Diagnostic Pathology: Open Access
ISSN: 2476-2024

Research Article Open Access

Characterization of Breast Cancer Subtypes and Associated Clinico-Pathological Outcomes in Rwandan Women with Breast Cancer: A Retrospective Study

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Abstract

Background: Breast cancer subtypes were designed not only to guide decision regarding targeted therapy but also to evaluate the prognosis of the disease together with other pathological factors. This study aimed at determining the distribution of breast cancer molecular subtypes, and their association with clinical and pathological outcomes in Rwandan women diagnosed with breast cancer.

Methodology: This is a retrospective study designed to document clinical and pathological data from breast cancer patients in Rwanda from January 2014 to June 2021. Records of patients with confirmed breast cancer were documented from 4 cancer centers.

Results: Histological grade I, II and III were 10.2%, 37.7% and 39.1%, respectively. The invasive ductal and lobular carcinoma were 89%, and 3.1%, respectively, while the mixed ductal and lobular was 1.4%. The most represented pathology stages were pT3 (19.1%), pT4 (18.9%) and pT2 (17.3%). Besides, the Lymphovascular invasion was present at 6.7%. Many patients expressed estrogen receptor (53.6%), followed by progesterone receptor (34.8%) and HER2 (34.2%). Luminal B was the most prevalent (29.3%), followed by TNBC (28.1%), luminal A (25.7%) and HER2-enriched (16.9%). These subtypes were found significantly different with regards tumour side ($p=0.019$), histological grades ($p=0.025$) and pathological stages ($p<0.001$).

Conclusion: This study demonstrated the predominance of luminal B and TNBC in breast cancer patients. Significant correlations between breast cancer subtypes, histological grades, and pathological stages supported the significance of these variables as prognostic factors in women breast cancer patients. To complete these findings, it will be necessary to evaluate the survival rates for various subtypes of breast cancer in conjunction with BI-RADs classification as well as the latest scientific evidence therapies being applied to the treatment of breast cancer patients.

Keywords: Breast cancer; Hormonal receptors; Human Epidermal Growth Factor Receptor 2(HER2); Breast cancer subtypes; Clinical histopathology

Introduction

Breast cancer survival rate in less developed countries including African countries is generally low where it is estimated at 60% in middle-income countries and 40% low-income countries. This has been attributed to lack of early detection programs and diagnostic and treatment facilities. Differences among breast cancer subtypes and their association with clinic-pathological features have been proven important for prognosis, prediction and treatment guidance. Studies have demonstrated that estrogen receptor positive and progesterone positive (ER+ and/or PR+) is at 55% to 65% of breast tumours respectively [1], among which 75% to 85% are responsive to endocrine treatment. Comparing with the other subgroups, patients having the mentioned tumours are linked with older age, lower grade, smaller

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Received: 11-Aug-2023, Manuscript No. DPO-23-110208; **Editor assigned:** 14-Aug-2023, PreQC No. DPO-23-110208(PQ); **Reviewed:** 28- Aug-2023, QC No. DPO-23-110208; **Revised:** 04-Sep-2023, Manuscript No. DPO-23-110208(R); **Published:** 11-Sep-2023, DOI: 10.4172/2476-2024.8.3.219

Citation: Musanabaganwa C, Ruton H, Ruhangaza D, Nsabimana N, Kayitare E, et al. (2023) Characterization of Breast Cancer Subtypes and Associated Clinico-Pathological Outcomes in Rwandan Women with Breast Cancer: A Retrospective Study. Diagnos Pathol Open 8:219.

tumour size and lower mortality rate [2].

On the other hand, estrogen and progesterone receptor negatives (ER-PR-) comprises 18% to 25% of the tumours, among which around 85% are of higher grade like 3 [3]. The later ones are associated with a higher recurrence rate, lower overall survival and do not respond to endocrine therapy [4]. ER+ PR+ is the most favorable compared to ER-PR- which is the most hostile cancers vis-à-vis tumour size, grade, stage, patient outcome, and response to hormonal therapies [5]. Studies reported that ER positive tumours account for 70% of breast cancer. Moreover, ER positive tumours constitute 65% and 80%, respectively, of patients under and above 50 years [6]. ER positive tumours are mainly well-differentiated, and they result in better outcome than ER-negative. ER-negative tumours are hormone-independent and considered to show aggressive behavior. In addition, ER negative tumours show less chance to respond to endocrine therapy [3]. PR is induced by estrogen and is a favorable prognostic marker. PR positive tumours comprise 65% to 75% breast cancers. ER -PR+ patients benefit from endocrine therapy which would be excluded from such treatment if the decision was based on ER status alone. Nearly 40% ER positive tumours are PR negative [7]. ER+PR- tumours are less responsive to endocrine treatment than ER+PR+ tumours [8]. PR is conventionally used together with ER in breast tumour subtyping classified as follow: ER+PR+, ER+PR, ER-PR+, ER-PR- [9] . ER and PR combination along with other factors such as HER2 expression and individual characteristics improve breast cancer subtypes classification including treatment decision trees guide [10].

Human Epidermal Growth Receptor 2 (HER2) is the most well-known prognostic member of the epidermal growth factor receptor family. Studies revealed that HER2 gene amplification or protein over-expression is associated with poor prediction and good clinical outcome when using systemic chemotherapy treatment. Triple Negative Phenotypic Tumours (TNP) frequently demonstrate clinically poor prognosis and difficult to treat. The protein over-expression and gene amplification of HER2 happen in 13% to 20% of invasive ductal breast cancer, which mostly appear to account approximately 55% as ER-PR-[5-7].The prognostic value of HER2 positivity is higher in node-positive than node-negative patients. HER2 is considered as an essential target of a diversity of novel cancer therapies. It is reported that triple positive (ER+PR+HER2+) tumours have a promising prognosis regardless of the achievement of a pathological complete response. On the other hand patients with ER-PR-HER2+ and ER-PR-HER2- tumours demonstrate the worst prognosis [8,11].

In Rwanda, a study done on the effects of fixation on hormone receptor of primary breast cancer and the receptor proportion at one referral, city-based hospital setting showed that Molecular types were luminal A (47.8%), luminal B (15.2%), HER2+ (8.7%) and triple negative (28.3%) [12]. Recently, Uyisenga et al. reported an association between histological characteristics and ages and tumour stages showing dominance of TNBC regardless their ages and tumour stages [13]. So far, there is no study conducted in Rwanda to assess the association between all available clinico-pathological characteristics and breast cancer subtypes. This study aimed to investigate the distribution of molecular subtypes and their association with clinic-pathological prognostic factors in Rwandan women with breast cancer.

Materials and Methods

Study design and population

A retrospective study was conducted at Butaro District Hospital (BDH) Rwanda Military Hospital (RMH), King Faisal Hospital (KFH), and University teaching hospital of Kigali (CHUK), where patients' charts reviewed from January 2014 to June 2021. Clinical and pathological data of women diagnosed with breast cancer were extracted from hospital patients' records. Women with tissue confirmed breast cancer (N=491) from 2014 to 2021 were included in this study.

Data collection techniques

Demographic, pathological, and clinical information were retrieved from patient files. These included age, menopausal status, tumour location in quadrants or specimen laterality (left breast, right breast), tumour characteristics (histology types, grade and size, ER/PR and Her2 expression, tumor stage at diagnosis, resection margin status, lymphovascular invasion. The date of incidence was defined as the first consultation at the hospital for breast cancer followed by a confirmatory diagnosis. This is based on universally accepted cancer registry coding standards [14].

Sample size and sampling techniques

The total number of women with confirmed breast cancer from 2014 until 2021 was considered as the study sample size for retrospective phase and data documents for all breast cancer patients diagnosed in 4 cancer centers. A subset of 491 patients was only considered for having complete information with immunohistochemistry for ER, PR and HER2.

Data analysis

A Statistical Package for the Social Sciences (PSS version 25) was used to quantify and clean raw data received from enumerators. The proportion of ER/PR/HER2 in patients diagnosed with breast cancer was estimated based on 95% confidence intervals. Association between clinical characteristics of breast cancer study participants and tumor features (tumor size, lymph node, histology grade, HR (estrogen receptor and progesterone receptor status, Human Epidermal Growth Factor Receptor 2 (HER2) status) was assessed using chi-square test.

Results

Epidemiological demographic characteristics

Data of 491 women patients with breast cancer have been documented in the four cancer centers in Rwanda. The mean age of participants was 50 years old (sd. ± 12.6) and the most represented group was 41-60 years of age (53.8%) followed by women at age less than 41years (26.7%). who are considered as Early-Onset Breast Cancer (EOBC). The distribution of participants across menopausal status such as pre-menopause, menopause and post-menopause was approximately equal (36.7%, 30.5% and 32.8%t respectively). Among all participants, 70.7% were from BDH and less than 30% of remaining were managed by King Faisal Hospital (12.4%), CHUK (10.2%), and Rwanda Military Hospital (6.7%). Almost all participants were from Rwanda (88.6%). More than half of participants (58.7%) covered their treatment expenses with Community Based Health Insurance (CBHI) and FARG, 12.4% were private without insurance, RAMA was used by 4.1% of patients and other insurance companies took 11.2% of patients (Table 1).

Clinical and pathological characteristics

Clinico-pathological features of breast cancer among patients: Among diagnosed breast cancer, 89% of were histologically invasive ductal carcinoma, while 3.1% were lobular carcinoma. A very low proportion of breast cancer was mixed ductal and lobular carcinoma (1.1%), whereas another non-classified histology was estimated at 6.5%. Among women diagnosed with breast cancer in this study, 39.1% were at histology grade III, 37.7% at grades II and 10.2% were at grade I, while 13% were not graded. Additionally, 18.9% of patients were at

pathology stage IV (pT4), 19.1% at pT3, 17.3% at pT2, and 5.5% were at pT1. However, staging of 39.1% of women diagnosed with breast cancer in this study was not determined. Among women diagnosed with breast cancer, 34.8% had negative Lymphovascular invasion, and 6.7% had positive Lymphovascular invasion. Regarding comorbidities, 8.4% were having hypertension, and 3.1% having HIV (Table 2).

Hormonal receptor status and HER2 status

Women diagnosed with breast cancer with receptor for either hormone were reported. For ER, 53.6% were ER+ while 46.4% were ER-. Regarding, PR 34.8% were PR+ while PR 65.2% were PR-. The proportion of positive HER2 was 34.2% whereas 59.1% were HER2- and 6.7% were equivocal (Table 3).

Association between clinico-pathological characteristics and molecular breast cancer subtypes

The molecular breast cancer subtypes as approximated with immunohistochemistry were produced using Immunohistochemical (IHC) tests (expression of ER, PR and/or HER2) [15,16]. Four subtypes were considered through a combination of these 3 receptors, such as Luminal A, Luminal B, HER2-enriched and Triple Negative Breast Cancer (TNBC) (Table 4).

Out of 491 participants, the most prevalent subtype was luminal B 29.3%), followed by TNBC (28.1%), luminal A (25.7%), and less prevalent was HER2-enriched (16.9%). These molecular subtypes were compared with different clinical and pathological features of breast cancer, including ages, menopausal status, histological grades, histological types, and different therapy. Findings showed that the 4 subtypes differed significantly with regards to tumour side (p=0.019) histology grades (p=0.025) and pathology stages (p<0.001), whereas other characteristics such ages, menopausal status, histology types, and lymphovascular invasion were not statistically significant difference along the 4 subtypes (Table 5).

Subjects characteristics	Frequency	Percentage (%)	Percentage (%)
Age at diagnosis	**50 (mean)**	**12.6 (sd.)**	
Age group			
≤ 40	131	26.7	26.7
41-60	264	53.8	80.4
61-80	90	18.3	98.8
≥ 81	6	1.2	100
Hospital			
RMH	33	6.7	6.7
KFH	61	12.4	19.1
CHUK	50	10.2	29.3
BDH	347	70.7	100
Menopausal status			
Pre-menopause	180	36.7	36.7
Menopause	150	30.5	67.2
Post-menopause	161	32.8	100
Health insurance			
CBHI	289	58.9	58.9
RAMA	20	4.1	62.9
Private	61	12.4	75.4
Others	55	11.2	86.6
Unknown	66	13.4	100
Nationality			
Rwanda	435	88.6	88.6
Foreigner	56	11.4	100
Total	491	100	-

Note: RMH: Rwanda Military Hospital; KFH:King Faisal Hospital; CHUK:Centre Hospitalier Universitaire De Kigal; BDH: Bungoma District Hospital; CBHI: Community Based Health Insurance; RAMA: The Rwandaise D'assurance Maladie

Table 1: Demographic characteristics of participants (n=491).

Subjects' characteristics	Frequency	Percentage
Tumour side		
Left	239	48.7
Right	238	48.5
Bilateral	5	1
Unspecified	9	1.8
Histologic type		
Ductal carcinoma	437	89
Lobular carcinoma	15	3.1
Mixed ductal and lobular	7	1.4
Others	32	6.5

Histologic grade		
I	50	10.2
II	185	37.7
III	192	39.1
Not reported	64	13
Pathology stage		
pT1	27	5.5
pT2	85	17.3
pT3	94	19.1
pT4	93	18.9
Not reported	192	39.1
Lymphovascular invasion		
Absent	171	34.8
Present	33	6.7
Not reported	287	58.5
Comorbidities		
Hypertension	41	8.4
HIV	15	3.1
Not reported	435	88.6

Table 2: Clinicopathological characteristics of participants (n=491).

Receptor		Frequency	Percentage	p-value
Estrogen receptor	Negative	228	46.4	0.114
	Positive	263	53.6	
Progsterone receptor	Negative	320	65.2	< 0.001
	Positive	171	34.8	
HER-2/neu	Negative	290	59.1	< 0.001
	Positive	168	34.2	
	Equivocal	33	6.7	

Table 3: ER, PR and HER2 status of the study patients (n=491).

Receptor	Luminal A	Luminal B		HER2-enriched	TNBC
		HER2 positive	HER2 negative		
Estrogen	+	+	+	-	-
Progesterone	+	-	+	-	-
HER2/neu	-	-	+	+	-
Note: (+): Positive; (-):Negative					

Table 4: Molecular breast cancer subtypes according to immunohistochemical result [15].

Characteristics			Luminal A	Luminal B	HER2-enriched	TNBC	p. value
Age groups	≤ 40	131	39 (29.8)	39 (29.8)	20 (15.2)	33 (25.2)	0.732
	41-60	264	58 (22.0)	78 (29.5)	47 (17.8)	81 (30.7)	
	61-80	90	27 (30.0)	25 (27.8)	16 (17.8)	22 (24.4)	
	≥ 81	6	2 (33.3)	2 (33.3)	0 (0.0)	2 (33.3)	
Menopausal status	Pre-menopause	180	49 (27.2)	51 (28.3)	34 (18.9)	46 (25.6)	0.733
	Menopause	150	34 (22.7)	49 (32.7)	21 (14.0)	46 (30.7)	
	Post-menopause	161	43 (26.7)	44 (27.3)	28 (17.4)	46 (28.6)	
Tumour laterality	Left	239	59 (24.7)	70 (29.3)	49 (20.5)	61 (25.5)	0.019
	Right	238	65 (27.3)	72 (30.3)	31 (13.0)	70 (29.4)	
	Bilateral	5	1 (20.0)	2 (40.0)	2 (40.0)	0 (0.0)	
	Unspecified	9	1 (11.1)	0 (0.0)	1 (11.1)	7 (77.8)	
Histologic type	Ductal carcinoma	437	110 (25.2)	133 (30.4)	72 (16.5)	122 (27.9)	0.217
	Lobular carcinoma	15	3 (20.0)	6 (40.0)	3 (20.0)	3 (20.0)	
	Both	7	1 (14.3)	3 (42.9)	2 (28.6)	1 (14.3)	

Histologic grade	I	50	11 (22.0)	16 (32.0)	6 (12.0)	17 (34.0)	0.025
	II	185	47 (25.4)	60 (32.4)	31 (16.8)	47 (25.4)	
	III	192	41 (21.4)	56 (29.2)	41 (21.4)	54 (28.1)	
Pathology stage	pT1	27	6 (22.2)	5 (18.5)	0 (0.0)	16 (59.3)	<0.001
	pT2	85	19 (22.4)	2 (2.4)	25 (29.4)	39 (45.9)	
	pT3	94	23 (24.5)	17 (18.1)	51 (54.3)	3 (3.2)	
	pT4	93	31 (33.3)	60 (64.5)	0 (0.0)	2 (2.2)	
Lymphovascular invasion	Absent	171	39 (22.8)	54 (31.6)	32 (18.7)	46	0.245
	Present	33	9 (27.3)	12 (36.4)	8 (24.2)	4 (12.1)	
	Not reported	287	78 (27.2)	78 (27.2)	43 (15.0)	88 (30.7)	

Table 5: Association of clinico-pathological characteristics and breast cancer molecular subtypes.

Discussion

The breast cancer molecular subtypes were designed to decide about precision therapy and to look at any improvement in breast cancer management [17]. This study aimed to assess the prevalence of breast cancer subtypes among women diagnosed with breast cancer who got tested for the three immunohistochemistry biomarkers and their association with different clinical and pathological outcomes. Findings showed a proportion of the luminal B subtype (29.3%), which was closely equal to the basal-like or TNBC subtype (28.1%). A study conducted in Kenya, relating breast cancer risk factors to molecular subtypes, reported TNBC with 18.6% whereas luminal B was 35.8% [18]. This is not similar to what have been recently reported in previous studies carried out in Rwanda, which ranked TNBC as the most prevalent subtype (37.7%) [13]. These results also were in contrast to those reported in a study carried out in Indonesian women when assessing the association between molecular subtypes and histological grades and lymph node metastasis showed that luminal A was the most prevalent subtype [19]. However, the same study is in accordance with the current study for TNBC which also ranked second (25.5%). Different reasons may explain these discrepancies: First of all, some of those subtypes overlapped, especially in luminal groups. This classification used in this study was also reported in 2014 by Yersal and Barutca in their review focused on prognostic and predictive factors regarding different biological subtypes of breast cancer [15]. These authors included triple positive in luminal B subtypes, a reason why this study ranked luminal B the most prevalent subtype. This classification is supported by a retrospective study conducted to assess the Triple Positive Breast Cancer (TPBC), despite the fact that the patient with these characteristics responded well to trastuzumab, a targeted therapy actually used to manage people with breast cancer with HER2 overexpression [20]. The same authors reported a lower Pathologic Complete Response (pCR) TPBC than in HER2-enriched patients. The way to classify luminal groups were not really accurate in this study, considering that the expression of Ki67 index was not recorded. Accordingly, previous studies classified both luminal groups A and B focusing on the fact that Ki67 index is lowly express or highly expressed (<14% or >14%; <20% or >20%) [19,21,22]. Moreover, recently, Bliss et al. showed the importance of Ki67 in treatment decision or in clinical trials when assessing a new treatment [23]. In this study, the classification was based only on the expression of HRs either both (luminal A and B) or 1 especially for luminal B and the absence of HER2 (luminal A and B) or presence of HER2 (luminal B) [15,19,21,22,24,25]. In this study, the EOBC was 26.7% of included patients. This proportion is closely similar to that reported in Ghana (20.2%) in a comparative study of clinicopathologic characteristics between EOBC and Late-Onset Breast Cancer (LOBC) [26]. Contrary, in developed countries, the proportion of EOBC is very low, ranging between 5 and 7 [27]. This may be due a substantially young population and no common practice of routine screening in developing countries. Accordingly, a study conducted in the United States reported 5.6% of EOBC [28]. Additionally, most of patients in this group (59.6%) were more prevalent in luminal subtypes A and B (distributed equally) and HER2-enriched was the less presented subtype (15.2%). Akakpo et al. Reported luminal B as the most represented (28.5%), followed by TNBC (24.3%), whereas HER2-enriched also was the less prevalent [26].

Regarding the association of clinicopathological characteristics and breast cancer molecular subtypes, this study showed a statistically significant difference among breast cancer subtypes across histological grades. This is consistent with previous epidemiological studies that have shown significant difference of the 4 subtypes regarding histological grades of Eastern Moroccan population [22] and Indonesians women [19]. Onitilo et al. reported a significant difference of breast cancer subtypes by histological grades in their study when comparing clinicopathologic features and survival across 4 breast cancer subtypes [11]. Histological grades have been demonstrated as an independent prognostic factor in ER+ breast cancer [29]. The findings of this study showed that grade III was more prevalent, especially in subgroups with ER- status such as TNBC and HER2-enriched subtypes. This may help explain the poor prognosis in ER- breast cancer. Accordingly, Wirapati et al. demonstrated a bad outcome of ER- status [30]. Breast cancer subtypes differed significantly across pathological stages, and the highest stage was more prevalent in luminal B followed by luminal A subtypes. Majority of breast cancer were at pathological stages pT3 and pT4 (31.4 and 31.1, respectively) and with many cases in luminal B. These findings were slightly similar to those reported in a retrospective study conducted in Kenya to assess the clinical characteristics of women with metastatic breast cancer between 2012 to 2018 showed pT3 with 36% and pT4 with 32% of the included subjects [31]. Another retrospective study carried out in Morocco on confirmed TNBC females between 2007 to 2008 reported pT4 as the lowest represented stage (4%) whereas pT3 was at 28% [32]. A lower proportion of stage IV (6.8%) was also reported in study conducted in Iraq to correlate clinical features and survival rates in females with breast cancer with molecular subtypes where stage IIB was the commonest stage [16]. There was no significant difference in subtypes across the age groups, menopausal status, histologic types, and lymphovascular invasion. A study conducted in Morocco showed the opposite by demonstrating a significance difference across the menopausal status, age mean and histologic types [22].

Conclusion

This study showed the dominance of luminal B and TNBC in women diagnosed with breast cancer in Rwanda. This was accompanied with the highest level of histologic grade in both luminal B and TNBC, and pathologic stage in luminal B. ER was the commonest positive marker (53.6%) while the positivity of other markers (PR and HER2) was slightly equal (34.8% and 34.2%). A significant association between breast cancer subtypes and histological grades and pathological stages demonstrated their importance as prognostic factors in women patient with breast cancer. These results need to be completed by the assessment of survival rates across different breast cancer subtypes, comorbidities and the treatment under use in the management of women with breast cancer.

Ethical Consideration

Ethical approval of the study was obtained from the National Health Research committee and National Ethics Committee (no.124/RNEC/2023). The retrospective phase was conducted without individual informed consent as it relied on retrospective data which was put together as part of routine care of patients. Confidentiality was enhanced using codes instead of names.

Acknowledgment

The authors wish to thank the personnel of the Pathology Departments and leadership of the participating Hospitals. Furthermore, we thank the National Council for Science and Technology for funding this study and Rwanda Biomedical Centre for the great support.

Ethical Approval

The approvals to carry out this study have been obtained from the National Health Research Committee and National Ethics Committee. These approvals were used to obtain permission to conduct the study at each of the participating Hospitals.

Consent to Participate

Not applicable

Consent to Publish

Not applicable.

Competing Interests

No competing interests are disclosed by the authors.

Author's Contributions

C.M, J.B.M and L.M contributed to the project conceptualization, implementation and manuscript development. D.R, P.C.M, N.N, E.K, T.Z.M, M.S, F.N, M.E, J.N, E.H, A.N, F.M, A.U, J.G, L.N and C.M.M contributed to the implementation, analysis, preparation and review of the manuscript.

Funding

This study has been sponsored by National Council for Science and Technology (Grant number NCST-ERG-BATCH1/P01/2019).

Availability of Data and Materials

The raw data used in this study can be obtained from the corresponding author upon reasonable request.

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