38 (27-49)	33 (22-44)	29 (19-40)	52
Marital Status	Married % (9 5% CI)	Unmarried % (95 % CI)	Single% (95 % CI)	
Africa Overall	62 (50-69)	19 (11-26)	20 (12-27)	97
Africa (2011-2019)	59 (39-72)	19 (7-33)	22 (9-36)	98
Africa (2000-2010)	65 (47-77)	20 (8-33)	16 (6-28)	96
By-region				
EA	62 (49-72)	27 (17-37)	11 (5-19)	91
SNA	43 (39-47)	33 (30-37)	24 (21-27)	0
WA	71 (64-78)	15 (9-20)	14 (9-20)	90
By-country				
Ghana	67 (47-82)	17 (5.0- 32)	16 (4-32)	96
Nigeria	73 (59-84)	15 (6-26)	12 (4.0-22)	91
Laterality	Right % (95 % CI)	Left % (95 % CI)	Bilateral% (95 % CI)	
Africa Overall	46 (41-51)	51 (40-55)	3 (2-6)	80
By-region				
WA	44 (32-56)	53 (40-64)	3 (0-9)	84
EA	52 (43-61)	45 (35-53)	3 (0-9)	85

Table 3. Demographic Characteristics and Time to the Presentation of African Breast Cancer Patients, Overall and by Region/country where Available.

Stage distribution

Fifteen articles (9,185) contributed to carcinoma-in- situ analysis. Prevalence of carcinoma in-situ was generally low in all regions (CA- 4%, EA-2%, and NA-1%, SNA, and WA-1%). The highest

proportion of carcinoma-in-situ in individual publications was 6% reported in Central African Republic and 5% in Malawi.

Overall, 98% of BCs were invasive based on analysis of 30 articles (10,352 subjects). Advanced BC (AJCC stage III or IV) accounted for 67%. Overall, 7% (95% CI 4.0-9.0, I2= 98%) of patients were diagnosed stage I disease, ranging from 2-10% in each region. Twenty-six per-cent of disease was stage II, ranging from 21-35% in each region, 50% of disease was stage III, ranging from 39-74% in each region, and 17% of disease was stage IV, ranging from 3-21% in each region. The earliest tumors were in NA; 74%, and 81% were Stage II or III in SNA and NA, respectively, while 70% or above were Stage III or IV in other regions (Figure 4 and Supplementary File).

Figure 4. AAA.

Trend analysis showed a decreasing prevalence of stage I (from 8% to 4%) and stage IV (from 24% to 12%) disease, with an increasing prevalence of stage II and III disease in the last decade (Figure 4).

Two articles (577 subjects) contributed to the clinical T-stage analysis, and seven articles (2151 subjects) contributed to the pathologic T-stage analysis. The majority of tumors were clinical T3 or T4, whereas the majority were pathologic T2 or T3. The prevalence of pathologic or clinical nodal positivity was 70% (99% CI 60-80), based on the analysis of 21 articles (8,357 subjects). WA had the highest prevalence of nodal disease (84%, 95% CI 71-94, I2=99%). By-country analysis showed that Nigeria (91%, 95% CI 75-100, I2=98) had the highest prevalence of lymph node positivity, and Eritrea (34%, 95% CI 28-41, I2=21) had the lowest.

Treatment modalities

Post hoc analysis of the treatment modalities in the continent showed that 72% of BC patients overall underwent surgery. Overall mastectomy prevalence was 71% (95% CI 51-88, I2=99%) while prevalence of breast-conserving surgery was 1.0% (95% CI 0-2, I2=0%). Eighty-three per-cent (64-96 I2=98%) of patients received chemotherapy, 18% (95% CI 4-33, I2 =94%) received radiotherapy, and 77% (95% CI 42-100 I2= 99) received hormonal therapy. Three studies reported routine hormonal therapy in all patients (see Supplementary File). There was no data on targeted-therapy.

Discussion

The African continent has a total population of approximately 1.34 billion inhabitants, accounting for 17% of the world’s population. The United Nations recognizes five African regions comprising 64 territories/ countries: EA (22 countries) 0.45 billion, WA (17 countries) 0.40 billion, NA (11 countries) 0.25 billion, CA (9 countries) 0.18 billion and SNA (5 countries) 0.07 billion. Together WA and EA account for more than 60% of Africa’s population, and South Africa (SA) alone accounts for 88% of the population of SNA.

We aggregated data from 80 articles published within the last decade, from 23 countries representing Africa’s regions. Our findings corroborated previous evidence that African BC patients are younger than those from Europe and the US. In this study, 6% of patients were <30 years of age compared to 0.43% in the UK, 28% were <40 years compared to 6.6% in the US [96, 97], and 58% were <50 years compared to 20% in Europe [98].

The age distribution of BC in South Africa showed a reverse pattern, mirroring the Caucasian age distribution seen in Europe. One explanation might be the proportion of Caucasian inhabitants in

SA. Nonetheless, in four of the seven studies included from SA where the race was reported, 90% were Black patients (Table 1). However, it was not reported whether these patients might have been mixed-race Black patients. Even then, previous report suggests that black BC patients in SA are older than other races with BC in SA [99], though this may be partially- attributable to under-reporting.

The declining age of BC found in this study in the setting of the increasing age of Africa's population overall [100] contradicts the view that the earlier age of BC onset can be entirely attributed to the younger population in Africa. Additionally, the elevated proportion of male breast cancer, 3% overall and 4% in the last decade, compared to approximately 1% reported globally [101, 102], and previously reported increased rates of triple negative disease raise questions regarding potential genetic predisposition and merit further investigation.

The early age of BC onset in Africa brings numerous challenges regarding screening, early diagnosis, and treatment compliance [103]. Young women may be less likely to complete the diagnostic process or treatment for BC due to social reasons, such as fertility issues and socio-cultural isolation. A report in Nigeria found that 31% of young women outrightly declined the diagnostic biopsy procedure, 60% of those who did not decline failed to return for the result of the biopsy, and only 45% of those offered mastectomy accepted treatment [103]. Future intervention should be directed toward improving early diagnosis and compliance with treatment in this patient population.

Even in high-income countries where screening is ubiquitous, it is recommended to begin after 40 years (or 50 according to some guidelines). A third of BC patients in Africa were <40 and would be missed by applying the same screening age guidelines as in the US. While population-based mammographic screening programs are not feasible in most African countries due to resource constraints, education of the general population, paired with clinical breast examination (CBE) has the ability to downstage clinically apparent disease, and age range recommendations should be based on available data.

Thirty-eight per-cent of breast cancer patients in this analysis had none or primary education, and education level varied widely by region. This underscores the importance of tailoring breast cancer education and breast health awareness for both patients and the general population to the local context, taking into account educational and cultural background.

Although unmarried BC patients' population appears to be increasing in Africa, perhaps due to delaying marriage for education, the current predominantly married BC patient population still provides opportunities to include men as potential intervention targets. Reports suggest men are willing to support women in BC control [104, 105].

In this analysis, nearly 90% of tumors were greater than 2cm, half were greater than 5cm, and one-quarter had skin or chest wall involvement. This preponderance of clinically-detectable disease means that the vast majority of patients have the potential for earlier detection by CBE. Marked regional variations in tumor size and stage across regions, might be explained in part by differences in health systems. Coordinating and centralizing local resources provided affordable, comprehensive health financing, and helped to downstage BC in NA [106]. Increasing awareness and reducing the distance and bottlenecks between BC patients and specialists aided downstaging in SA [9]. Countries in SSA could benefit from the experience in NA and SA to attain the goals of downstaging invasive BC. The smaller pathologic T staging compared to the clinical T staging in our analysis might be linked to the widespread use of neoadjuvant chemotherapy or errors of clinical or pathologic measurement and requires further investigation.

The decreasing rate of stage IV disease over time (24% to 12% in the first decade vs. the second decade of this analysis) shows promise for a slow, but positive trend toward earlier diagnosis, which is one of the most important factors in improving outcomes. The generally low prevalence of

carcinoma-in-situ, 2-4% in all regions, can be explained by the common lack of population- based screening. Population-based screening should not be considered until a health system has the resources and ability to effectively diagnose and treat clinically apparent disease. Nonetheless, it is important to note that the rise in the prevalence of small tumors (<1cm) and carcinoma-in- situ (from 2% to >20%) in developed countries was linked to screening [107]. In light of the emerging evidence supporting the use of ultrasound in detecting early BC in young women [96, 108, 109], when a health system is ready to consider targeted screening, ultrasound may be considered along with CBE.

The heterogeneity, narrow spread, and paucity of articles capturing some of the variables analyzed limit our findings. Notably, only SA contributed to the findings for SNA. Similarly, in a previous review [110], only SA contributed to the meta-analytical review of the stage at presentation in SNA because the literature on BC is scarce from other SNA countries. Also, the reporting of demographic variables was influenced by the region as articles from the same region reported similar data points in similar formats. The countries of WA and EA reported more information on patient demographics than in the other regions. Availability of data limited our ability to draw conclusions regarding certain critical variables of interest, such as immunohistochemistry or treatment modality by stage.

In conclusion, Africa has a common goal of downsizing and downstaging BC, which is achievable through the early diagnosis of clinically detectable disease. There is marked regional variation in the clinical pattern and patient demographics of BC in Africa, and the interventions developed should be tailored to the local context in each area, while allowing for countries and regions to benefit from shared knowledge and experiences.

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All data used in this article are freely available

Authors Contribution

Agodirin Contributed to all aspect of the research, all authors contributed to approval. Aremu contributed to conception, data acquisition, extraction , and review. Rahman contributed to conception, data interpretation, drafting, review. Olatoke contributed to conception, data interpretation and review. Olaogun contributed to draft, review and data interpretation, Akande contributed to data interpretation, drafting and review. Romanoff contributed to data interpretation, drafting and review.

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