



Prevalence of Histological Characteristics of Breast Cancer in Rwanda in Relation to Age and Tumor Stages

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Abstract

Breast cancer is a complex disease, and it is the most common cause of morbidity and mortality among women worldwide. In Sub-Saharan Africa, the clinical characteristics and tumor profiles of breast cancer are still unknown. In the present study we aimed to determine breast tumor profiles of the Rwandan patients in relation to age and tumor stages. We compare our findings to related results from other sub-Saharan Africa studies. Data on age at diagnosis, tumor stage, and hormonal profiles of 138 patients diagnosed between January 2015 and December 2018 were retrospectively retrieved from electronic medical records at three referral hospitals in Rwanda. We compared our results to related findings reported in other Sub-Saharan African countries. All statistical analyses were done using SPSS Inc., Chicago, IL, USA, version 20 and R software languages. The mean age at diagnosis was 49.7 years (SD = 13) and ranged from 17 to 86 years. The majority of patients (57.2%) were diagnosed before 50 years of age compared with 42.8% aged > 50 years. Tumor stage III was the commonest accounting for 62% followed by stage II with 24.8%. The distribution of breast tumor subtypes was ER-, PR-, HER2-: 37.7%; ER+, PR+, HER2-: 31.2%; ER-, PR-, HER2+: 14.5%; ER+, PR+, HER2+: 5.1%; and other subtypes represented 11.6%. There was no statistically significant difference in age and tumor stages between the molecular subtypes. Our findings revealed the predominance of hormonal negative tumors among Rwandan patients with breast cancer. Triple negative was found to be the most common breast tumor subtype regardless of age and tumor stage. Larger prospective studies could examine genetics and environmental factors that may play a role in the differences of tumor characteristics in Sub-Saharan populations.

Keywords Breast cancer · Molecular subtypes · Rwanda · Sub-Saharan Africa

Background

Breast cancer (BC) is the most commonly diagnosed and deadly malignancy in women in both developed and developing countries with about 2.1 million cases and 627,000 deaths registered in 2018 [1]. It causes 25.1% of all cancer deaths each year in developed countries and is the leading cause of mortality among women in developing countries with 14.3% of all deaths annually. The GLOBOCAN estimates that the BC incidence will double by the year 2050 [2].

In Sub-Saharan Africa (SSA), BC is becoming a serious public health issue with a significant increase in its incidence, and a high mortality rate as compared with developed parts of the world [3, 4]. In Rwanda, a small country of 26,338 km² and more than 12 million inhabitants, BC is currently the most commonly diagnosed cancer in women and the second cause of mortality after cervical cancer [5, 6]. It has been suggested that specific biological characteristics might explain the adverse prognosis of BC in Africa [7, 8].

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BC is a heterogeneous disease with different morphological and molecular subtypes [9, 10]. The treatment and routine clinical management of BC rely on hormonal receptor (HR) status such as the presence or absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) combined with other prognostic factors such as patient age, tumor histology, tumor stage, and nodal status [11, 12]. A combination of ER, PR, and HER2 defines distinct tumor classes of BC that are further defined by gene expression profiles. The knowledge of tumor subtype may enable more accurate diagnoses and support therapeutic decisions. In clinical settings, tumor subtypes are classified using immunohistochemistry (IHC) markers and guide prognosis and targeted therapies for ER/PR or HER2 positive tumors. ER/PR positive tumors are candidate for hormonal (endocrine) therapy, whereas HER2 positive tumors are targeted with anti-HER2 therapies. Triple negative (ERnegative, PR negative, HER2 negative) tumors lack any target therapy [13].

Little is known about the rate and features of BC in Africa. The few studies conducted in SSA on clinico-pathological and biological characteristics of BC report that it is characterized by an early age of onset and an advanced stage at diagnosis with poor prognosis. However, the reports concerning hormone receptor and molecular subtypes are contradictory. A review by Brinton et al. [14] found that most breast tumors in African women are hormone receptor negative, while others reported the predominance of hormone receptor positive breast tumors.

In the present study, we aimed at providing information on the clinical presentation and hormonal receptor profiles of breast cancer in Rwanda through a large collection of cases from three major hospitals. We also compared our results with reports from previous studies in other SSA countries.

Material and Methods

Study Design and Setting

This is a descriptive retrospective study conducted at three referral hospitals in Rwanda: University Teaching Hospital of Butare (CHUB) located in the Southern province, University Teaching Hospital of Kigali (CHUK), and Rwanda Military Hospital (RMH) at Kanombe, both located in Kigali, capital city of Rwanda. BC patients are referred from all over the country to these three referral hospitals.

Data Collection

Data including hormonal profile (ER, PR) and HER2 expression, demographic information (gender, age at diagnosis), and tumor characteristics (tumor stage or grade) were collected through review of patients electronic medical records from

January 2015 to December 2018. Immunohistochemistry (IHC) staining for ER, PR, and HER2 was performed at one referral hospital. The biopsy or surgical specimens received from all three hospitals were originally fixed in 10% formalin. They were then fixed in 10% neutral buffered formalin for 24 to 72 h and then processed for routine hematoxylin and eosin staining through the steps of dehydration, clearing, paraffin impregnation, and finally sectioning and staining. Hormonal receptor and HER2 statuses were identified by immunohistochemical (IHC) markers using EnVision™ Flex Kit (Dako, Denmark)–Manual protocol, and following the manufacturer instructions. For each run of staining, a positive and negative control slide was also prepared. The positive control slides were prepared from breast carcinoma known to be positive for the antigen under study. The negative control slides were prepared from the same tissue block but incubated with PBS instead of the primary antibody. A semi-quantitative histochemical score was used to record results of ER and PR staining according to the system established by Allred et al. [15]. This system considers both the proportion and intensity of stained cells. The intensity score (IS) ranges from 0 to 3, with 0 being no staining, 1 weak staining, 2 moderate staining, and 3 strong staining. The proportion score (PS) estimates the proportion of positive tumor cells and ranges from 0 to 5, with 0 being non-reacting, 1 for 1% reacting tumor cells, 2 for 10%, 3 for one-third, 4 for two-thirds, and 5 if 100% of tumor cells show reactivity. The PS and IS are added to obtain a total score (TS) that ranges from 0 to 8. Tumor cells with a total score of 3 to 8 were considered positive, whereas those with TS less than 3 were considered negative cases.

Her-2/neu was scored on a 0 to 3 scale according to the criteria for Intensity and Pattern of Cell Membrane Staining with pathway HER2. The staining was scored as negative (0) when no membrane staining was observed, or (1+) when membranous staining was faint, partial staining of the membrane in any proportion of the cancer cells; weakly positive (2+) if weak complete staining of the membrane, greater than 10% of cancer cells; and positive (3+) if intense complete staining of the membrane, greater than 10% of cancer cells. The procedure was standardized in comparison with the Hercep Test (DAKO) kit. Tumor grades were classified using the Nottingham Bloom-Richardson grading system [16], and clinical tumor stages were classified according to American Joint Committee on Cancer and TNM classification [17]. All histological evaluations and pathological reporting were in compliance with the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) Guidelines as updated (www.cap.org).

We also reviewed published studies from SSA countries paying attention to data concerning the mean/median age, the proportions of patients aged of 50 years or less, the percentage of stage III&IV tumors, the percentage of triple negative tumors, and the percentage of HER2-enriched tumors.

Data Analysis

Data were organized into a secure, electronic database and checked for duplications and errors by independent people. We used descriptive statistics to report the mean and standard deviation (SD) for continuous data and frequencies and proportions for categorical data. Chi-square or ANOVA test was used to evaluate the statistical significance of the association between hormonal/ tumor subtypes with patient's age and tumor stage. We classified hormonal statuses into five tumor subtypes: ER+, PR+, HER2+ (triple positive), ER-, PR-, HER2- (triple negative), ER+, PR+, HER2-, ER-, PR-, HER2+ (HER2-enriched), and others (ER-, PR+, HER2+; ER-, PR+, HER2-; ER+, PR-, HER2-). To test for age, two groups were considered: young (patients aged 50 years and under) and old (patients above 50 years). The tumor stages were divided into three categories: early stage (stages I and II), locally advanced (stage III), and metastatic (IV).

Results from studies in SSA on proportions of young patients, advanced tumor stage, triple negative tumors, and HER2-enriched were summarized in the table. Proportions of triple negative tumors from those studies were grouped according to geographical location in Africa and meta-analyzed using an inverse variance method. The proportion estimates were calculated under the random effect model. Confidence intervals for proportions were calculated using the exact binomial method.

The significance level was fixed at 5%. Data analysis was performed using SPSS Inc., Chicago, IL, USA, version 20, and meta-proportions were plotted using R software language.

Ethical Consideration

Ethical approval was obtained from the Institutional Review Board of the College of Medicine and Health Sciences (CMHS) at University of Rwanda (Reference No 209/CMHS IRB/2017).

Results

Clinical Pathology Characteristics of Study Participants

A total number of 138 breast cancer cases with available data for all variables considered in the present study were recorded. Of all cases, 98% was female while only 2% was male. The mean age at diagnosis was 49.7 years (SD = 13) and ranged from 17 to 86 years. The majority of patients (57.2%) were diagnosed before the age of 50 years compared with 42.8% aged > 50 years. Among these, 9.4% was younger than 35 years old. Bilateral breast cancer was recorded in 2 (1.4%) patients.

Histologically, invasive ductal carcinoma accounted for the majority of the patients with 81.9% of cases, followed distantly by invasive lobular carcinoma with 8.7%.

The tumor stage III was the commonest accounting for 62.5% (80/128) followed by stage II with 24.8%. Stage I and stage IV represented 7.0% and 7.8% of all cases, respectively.

Lymph node invasion was observed in the majority of patients 70.6% (77/109) compared with 29.4% (32/109) node negative tumors (Table 1).

Hormonal Receptor Profiles in Relation with Age and Tumor Stage at Presentation

In general, hormonal receptor negative tumors were predominant compared with hormonal receptor positive: 55.1% ER-

Table 1 Clinical pathology characteristics of study participants

Variables	Frequency (n = 138)	Percentage
Age: mean \pm SD: 49.7 \pm 12.98		
Range 17–86		
< 35	13	9.4
35–50	66	47.8
> 50	59	42.8
Gender		
F	135	97.8
M	3	2.2
Breast laterality		
Left	72	52.2
Right	45	32.6
Bilateral	2	1.4
Missing	19	13.8
Histology		
Ductal carcinoma in situ	2	1.4
Invasive ductal carcinoma	113	81.9
Invasive lobular carcinoma	12	8.7
Medullary	5	3.6
Metaplastic	3	2.2
Sarcoma of the breast	1	0.7
Colloid carcinoma	1	0.7
Tumor stage		
I	9	6.5
II	38	27.5
III	73	52.9
IV	10	7.2
Missing	8	5.8
Lymph node involvement		
Yes	77	55.8
No	32	23.2
Missing	28	20.3

vs. 44.9% ER+, 63.8% PR- vs. 36.2 PR+, and 78.3% HER2- vs. 21.7 HER2+. Hormonal receptor negative tumors were most common in the younger age group (≤ 50 years) and at advanced tumor stages. However, the association between age and hormonal status was not statistically significant ($p > 0.05$). We observed a statistically significant association between tumor stage and ER status ($p = 0.00097$). However, the association between PR, HER2, and tumor stages was not statistically significant ($p > 0.05$) (Table 2).

The most commonly detected tumor subtype was triple negative (ER-, PR-, HER2-) representing 37.7% of all cases, followed by ER+, PR+, HER2- with 31.2% of cases, and HER2-enriched (ER-, PR-, HER2+) with 14.5% of cases. The mean ages across all tumor subtypes were not statistically significantly different ($p = 0.558$). Across all tumor subtypes, the majority of patients had locally advanced tumors and was in the younger age group. However, the relationship between tumor subtypes, tumor stage, and age of patients was not statistically significant ($p = 0.097$) (Table 3).

Age at Diagnosis, Tumor Stage, and Molecular Subtypes of Breast Cancer in SSA

The results reported in previous studies conducted in SSA countries evaluating the age at diagnosis, tumor stage, and tumor subtypes of breast cancers are aggregated in Table 4. These results showed a high proportion of young patients in SSA (52–86%) with median ages ranging between 42 and 53 years. Tumor stage III was observed in 38–81%. The overall proportion of triple negative subtype was 31% ranging from 15 to 53% with the highest proportions in Western countries compared with East and Southern countries (Fig. 1).

Discussion

The risk factors associated with BC disease in Africa and in Rwanda are still unknown. The increasing incidence is thought to be linked to an increase in life expectancy, adoption of western lifestyle including contraceptive use, and possible specific genetic predisposition [34].

Several studies in SSA reported the high prevalence of BC at younger ages with late stage at diagnosis and poor prognosis compared with western countries. Nevertheless, the results on hormone receptor and molecular subtype distribution in African population are still unclear [14].

In the present study, we analyzed the data from 138 confirmed BC cases, evaluating the association between age at diagnosis, tumor stage at presentation, and hormonal receptor profiles or subtypes.

We found that BC in Rwanda occurs at younger age with a mean age of 49 (SD = 13) and most patients (57.2%) below 50 years of age while 42.8% of patients were above 50 years. Furthermore, breast cancer was commonly diagnosed between 35 years and 50 years of age with 47.8% of all cases in this age range. The same observations were made in other SSA countries (Table 4). This finding raises the question of the implication of demographic, genetic, and environmental factors in BC development. The high frequency of young BC patients in Rwanda could be influenced by the demographics in Africa and in Rwanda, where a high number of women are aged less than 50 years in comparison to Europeans [35] (Fig. 2). For example, the Belgian and Rwandan demographic graphs indicate that with similar numbers of total inhabitants, the absolute numbers of women aged 30–49 or 50–69 are similar in Belgium, while in Rwanda, there are 2.4 times more women in the 30–49 than in the 50–69 age range. As there are 52.2% cancers in the 30–49 range vs. 37.7% in the 50–69 range, more than half of the difference when comparing with

Table 2 The relationship between hormonal receptor statuses, age at diagnosis, and tumor stages

HR n (%)	ER		PR		HER2	
Age n (%)	ER-	ER+	PR-	PR+	HER2-	HER2+
≤ 50 years	42 (55.3)	37 (59.7)	47 (53.4)	32 (64.0)	60 (55.6)	19 (63.3)
<i>n</i> = 79						
> 50 years	34 (44.7)	25 (40.3)	41 (46.6)	18 (36.0)	48 (44.4)	11 (36.7)
<i>n</i> = 59						
<i>p</i> value	0.72		0.30		0.533	
Locally advanced	52 (68.4)	21 (33.9)	55 (62.5)	18 (36.0)	56 (51.8)	17 (56.7)
<i>n</i> = 73						
Metastatic	4 (5.3)	6 (9.7)	7 (7.9)	3 (6.0)	6 (5.6)	4 (1.3)
<i>n</i> = 10						
Missing+	2 (2.6)	6 (9.7)	4 (4.5)	4 (8.0)	8 (7.4)	0 (0.0)
<i>p</i> value	0.00097*		0.0642		0.483	

*Statistically significant

+Missing data were not considered in the analysis

Table 3 Tumor subtypes in relation to age at diagnosis and tumor stages

Tumor subtype	ER + PR + HER2+ (Triple positive)	ER + PR + HER2–	ER – PR – HER2+ (HER2-enriched)	ER – PR – HER2– (Triple negative)	Others	<i>p</i> value
Mean ± SD	7 (5.1) 47.3 ± 9.9	43 (31.2) 49.9 ± 11.9	20 (14.5) 47.3 ± 10.1	52 (37.7) 51.9 ± 14.7	16 (11.6) 47.3 ± 12.9	0.558
Age ≤ 50 years <i>n</i> = 79	4 (57.1)	26 (60.5)	13 (65.0)	26 (50.0)	10 (62.5)	0.752
Age > 50 years <i>n</i> = 59	3 (42.9)	17 (39.5)	7 (35.0)	26 (50.0)	6 (37.5)	
Tumor stage: <i>n</i> (%)						
Early stage <i>n</i> = 47	2 (28.6)	23 (53.5)	5 (25.0)	12 (23.1)	5 (31.3)	0.097
Locally advanced <i>n</i> = 73	3 (42.8)	12 (27.9)	13 (65.0)	36 (69.2)	9 (56.2)	
Metastatic <i>n</i> = 10	2 (28.6)	4 (9.3)	2 (10.0)	2 (3.8)	0	
Missing+ <i>n</i> = 8	0	4 (9.3)	0	2 (3.8)	2 (12.5)	

*Statistically significant

+Missing data were not considered in analysis

European countries can be explained by the demographic effect. Moreover, it has been estimated that mammography screening programs targeting women between 50 and 69 lead to an over-diagnosis rate of 12–20%, and thus further increase the number of diagnoses in that age range in Europe [36]. Taking together these aspects, it is difficult to conclude that the mean age of BC incidence is significantly lower in SSA than in European countries.

Breast tumor stage is considered as a major determinant of survival from breast cancer where early stage tumor is associated with a better prognosis and a higher survival rate than advanced or tumors [15, 36]. In our study, tumor stage III was the most common with 62%, while metastatic tumors (stage IV) represented 7.8% of cases. More than 50% of patients were clinically node positive at presentation. The high frequency of advanced BC in our settings is due to a delay in seeking treatment or a system delay in providing care. The reasons for delay in seeking treatment could be the low educational level of patients, a lack of awareness about BC and associated healthcare, cultural beliefs, and fear of not being considered desirable by marriage partners after mastectomy. In addition, health care services can also be at a long distance from home for the majority of patients. Finally, in many parts of Africa, Rwanda included, patients first consult traditional healers before going to hospitals. System delay can be due to an insufficient medical infrastructure and trained personnel to handle the disease, as well as to the structure of health system in Rwanda. Many Rwandan patients are covered by public insurance, and they have to first consult a local health center then obtain a transfer to a district hospital before accessing a high-level health care provider at a referral hospital. This

complicated channel results in disease progression and delays in proper diagnosis and treatment [8].

The relatively young age of women with BC and the predominance of advanced tumor stages were reported in several studies in SSA [19, 37–43]. In Western countries the majority of BC patients present when they are still at an early stage, with a mean age greater than 60 years old, more than 10 years older than in African countries [44, 45].

With regard to hormonal receptor and tumor subtype profiles, hormonal receptor negative and TN subtype tumors were the most predominant with 55.1% ER–, 63.8% PR–, 78.3% HER2–, and 37.7% TN tumors. No statistically significant association between hormonal receptors, tumor subtypes, and age of patients was observed ($p > 0.05$). However, a statistically significant association was observed between ER status and tumor stage ($p = 0.0009$). The predominance of hormone receptor negative observed in our study participants may be due to the biological characteristics of patients, or to the poor tissue handling. Tissues that are damaged by poor tissue handling are more likely to have incorrect IHC results and may be more likely to be interpreted as TN. Rugwizangoga et al. [46] showed that in our setting only 23.6% of tissues were processed properly; but the authors did not find any statistical significance between duration of tissue fixation and molecular characteristics of tumors.

Nevertheless, our findings were consistent with other findings reported in African American (AA) and European women with African Descent [47, 48]. Studies in African American women reported that the prevalence of TNBC was 2–3 fold higher compared with White women, ranging from 29.8

Table 4 Comparison of distribution of aggressive molecular subtypes, younger age at diagnosis, and advanced tumor stage of breast cancer from selected Sub-Saharan African studies

Authors (year)	Location	Sample size	Age at diagnostic (mean ± SD)/ Median (Range)	Age ≤ 50 n (%)	Advanced tumors		n (%)/n (%) Triple negative	HER2-enriched n (%)	Reference
					n (%) Stage III	Metastatic n (%) (Stage IV)			
	Eastern/Middle Africa								
Our study	Rwanda	138	49.7 ± 12.9	79 (57.2)	73/128 (57.03)	10/128 (7.8)	52 (37.7)	20 (14.5)	
Sayed et al. (2014)	Kenya, Nairobi	301	48.2 ± 10.9	164 (54.0)	43/99 (43.4)	18/99 (18.2)	60 (20.2)	22 (7.7)	[18]
Rambau et al. (2014)	Tanzania, North-West	52	46 (25–82)	27 (51.9)	40 (76.9)	NA	19 (38.4)	5 (9.6)	[19]
Galukande et al. (2014)	Uganda, Mulago	226	50 ± 13	152 (67.3)	110/169 (65.1)	31/169 (18.3)	76 (34.07)	49 (22.0)	aaa [20]
Luyeye et al. (2015)	Democratic Republic of Congo, Kinshasa	87	47.5 (19–94)	49 (56.3)	65 (74.7)	NA	13 (14.99)	7 (8.05)	[21]
Hadgu et al. (2018)	Ethiopia, Addis Ababa	112	43 ± 14	70 (62.5)	36 (37.0)	4 (4.0)	25 (23)	11 (10.0)	[22]
Eber-Schulz et al. (2018)	Ethiopia, Western	107	43 ± 14.3	80 (74.8)	59 (57.3)	7 (6.5)	26 (24.8)	23 (20.9)	[23]
Jiagge et al. (2016)	Ethiopia, Addis Ababa	93	43 (23–76)	NA	44 (53.6)	NA	13 (15)	12 (12.6)	[24]
Sengal et al. (2017)	Erythrea and Sudan	678	55.5 ± 14.3	452 (66.7)	294 (43.5)	NA	232 (34.3)	85 (16.0)	[25]
	Western Africa								
Traoré et al. (2019)	Guinea	58	45 ± 14	32 (55.2)	28 (48.3)	11 (19.0)	15 (25.9)	13 (22.4)	[26]
Ly et al. (2012)	Mali, Bamako	114	48.8 ± 0.53	74 (68.0)	91 (80.0)	49 (43.0)	52 (46.0)	5 (4.0)	[27]
Jiagge et al. (2016)	Ghana, Kumasi	234	49 (24–92)	NA	84 (53.8)	NA	124 (53.2)	27 (11.6)	[24]
Usman et al. (2019)	Nigeria	478	46.3 (24–85)	271 (56.7)	169 (37.6)	NA	55/118 (46.7)	21/118 (17.9)	[28]
Ukah et al. (2017)	Nigeria, South	123	46.9 ± 13	75 (61.06)	66 (53.7)	NA	50 (40.7)	13 (10.6)	[29]
Titloye et al. (2016)	Nigeria	835	48.6 ± 12.4	712 (85.5)	388 (46.5)	NA	396 (47.7)	164 (19.6)	[30]
Huo et al. (2009)	Nigeria and Senegal	378	44.8 ± 11.8	251 (66.0)	168 (44.4)	NA	102 (27.2)	57 (15.1)	[31]
	Southern Africa								
McCormack et al. (2013)	South Africa, Soweto	1216	48.1 ± 13.1	472 (38.8)	533 (43.8)	107 (8.9)	246 (20.4)	117 (11.04)	[32]
Miguel et al. (2017)	Angola, Luanda	140	47 (24–84)	NA	91 (65.0)	5 (3.6)	44 (31.4)	22 (15.7)	[33]

[24] to 46.6% [49]. For example, Carey et al. [50] in Carolina Breast Cancer Study found the predominance of TN tumor in AA women in comparison to White American women (39% vs 16%). Clarke et al. [51] and Lund et al. [49] reported a higher rate of TN cases in black women compared with white women in each age group [51]. Keenan et al. [52] made similar conclusions after analyzing TN cases from The Cancer Genome Atlas (TCGA) and showed that TN and basal tumors

were more prevalent in AA in comparison to white women (33.3% vs. 14.19% TN and 34.8% vs. 16.1 basal). In UK, Bowen et al. amazed data from UK-based BC cohort and found that 22% of black women had TN tumors in comparison to 15% of white women [53].

Inversely, in Western countries, BC is shown to be hormone receptor positive in 70–80% and only 10–20% of tumors are found to be TN [54–56].

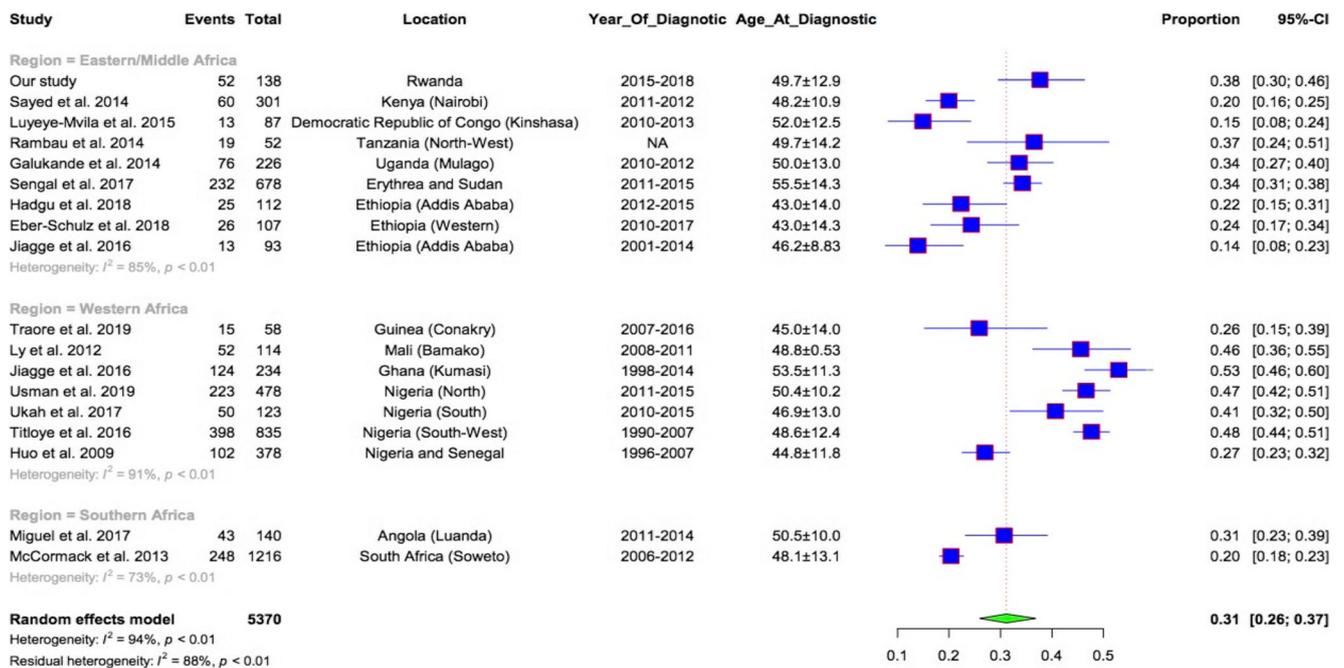


Fig. 1 Comparison of proportions of triple negative breast tumors reported in SSA studies

To compare our results, we have reviewed the studies conducted in SSA countries evaluating the age at diagnosis, stage at presentation, and tumor subtypes (Table 4).

Studies conducted in Eastern African countries such as Uganda [20], Tanzania [19], Erythrea, and Sudan [25], and Ethiopia [22, 24] reported a predominance of hormone receptor negative with proportions of TNBC slightly higher than in the South of Africa. In this region where Rwanda is located, the proportions of TN were compared with our results and vary from 30 to 39%. Nevertheless, other studies from Kenya [18] and Democratic Republic of Congo [21] reported the predominance of hormone receptor positive with a low proportion of TN tumors (20% and 15%, respectively).

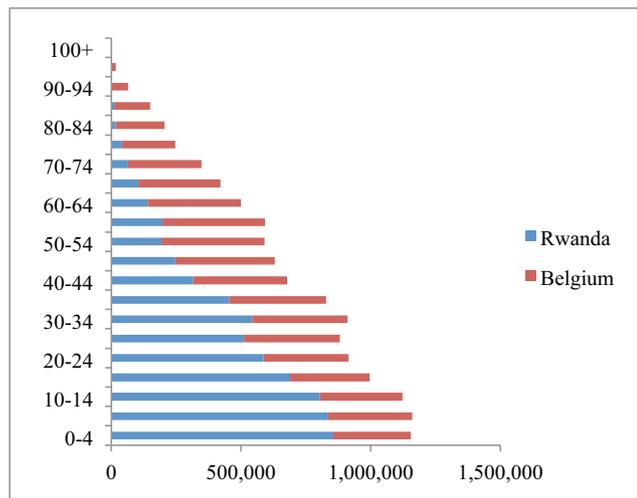


Fig. 2 Comparison of distribution of female population between Rwanda and Belgium in relation to age

In the Western region of Africa, the highest proportions of hormones receptor negatives and TNBC tumors were reported. A study conducted in six geographic areas of Nigeria and Senegal showed that ER- negative tumors were the most predominant comprising 76% of cases. In Mali, Ly et al. found a high frequency of TN tumors with 46% [27]. In Nigeria, the frequency of TN tumors was 40–48% [54–56]. In Kumasi, Ghana, the same high proportions of TN (53.2% and 53.8%) were reported [22, 24]. However, studies conducted in Southern African countries like South Africa, Namibia, and Angola [18, 22, 25] found that the majority of tumors were ER positive. TN tumors represented 20–32% with a high frequency in black women as compared with white patients. Figure 1 shows that the overall proportion of triple negative in Africa was 31% (95% CI = 26–37%), which is superior to the proportions of TNBC reported in Western countries (10–20%). The distribution of hormone receptor negative and TN subtype increases from South to North and from East/Middle to Western Africa with a slight variability within each region. This may be partly confirmed by the study conducted by Jiagge et al., where ER negative and TNBC in Ghana (West Africa) were higher with 71.1% and 53.8%, respectively, than in Ethiopia (East Africa) with 28.6 ER negative and 15% of TNBC [24]. In our study, the proportions of TNBC (37.7%) observed from Rwanda (Middle Africa) was higher than observations made in Ethiopia, but less than the TN cases observed in Ghana, suggesting that Middle Africa may be an intermediate between East and Western Africa. The differences of tumor subtypes in SSA could be linked to environmental or genetic factors related to geographical location but will have to be confirmed in large Pan-African studies with a unique methodology.

A study conducted by Sung et al. confirmed the variability of prevalence of TN breast tumors in black women according to geographical origin. Sung et al. evaluated breast cancer subtypes among Black American women in the USA from different birthplaces and found that the proportion of TNBC was higher in US born followed by Western-Africa born followed by Caribbean-born and then Eastern-African black born women [57]. Our findings add more evidence to the suggestions made by Sung et al. that it is important to consider geographical origin in studies characterizing BC in women with African descent.

This is the first study that provides data on hormone profiles and tumor subtypes of BC in Rwanda compared with age at diagnosis and tumor stages. One of the limitations of our study was the lack of available data on hormonal receptor status, age at diagnosis, and/or stage at presentation. Therefore, a high number of patients were excluded from the analysis because of missing data on these key variables considered in our study. In addition, information about patients' treatment and mortality was often missing. This would have allowed us to calculate the responses to treatment and survival rate after diagnosis according to tumor subtypes. Nevertheless, our results provide important information about tumor characteristics of BC in Rwanda and in Africa. Future large studies investigating BC in SSA are required.

Conclusion

The present study showed that in Rwanda, BC is characterized by the predominance of hormone negative and triple negative tumor subtypes, with a young age at diagnosis and a high frequency of advanced tumors. However, no statistically significant association of tumor subtypes, age, and tumor stage was observed. Larger prospective studies of BC series are necessary to confirm the present results and to provide an accurate portrait of the disease presentation and progression in various African regions for a better disease management.

Indeed, our findings and results from other SSA studies suggest that there is a geographic variability in the distribution of hormonal receptor and tumor subtypes. Further confirmatory studies could examine genetics and environmental factors that may play a role in the differences of tumor characteristics in SSA populations.

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Author's Contribution All authors contributed to the study conception and design. Material and methods, data collection, and analysis were performed by Jeanne P. Uyisenga, Yvan Butera, Ahmed Debit, Claire Josse, Costa C. Ainhwa, Emile Kalinganire, Aimée P. Cyuzuzo Nicole, Umurungi, Yves Kalinjabo, and Simeon Uwimana. The first draft of the

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Data Availability The datasets used generated during and /or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study were in accordance of the ethical standards of the Institutional Review Board of the College of Medicine and Health Sciences at University of Rwanda (No. 209/CMHS IRB/2017) and with the 1964 Helsinki declaration of and its later amendments or comparable ethical standards.

Consent to Participate This research was a retrospective descriptive study, which used patient electronic medical record files to get clinical information. The approval was obtained from the central Institutional Review Board of College of Medicine and Health Sciences of the University of Rwanda, which ensured that the data were handled anonymously and in a strict confidential way.

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