# Breast Cancer Molecular Subtypes in Relation to Age, Stage and Grade among Sudanese Women Patients in Khartoum specialized oncology center (2013 – 2017)


## Abstract

**Background: -**

There is a lack of data regarding molecular subtypes of breast cancer among Sudanese female patients. Moreover to the best of our knowledge no study had correlated the molecular subtypes with age, stage and grade till date. This study aimed to determine breast cancer molecular subtypes among Sudanese women in relation to age, clinical stage and grade and to compare the findings to other related researches.

**Methods:** Retrospective Study of (255) Sudanese female patients diagnosed with breast cancer from September 2013 to August 2017 in Khartoum Specialized Oncology Center, an information sheet was used to collect data from patients medical records.

**Results:** The results demonstrated that, the most commonly detected molecular subtype was luminal B (34.9%), followed by triple negative and HER-2 enriched, (31.4%) and (19.2%) respectively. The least common subtype was luminal A, (14. 5%). Additionally, over half of the patients (54.4%) were classified as grade 3 and (22.4%) were diagnosed as stage IIIb.

**Conclusion:** The main conclusion that can be drawn is that, luminal B was the most commonly diagnosed subtype and it was more common in younger age group in comparison to luminal A. The majority of the patients in the study were grade 3 and stage IIIb and were diagnosed between the age of 41 and 50. Moreover, triple negative subtype was high among Sudanese women and was associated with advance grade breast cancer.



**Key words: Subtypes, Breast Cancer, Sudanese, Women**

## 1. Introduction:

Breast cancer is the top cancer in females leading to 327,000 deaths annually [1, 2]. In 2018, WHO reported nearly 2.1 million newly diagnosed female with breast cancer [3]. The global cancer burden of breast cancer is 11.6% [4]. According to the latest data of Globocan 2018, breast cancer ranked the most frequent cancer among women in Sudan and a total of 5,677 (36.69%) Sudanese women were newly diagnosed with breast cancer [5].

Several clinical and pathological parameters are used to classify the breast cancer subtypes, namely; lymph node (LN) status, tumor size, tumor grade, age, menopausal status, clinical and pathological stage, histological type as well as estrogen (ER), progesterone (PR) and HER-2 receptors [6]. Detecting the molecular subtype of breast cancer is a recent and advance technique for early detection and evaluation of the prognosis and management of breast cancer [7]. Thus, management options in Sudan are adapted according to breast cancer molecular subtype. The treatment guidelines in Sudan are based on the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology(ESMO) guidelines which includes; screening, diagnosing, staging, management of local/loco- regional disease, endocrine treatment in pre- and post-menopausal patients, chemotherapy and HER2-directed therapy [8, 9]. Undoubtedly molecular subtypes could provide promising prognostic and predictive information and may help identify new therapeutic targets. However, it is important to understand their limitations and to evaluate their role in improving breast cancer prognosis beyond the traditional expected outcomes in a practical and cost-effective manner [10].

Breast cancer is divided into four major molecular subtypes; the most frequent type is luminal A which is present in 50-60% of breast cancer patients and has the best prognosis rates. The second subtype, luminal B is characterized by higher histological grade and is found in 15-20% of patients [11]. The third subtype triple negative breast cancer (TNBC) which varies according to patient race and ethnicity. Furthermore, it impacts patient's survival rates and may affects management options [12]. The fourth molecular subtype, HER2-enriched (previously the HER2+/ER- subtype) is characterized by aggressive behavior [13]. There is a variation in the prevalence of molecular subtypes worldwide. Luminal A tumors were the most common tumors among some Middle East countries, namely; Saudi Arabia [14], Jordon [15] and Egypt [16] and in a number of western countries; Italy [17], Germany [18] and Atlanta (America) [19].

Regarding Asian countries, studies revealed that luminal A was high among Iranian patients [20], while Luminal B was more commonly found in Japanese [21] and Pakistani patients [22]. Studies in African countries unveiled that ; in Morocco (North Africa), Luminal B was the most common subtype [23], while triple negative had high prevalence rates in Nigeria (West Africa) [24], Uganda (sub-Saharan Africa) [25], Sudan and Eretria (North East and East Africa) [26]. Regarding race, TNBC was found to be the most prevalent subtype in African-American women [27]. Another study conducted to compare molecular subtypes between Sudanese and German women showed that triple-negative subtype was more frequent in Sudanese than German women [28].

Few studies have investigated breast cancer molecular subtypes in Sudan. Furthermore, there is no research relating molecular subtypes to age, stage and grade of breast cancer to date. Thus, in our research we tried to classify patients according to breast cancer molecular subtypes.

The aim of this study is to determine breast cancer molecular subtype among Sudanese women in relation to age, clinical stage and grade and to compare the results to other related researches.

## 2. Materials and Methods

### 2.1Study design and setting

This is a retrospective study of histologically confirmed Sudanese women with breast at Khartoum Specialized Oncology center, in the period from September 2013 to August 2017. Khartoum Specialized Oncology center is a specialized tertiary hospital that offers chemotherapy and radiotherapy for cancer patients, located in Khartoum State, Capital of Sudan. Entitled patients are referred from all over Sudan and hence, this study's sample is therefore representative of the Sudanese population.

### 2.2 Sampling

255 medical records of histologically confirmed breast cancer patients were included in the study.

### 2.3 Data collection tools

An information sheet has been used for data collection from patient's medical records.

The data retrieved included the following:-

-Patients age when diagnosed was distributed into two groups; younger age group (50 years or less) and older age group (above 50 years).

-Molecular subtypes which were identified by Immunohistochemical (IHC) markers (ER/PR/HER2). Four subtypes were defined, namely; luminal A, luminal b, triple negative and HER-2 enriched.

-Breast cancer grades (I, II and III) were detected using Nottingham Bloom-Richardson grading system [29].

-The Clinical stage of the disease was estimated from the clinical examination and was classified according to American Joint Committee (AJC) and TNM classification [30].

**2.4 Statistical analysis**

Data was entered and analyzed using the Statistical Package for the Social Sciences (version 21.0). Chi-square Test was used to evaluate the correlation between molecular subtypes and age, stage and grade were used. The results were considered significant when p (degree of significance) was less than 0.05.

**3. Results:**

A total of 255 records of female patients diagnosed with breast cancer were enrolled in the study. The mean patient's age at diagnosis was 48.8 ± 11.3 years. The majority of the patients (78.2%) were diagnosed with breast cancer before the age of 60. However, only (20.8%) of the cases were diagnosed above the age of 60 (Table 1).

The most commonly detected molecular subtype was luminal B (34.9%), followed by triple negative and HER-2 enriched, (31.4%) and (19.2%), respectively. The least common subtype was luminal A (14.5%) (Fig.2). The vast majority of patients (22.4%) were stage IIIb, followed by stage IIa and IIb (21.1% ). Furthermore, (15.7%), (8.6%) and (6.7%) of the cases were diagnosed as stage IIIa, IV and I, respectively. A small minority, (4.3%) were diagnosed as stage IIIc (Table 2). (54.4%) of the breast cancer patients were diagnosed as grade 3, while (39.2%) were classified grade 2 and only (9.4% )were diagnosed as grade 1 ( Fig. 1).

Out of the (255) cases, 135) cases (52.9%) were in the younger age group (≤ 50) and 120 cases (47.1%) were in the older age group (>50 years). Most cases (34.9%) (n=89) were classified as luminal B subtype, (51.7%) of which were in the younger age group, while (48.3%) (n=43) were in the older age group. Moreover, (31.4%)(n=80) of the cases were classified as triple negative subtype, (56.3%) (n=45) were in the younger age group and (47.7%) were in the older age group. (14.5%) (n=37)of the cases were classified as luminal A subclass, (37.8%) (n=14) were in the younger age group and (62.7%)(n=23) were in the older age group. (19.2%)(n=49) were

classified as HER-2 enriched subclass, (61.2%)(n=30) were in the younger age group and (38.8%) (n=19) were in the older age group. However, the relationship between molecular subtype of breast cancer and patients age at diagnosis was not statistically significant (p=0.162) (Table 3).

Concerning the relationship between molecular subtypes and breast cancer stages, there was no significant association (p=0.257). For patients with HER-2 enriched molecular subtypes, the frequency of stage I, IIa, IIb IIIa, IIIb, IIIc and IV breast cancer, were (2%),(16%),(24.4%),(18.3%),(26.5),(2%),and (10.2%), respectively. Regarding patients with Luminal A molecular subtypes, stage I, IIa, IIb IIIa, IIIb, IIIc and IV breast cancer, were (16%),(32%),(18.9%),(10.8%),(16.2%) and (2.7%), respectively. For patients with Luminal B molecular subtypes, stage I, IIa, IIb IIIa, IIIb, IIIc and IV breast cancer, were (5.6%),(22.4%),(19%),(13.4%),(22.4%),(3.4%) and (13.4%), respectively. For patients with Triple negative molecular subtypes, stage I, IIa, IIb IIIa, IIIb, IIIc and IV breast cancer, were (6.3%),(17.5%)(22.5%),(18.8%),(22.4%),(7.5%)and (5%), respectively (Table 4).

The molecular subtypes were found to be significantly associated with breast cancer grade (p=0.012). Luminal B frequency of grade 1, 2 and 3 was (3.5%), 16.1%) and (15.3%), respectively, while the distribution of Luminal A was (2.4%) for grade 1, (7.8%) for grade 2 and (4.3%) for grade 3. (19.2%) of triple negative were grade 3, (9.8%) were grade 2, while only (2.4%) were grade 1. (12.5%) of Her-2 enriched were grade 3, (5.5%) were grade 2 and (1.2%) were grade1.

## 4: Discussion

In the current study most of the patients were fifty years and above (52.9%), while patients under fifty were (47. 1%). Furthermore, the vast majority of patients were diagnosed with breast cancer between the age of 41 and 50. A similar conclusion was suggested by a study done in Nigeria [24]. According to the present study most of the cases were grade 3(54.4%) and (39.9%) were grade 2. However, a different finding was reported by another study, which revealed that grade 2 breast cancer was more frequent among Sudanese, German and Nigerian female patients, (54.6%), (60%) and (48.57%) respectively, while the percentage of stage 2 cancer in Sudanese women was (41.8%), German women (22%) and (43.57%) for Nigerian women. The latter finding could be partially explained by the late detection of cancer cases in Sudan.

From the results, (22.4%) of female patients were diagnosed as stage IIIb cancer, that may be attributed to lack of awareness, difficult accessibility services and absence of cancer screening programs.

With regard to molecular subtypes, luminal A is found in (50%-60%) of the patients and luminal B in (15%-20%), however, in our group the majority of the cases were classified as luminal B (34.9%) and only (14.5%) were luminal A [11]. A different conclusion was obtained from a study done in middle east countries; where percentage of patients with luminal A subtype in Saudi Arabia, Jordon and Egypt was (58.5%), (60%) and (45%,) respectively [14,15 and 16]. Another similar study conducted in some western countries showed the following; Italy (34%), Germany (44.7%) and Atlanta (51.1%), [17, 18 and 19]. Furthermore, the prevalence of Luminal A subtype was (63.8%) according to an Iranian study [20]. In Japan, Pakistan and Morocco, the percentage of luminal B was (71%), (69%) and (41.8%), respectively [21, 22 and 23] which was higher than our finding. The variation in the results could be linked to the distribution of the different age groups in the studies.

The prevalence of Triple negative breast cancer subtype (TNBC) in Nigerian women was (26.53%) and (21.2%) among African-American women [24, 27], nonetheless, a lower result was attained by our study (31.4%). A slightly comparable value to our finding was found in Ugandan women (34%) and Sudanese- Eritrean women (34.5%), [25, 26 and 28].

In our examination, HER-2 enriched was found in (19.2%) of the breast cancer patients. Nevertheless, a lower finding was cited by another study; the HER-2 enriched frequency among Jordanian women was (12%) [15], Sudanese women (15.7%), German women (6.8%) [28], Sudanese Eritrean women (16%) and (9.2%) among Moroccan women [23, 26].

Luminal B subtype was present in (51.7%) of patients fifty years or less. whereas, the percentage in older patients (i.e. above fifty) was (48.3%). On the other hand, Luminal A subtype prevailed in patients over fifty years old (62.2%), while (37.8. %) was detected in younger ages (fifty years or less). A similar pattern of result was obtained in Jordan, where (72%) of luminal A subtype were above fifty years old [15].

Triple negative and HER-2 enriched subtypes were more prominent in the younger ages (fifty years or less), (56.3%) and (61.2%), respectively. In patients over fifty years old, Triple negative

subtype was detected in (43.7%) of the patients and Her-2 enriched in (38.8%). This was consistent with a study done among Sudanese and German women [28].

(7.8%) of Luminal B breast cancer subtype was stage IIIb, while only (2.4%) of luminal A was stage IIIb, which indicates that, Luminal B is more aggressive than luminal. With regard to cancer grades, the majority of luminal A breast cancer subtype (7.8%) was Grade 2. On the other hand, in Grade 3, luminal B prevailed over luminal A, (15.3%) and (4.3%) respectively. Therefore, it's suggested that, luminal B is associated with higher histological grades [11]. Another finding was that, high frequencies for grade 3 cancer was registered by Triple negative and Her-2 enriched Subtypes (19.2%) and (12.5%), respectively. This implies that Triple negative and Her-2 enriched are associated with aggressive and advanced stages of breast cancer [13].

**5. Conclusion and recommendation: -**

Most of the Sudanese women were diagnosed with breast cancer between (41-50) years old.

Moreover, most of them ~~were~~ presented with grade 3 and stage IIIb breast cancer.

Luminal B was the most prevailed molecular subtypes, followed by Triple negative.

Luminal A was more common among old age groups (over fifty). However, Her-2 enriched and TNBC subtypes were mostly Grade 3 and prevailed among younger Sudanese women.

Detecting the subtype of breast cancer is not only essential for following disease prognosis but also for the management of the breast cancer.

Breast cancer screening programs and self-examination are highly recommended for the early detection of the disease.

The effect of determining molecular subtype on survival rates is an issue for future research to explore.

**Ethical approval**

Ethical approval was obtained from Institutional review board of Omdurman Islamic university-Faculty of Medicine. Data were collected after taking the necessary agreement from Khartoum State Ministry of Health and Khartoum Specialized Oncology Center.

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Table1- Distribution of patients according to the age of breast cancer at diagnosis.

| Age group | Frequency | Percent |
|---|---|---|
| <30 | 7 | 2.7 |
| 30-40 | 54 | 21.2 |
| 41-50 | 74 | 29.0 |
| 51- 60 | 67 | 26.3 |
| >60 | 53 | 20.8 |
| Total | 255 | 100.0 |

Table 2- Distribution of patients according to the stages of breast cancer at diagnosis.

| **Stage** | **N** | **%** |
|---|---|---|
| I | 17 | 6.7 |
| IIa | 54 | 21.2 |
| IIb | 54 | 21.2 |
| IIIa | 40 | 15.7 |
| IIIb | 57 | 22.4 |
| IIIc | 11 | 4.3 |
| IV | 22 | 8.6 |
| **Total** | **255** | **100.0** |

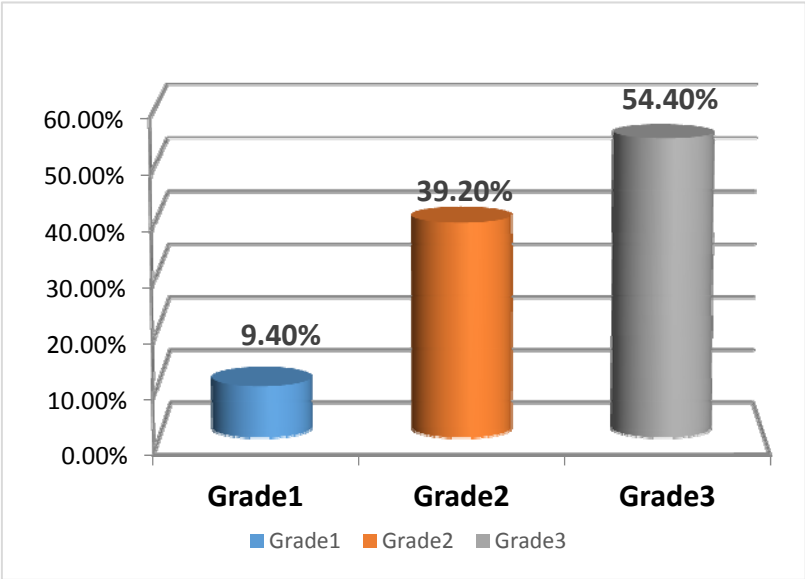


Fig.1- Distribution of patients according to the grade of breast cancer at diagnosis.

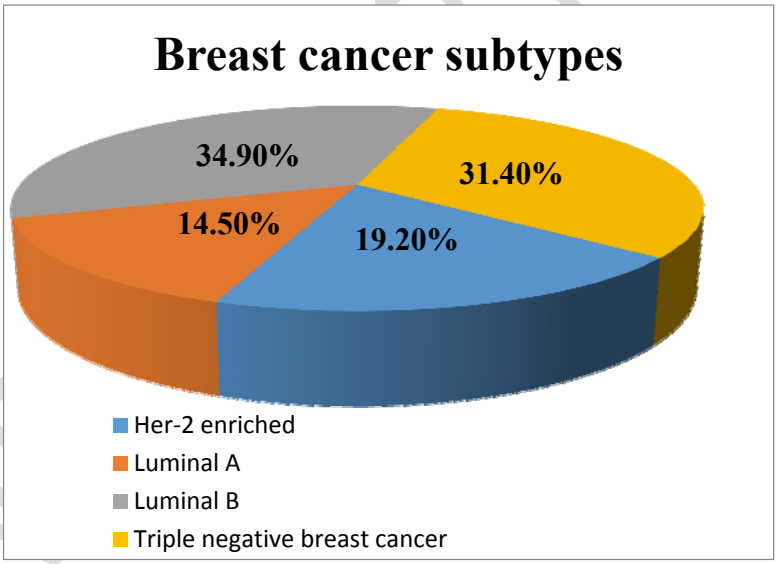


Fig.2- Distribution of patients according to the molecular subtypes of breast cancer at diagnosis.

**Table 3- The relationship between molecular subtype of breast cancer and age at diagnosis.**

| Molecular subtype | Cases ≤50 years N(%) | Cases >50 years N(%) | Total N(%) | P-Value |
|---|---|---|---|---|
| **HER-2 enriched** | 30(61.2) | 19(38.8) | **49(19.2)** | 0.162 |
| **Luminal A** | 14(37.8) | 23(62.7) | **37(14.5)** | |
| **Luminal B** | 46(51.7) | 43(48.3) | **89(34.9)** | |
| **Triple negative** | 45(56.3) | 35(47.7) | **80(31.4)** | |
| **Total** | **135(52.9)** | **120(47.1)** | **255(100)** | |

**Table 4- The relationship between Molecular subtype of breast cancer and stage at diagnosis.**

| | | | Stage | | | | | | | Total | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | I | II a | II b | III a | III b | III c | IV | | |
| **Molecular subtype** | **HER-2 enriched** | **N (%)** | **1 ( 2 )** | **8 (16)** | **12 (24.4 )** | **9 (18.3)** | **13 (26.5)** | **1 (2)** | **5 (10. 2)** | **49 (19.2)** | **0.257** |
| | **Luminal A** | **N (%)** | **6 (16)** | **12 (32)** | **7 (18.9)** | **4 (10.8)** | **6 (16.2)** | **1 (2.7)** | **1 (2.7)** | **37 (14.5)** | |
| | **Luminal B** | **N (%)** | **5 (5.6)** | **20 (22.4)** | **17 (19)** | **12 (13.4)** | **20 (22.4)** | **3 (3.4)** | **12 (13.4)** | **89 (34.9)** | |
| | **Triple negative** | **N (%)** | **5 (6.3)** | **14 (17.5)** | **18 (22.5)** | **15 (18.8)** | **18 (22.5)** | **6 (7.5)** | **4 (5)** | **80 (31.4)** | |
| **Total** | | | **17 (6.7)** | **54 (21.2)** | **54 (21.2)** | **57 (22.4)** | **40 (15.7)** | **11 (4.3)** | **22 (8.6)** | **255 (100)** | |

Table 5: The relationship between Molecular subtypes of breast cancer and histological grades.

| | | | Grade | | | Total | P-Value |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | | |
| Molecular subtype | HER-2enriched | N (%) | 3 (6.1) | 14 (28.6) | 32 (65.3) | 49 (19.2) | 0.012 |
| | Luminal A | N (%) | 6 (16.2) | 20 (54.1) | 11 (29.7) | 37 (14.5) | |
| | Luminal B | N (%) | 9 (10.1) | 41 (46.1) | 39 (43.8) | 89 (34.9) | |
| | Triple negative | N (%) | 6 (7.5 | 25 (31.2) | 49 (61.3) | 80 (31.4) | |
| **Total** | | N (%) | **24 (9.4)** | **100 (39.2)** | **131 (51.4)** | **255 (100)** | |