Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.2025121101-106

Comparison of Breast Cancer Characteristics in Women below and above 50 at Mankweng Hospital in Limpopo Province, South Africa

Mirza Mohamod Zahir Uddin Bhuiyan[a]

[a]*Department of General Surgery, Mankweng Hospital, Faculty of Health Science, University of Limpopo, South Africa*

ARTICLE INFO

Received:
18 October 2024
Revised:
1 December 2024
Accepted:
16 December 2024

Keywords:
Breast cancer, stage, Molecular subtype

ABSTRACT

Background: Breast cancer normally occurs in elderly women, although it also affects young women. In the Limpopo province, South Africa, over 38% of breast cancer occurs in younger women under 50 years of age. The main objectives of the study were to identify the characteristics of breast cancer in women ≥50 years and <50 years and to categorise any differences (histological type, stage, grading and molecular subtype) between these two groups of breast cancer patients.

Methods: This was a cross-sectional design study to analyse the profile of women ≥50 and <50 years with breast cancer who attended Mankweng Breast Oncology Clinic from July 2020 to December 2021. Patient demographics were summarised using descriptive statistics. Categorical variables were expressed as proportions and frequencies. The correlation between categorical variables was assessed using a Chi-square test.

Results: A total of 222 patients participated in the study. The following results were obtained: Age: ≥50 years-old: 131 (59%); <50 years old: 91 (41%). Age: ≥50 years group: Early stage: 49 (37.4%), late stage: 82 (62.6%). Molecular subtype: luminal A: 23 (17.6%); luminal B: 67 (51.2%); HER-2 overexpression: 21 (16%); triple negative: 20 (15.3%). Histological type: invasive ductal carcinoma: 126 (96.2%). Age: <50 years group: Early stage: 31 (34.1%), late stage: 60 (65.9%). Molecular subtype: luminal A: 28 (30.8%); luminal B: 40 (44%); HER-2 overexpression: 5 (5.5%); triple negative: 18 (19.8%). Histological type: invasive ductal carcinoma: 89 (98%).

Conclusion: Majority of patients presented at an advanced stage in both groups. HER2 overexpression molecular subtype was higher in the ≥50-year patient group compared to <50 year old group (P = 0.016). Health education and breast cancer awareness campaigns are essential for all women, young and elderly in the Limpopo province.

INTRODUCTION

Breast cancer is the most frequent cancer in women, accounting for 6.9% of all cancer deaths globally.[1] In 2022, breast cancer represented 11.6% of all cancer cases with an incidence of 2.3 million and the highest incidence rates observed in France, Australia and New Zealand.[1] There is a high prevalence of breast cancer among elderly women particularly in Europe and America. However, in Africa, it occurs predominantly among younger women. [2,3] In Limpopo province, South Africa over 38% of breast cancer cases occurred in younger

***Address for correspondence:**
Mirza Mohamod Zahir Uddin Bhuiyan, MBBS(Ctg), DTH (U. Pretoria), FRCS (Glasgow), M. Med (MEDUNSA), Department of General Surgery, Mankweng Hospital, Faculty of Health Science, University of Limpopo, South Africa
Email: bhuiyanmirza@gmail.com (Mirza Bhuiyan)

women under 50 years of age. [3] In a study in Nigeria, the mean age of women with breast cancer was reported to be 49. [4] Vanderpuye *et al*. mentioned that the age range of women with breast cancer in Kenya and Tanzania was from 35 to 45 years.[5] In Africa, patients with breast cancer tend to present at an advanced stage. A study in Limpopo, South Africa, showed that 76% of female breast cancer patients presented at a late stage. [6] Advanced-stage diagnoses are common in low- and middle-income countries[7] and in many sub-Saharan African countries.[8,9]

Breast cancer is a heterogeneous disorder, involving different patterns of cellular compositions, molecular variations and clinical behaviour.[10] Phenotypically and histologically identical breast tumors can have a wide range of clinical outcomes and responses to therapy due to the presence or absence of hormones receptors and human epithelial growth factor 2 (HER2/neu) and classification methods have been developed based on immunohistochemistry and molecular findings. [11,12] Molecular subtypes of breast cancer are classified based on immunohistochemistry into Luminal A (ER+/PR+/HER2-/lowKi-67); Luminal B (ER+/PR+/HER2-/+/high Ki-67); HER2-overexpression (ER-/PR-/HER2+) and triple negative breast cancers/TNBCs (ER-/PR-/HER2-).[12] Molecular classifications are considered as a useful tool in predicting the response to treatment. These classifications have been used to predict prognosis and guide therapy in patients with breast cancer. [10,11,12] Luminal A breast cancer is hormone-receptor positive (oestrogen-receptor and/or progesterone-receptor positive), HER2 negative, and possess low levels of the protein Ki-67. Luminal A cancers are low-grade, tend to grow slowly and have the best prognosis. Luminal B breast cancer is hormone-receptor positive (oestrogen-receptor and/or progesterone-receptor positive), and either HER2 positive or HER2 negative with high levels of Ki-67. The growth of Luminal B cancers is generally slightly faster than that of luminal A cancers and their prognosis is slightly worse, but both Luminal A and Luminal respond to hormonal therapy. HER2-enriched breast cancer is hormone-receptor negative (oestrogen-receptor and progesterone-receptor negative) and HER2 positive. The growth of HER2-enriched cancers tends to be faster than that of luminal cancers and can have a worse prognosis; nonetheless, they are often successfully treated with targeted therapies aimed at the HER2 protein such as trastuzumab, pertuzumab, lapatinib, neratinib, and T-DM1 or ado-trastuzumab emtansine. Triple-negative/basal-like breast cancer is hormone-receptor negative (oestrogen-receptor and progesterone-receptor negative) and HER2 negative with poor prognosis. Ki-67 is an indication of tumor proliferation and an elevated/high Ki-67 is associated with poor prognosis. [13,14,15,16]

Systemic therapy and management strategies for patients with breast cancer have been developed based on molecular subtypes. Endocrine receptor positive cancers had been reported to have good clinical response to the endocrine therapy, while non-endocrine receptor cancers have been shown to respond to cytotoxic therapy. [12,17] Therefore, it is vital to identify patients benefiting from hormonal therapy and treatment targeting the HER-2/neu receptors.

The main objectives of the study were to identify the characteristics of breast cancer in women ≥50 and <50 years and to categorise any differences (histological type, stage, grading and molecular subtype) that exist between these two groups of breast cancer patients in the Limpopo province. Based on the findings of this study, a recommendation could be made to the health authority to use prevention and management strategies for patients with breast cancer in Limpopo province.

METHODS

Study approach & design

This is a cross-sectional design study to analyse the profile of women <50 and ≥50 years of age with breast cancer who presented at the breast oncology clinic, at Mankweng Tertiary Academic Hospital, Limpopo province, South Africa.

Study population

All women with histologically confirmed breast cancers who attended Mankweng Breast Oncology Clinic from July 2020 to December 2021 were included in the study. Patients with missing information and those patients who did not have complete histology results with an immunohistochemistry report were excluded from the study.

Data collection

Patients' relevant records were reviewed to collect the information. Data collection sheets encompassed age, histological type of breast cancer, grading, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki67 index, molecular subtype, stage of cancer. Stages at presentation were grouped into early (0, I & II) and late (III & IV). Breast cancer was categorised into four molecular subtypes, determined by the status of three therapeutic receptors (ER, PR, and HER2) based on immunohistochemistry. These subtypes included luminal A (ER+/PR+/HER2-/low Ki-67), luminal B (ER+/PR+/HER2-/+/high Ki-67), HER2 overexpression (ER-/PR-/HER2+), and triple-

negative breast cancer (ER-/PR-/HER2-). [2,12] The collected data were entered into an Excel spreadsheet.

Statistical analysis

The statistical software package (SPSS_V29) was used for data analysis. The patient demographics were summarised using descriptive statistics. Categorical variables were expressed as proportions and frequencies. The correlation between categorical variables was assessed using a Chi-square test and a P-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 269 female breast cancer patients were reviewed and 47 were excluded owing to lack of complete histology results with immunohistochemistry and some information in the file missing. A total of 222 cases met the inclusion criteria of the present study. Of these, 131 (59%) were aged ≥50-years and 91 (41%) were aged <50 years. Regarding the stage of presentation, 80 (36%) presented at an early stage and 142 (64%) at a late stage. A detailed descriptive summary of the results is presented in Table 1, Figure 1 and Figure 2.

Table 1. Descriptive summary of the sample statistics in relation to breast cancer in patients ≥50 and <50 years old

Description	Age ≥50(n;%)	Age <50(n;%)	Total(n;%)	P-value
Number	131(59%)	91(41%)	222(100%)	
Stage				0.610
Early-stage (stage 0, I & II)	49(37.4%)	31(34.1%)	80(36%)	
Late stage (stage III & IV)	82(62.6%)	60(65.9%)	142(64%)	
Total	131(100%)	91(100%)	222(100%)	
Histology type				
Invasive ductal carcinoma (no special type)	126(96.2%)	89(98%)	215(96.8%)	
Invasive squamous carcinoma	1(0.8%)	1(1%)	2(0.9%)	
Invasive mucinous carcinoma	1(0.8%)		1(0.45%)	
Invasive micropapillary carcinoma	1(0.8%)		1(0.45%)	
Invasive neuroendocrine carcinoma		1(1%)	1(0.45%)	
Ductal carcinoma in-situ	1(0.8%)		1(0.45%)	
Ductal carcinoma in-situ mucinous	1(0.8%)		1(0.45%)	
Total	131(100%)	91(100%)	222(100%)	
Grade				0.375
Grade 1	16(12.2%)	6(6.6%)	22(9.9%)	
Grade 2	79(60.3%)	57(62.6%)	136(61.3%)	
Grade 3	36(27.5%)	28(30.8%)	64(28.8%)	
Total	131(100%)	91(100%)	222(100%)	
Molecular subtype				0.016
Luminal A	23(17.6%)	28(30.8%)	51(22.8%)	
Luminal B	67(51.2%)	40(44%)	107(53.3%)	
HER2+ overexpression	21(16%)	5(5.5%)	26(10.9%)	
Triple negative	20(15.3%)	18(19.8%)	38(13%)	
Total	131(100%)	91(100%)	222(100%)	

With regard to molecular type in this study, the luminal B molecular subtype type was more frequent in both groups (Figure 1), accounting for 51% in the ≥50-year group and 44% in the <50-year group. Luminal A accounted for 18%, triple negative for 15% and HER2 overexpression for 16% of cases in the ≥50-year group and luminal A accounted for 31%, triple negative for 20% and HER2 overexpression for 5% in the <50-year group.

When viewing the molecular subtype in relation to the age group, HER2 overexpression prevalence was found higher in the >50-year group at 16%, while in

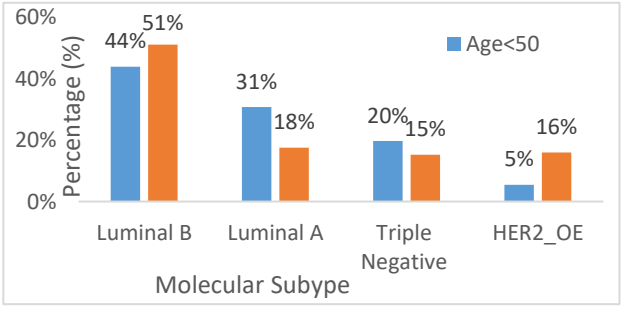

Figure 1. Molecular subtype according to the age group

the <50-year group, it was 5%. The prevalence of triple negative was 15% in the >50-year group and 20% in the <50-year group. Luminal A was more prevalent in the younger age group at 31%. A significant association was found between the HER2 overexpression molecular subtype and other molecular subtypes. HER2 overexpression was higher in the >50-year patient group (P-value 0.016).

In relation to the grading of the tumor, over 60% of the patients in both groups had a grade 2 tumor followed by a grade 3 tumor as the second most prevalent (Figure 2).

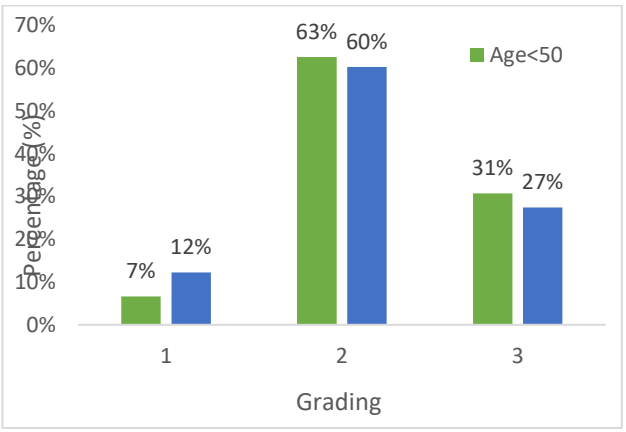

Figure 2. Grading according to the age group

DISCUSSION

In this study, 222 breast cancer patients were assessed, with the group of women ≥50 years of age comprising 59% of the sample and the group <50 years comprising 41%. Concerning the histological type of breast cancer, over 90% of the patients in both age groups had invasive ductal carcinoma (IDC). IDC is the most common histological type around the globe and in many sub-Saharan African countries. A study on breast cancer by Bhatia *et al. (2015)* found IDC to represent 86% of all cases in Malawi [18] and approximately 89% in Nigeria.[4]

In this study, the luminal B molecular subtype was more frequent in both groups (Figure 1). Across the globe, usually luminal A is the most common molecular subtype (50%-60%), with luminal B and HER2 overexpression cancer accounting for 15% - 20% of breast cancer subtypes. The triple negative subtype represents between 8% and 37% of all subtypes. [19] However, research has observed the luminal A subtype at 58.5%, followed by triple negative at 16%, luminal B at 14%, and HER2 overexpression to be the least prevalent at 11.5%. [10] Some studies have reported that luminal B, HER2 overexpression, and triple negative are more prevalent in younger women compared to older breast cancer patients. [20,21] Different populations have variations of incidences of molecular subtypes. Goldhirsch *et al.* have argued for endocrine therapy alone for patients with clinicopathologically classified 'Luminal A' disease (except in defined high-risk cases), chemo endocrine therapy for Luminal B, the addition of anti-HER2 therapy in the presence of 'HER2 positivity', and a reliance on chemotherapy for most patients with 'Triple negative' disease with invasive ductal carcinoma. [12]

In terms of prognosis, Luminal A and Luminal B have good prognosis and majority of these subtypes in both age groups respond better to hormonal therapy. HER2 overexpression was found to be higher in the >50-year patient group with worse prognosis than the Luminal type but a better response to targeted therapy (trastuzumab, pertuzumab, lapatinib). Triple negative was found to be higher in the <50-year group with poor short-term (5 years) prognosis not responding to hormonal and targeted therapy. [14,15,16] The triple negative type has a good prognosis for patients who survive the first 5 years after diagnosis. [15]

In relation to the grading of the tumor, no obvious difference was found between the two groups. However, when comparing grading with the molecular subtype of triple negative between the age groups, grade 3 was more prevalent in the <50-year group. Grade 3 was found in 65% of patients in the ≥50-year group and 83% of patients in the <50-year group (Figure 3). Overall, 38 patients had triple negative breast cancer, and no patient had grade 1 in the triple negative molecular subtype. This shows that the triple negative types are more aggressive appearing in tumor biology. Sheppard *et al.* found that triple negative disease patients usually present at an advanced stage, which is more common in women with BRCA1 gene mutations and among young black women. [16] Grade 3 had proportionally higher prevalence in triple negative molecular subtype in patients in the <50-year group compared to those in the ≥50-year group.

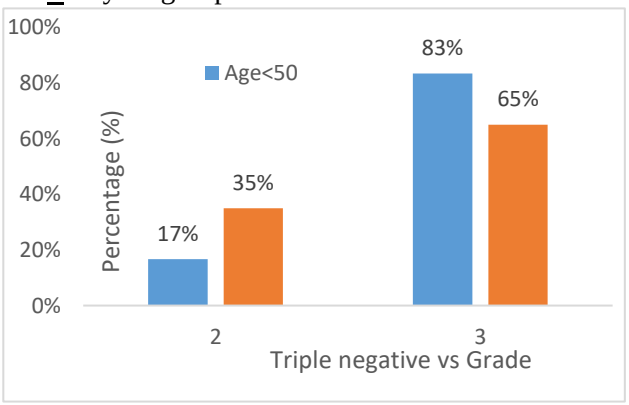

Figure 3. Comparison of triple -negative molecular subtype and grade between age groups

Regarding the stage of presentation, 36% of the sample presented at an early stage and 64% at a late

stage and no significant associations were found between the stage and patients' age in this study. The majority of patients in both age groups presented at an advanced stage (Figure 4). It is a big concern that women of Limpopo province are presenting late with an advanced stage of breast cancer. Awareness campaigns are essential for all women, young and elderly in the Limpopo province. Research has shown that in many sub-Saharan Africa and other low and middle-income countries patients usually present at an advanced stage. [7,9]

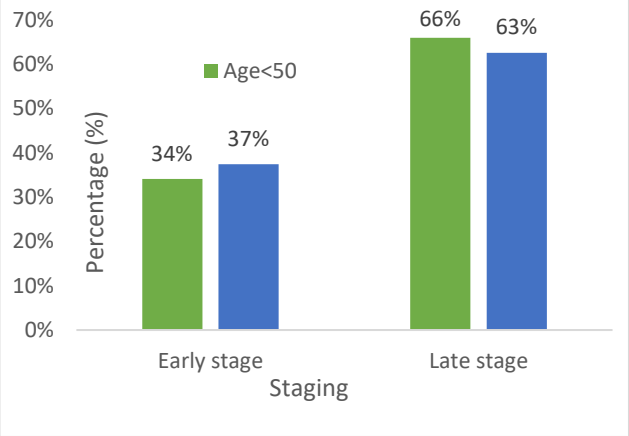

Figure 4. Stage according to age group

In many countries, there are many challenges, diagnostic delays, and limited awareness of female breast cancer. [2] A study in Johannesburg, South Africa found that limited education and lack of breast cancer knowledge were associated with an advanced stage diagnosis. [22] Another South African study found that low levels of education were a major factor causing a delayed diagnosis. [23] Furthermore, there is a lack of understanding of the severity of breast cancer responsible for presentation at the late stage in the rural population of KwaZulu-Natal, South Africa. [24] A previous study from Limpopo province, South Africa identified the most common reason for a delay in diagnosis to be a lack of knowledge about breast cancer and its symptoms. [6]

Early diagnosis of breast cancer is important for effective management as it reduces the suffering of the patient and increases the chances of survival. Costa *et al.* recommended increasing awareness and educational programs to identify signs and symptoms and to develop clear diagnostic guidelines and screening strategies.[2] The 2017 South African Breast Cancer Control Policy advocated for direct access to a specialist breast cancer clinic to reduce delays in presentation and improve time to diagnosis and care. [25]

Limitations

The present study was retrospective, and some information was missing to include all patients. Poor note-keeping was observed and it was impossible to trace patients' complete histology results.

CONCLUSION

Majority of patients presented at an advanced stage in both groups. Health education and breast cancer awareness campaigns are essential for all women, young and elderly in Limpopo province. Over 40% of the patients in this study were under 50 years of age. This showed that breast cancer screening should start earlier in Limpopo province. HER2 overexpression molecular subtype was higher in the ≥50-year patient group compared to <50 years of age group. In breast cancer patients under <50, triple negative molecular subtype is more prevalent. Further studies are required to elucidate the genetics, environmental influences, and clinical behaviors of breast cancer to guide our understanding and aid in the formulation of management protocols relevant to this population.

ACKNOWLEDGEMENTS

The author acknowledges Dr. Osvaldo Segura Sardiñas, Biostatistician and Family medicine specialist for his contribution to statistical inferences.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ETHICAL CONSIDERATIONS

The database documents were protected with only the researcher having the password. Permission for the study was obtained from the clinical Executive management of Mankweng Academic Hospital dated 09/10/2023.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

DATA AVAILABILITY

All relevant data are within the paper and its supporting information files. Anything else needed is available upon request.

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How to Cite This Article

Bhuiyan MMZU. Comparison of Breast Cancer Characteristics in Women below and above 50 at Mankweng Hospital in Limpopo Province, South Africa. Arch Breast Cancer. 2025; 12(1):101-6.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/1045