Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201853129-137

Prognostication of Breast Cancer in Ghanaian Women Receiving Modified Radical Mastectomy: A Retrospective Histopathological Study at Korle-Bu Teaching Hospital, Accra, Ghana

Edmund Muonir Der*[a,b], Richard Kwasi Gyasi[a] , Edwin Kwame Wiredu[a]

[a] *Department of Pathology, School of Biomedical Sciences, Korle-Bu Teaching Hospital, Northern Ghana*
[b] *Department of Pathology, School of Medicine and Health Sciences, UDS Tamale, Northern Ghana*

ARTICLE INFO

Received:
15 July 2018
Revised:
22 July 2018
Accepted:
25 July 2018

Key words:
Nottingham Prognostic Index, stratification, prognostication, Ghanaian women, breast cancer, mastectomy

ABSTRACT

Background: Making prognosis and identifying the patients at higher risk of mortality are important issues in breast cancer (BC) treatment. The aim of this study was to stratify BC case receiving mastectomy into prognostic risk categories using the Nottingham Prognostic Index (NPI).

Methods: This was a retrospective review from January 2002 to December 2014.

Results: Approximately 35% of all BCs diagnosed in our institution had undergone mastectomy. The mean age was 51.9 years. The mean size of the primary breast tumor was 5.8 cm and showed significant association with the histologic grade ($P = 0.001$), nodal involvement ($P < 0.001$), positive tumor margins ($P = 0.027$), and the cancer stage ($P < 0.001$). Based on the NPI sores, 1.5% of the cases would have an excellent prognosis, 10.8% a good prognosis, 55.8% a moderate prognosis, and 31.9% a poor prognosis.

Conclusion: The current study found that 87.7% of the women with breast had moderate to poor prognosis at the time of diagnosis. Patients are found to present late when the disease is advanced.

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women globally and in Ghana.[1-3] Previous institution-based publications on BC in Ghana[4] and other African countries[5] have found the disease to be common among younger women, with advanced stage at presentation.[6-11] Unfortunately, none of the previous BC publications from Ghana included data on prognostic grouping of Ghanaian women diagnosed with the disease. A number of putative prognostic factors for human BC have been reported by the American Joint Committee on Cancer (AJCC). Recognizing the prognostic factors enables greater accuracy in predicting the outcome of BC treatment. The universally acknowledged prognostic factors for BCs are the age at diagnosis, tumor size, histologic type, tumor grade, lymph node status, metastases to other organs, estrogen and progesterone receptor expression, HER2 expression, and the proliferation index. Combining these factors is of greater clinical value than considering each in isolation, and this is the basis for a number of schemes that are used to group patients into various risk categories. One of such schemes is the Nottingham Prognostic Index (NPI), which we used to group Ghanaian women with BC into prognostic categories. The aim of this study was to stratify BCs undergoing modified radical mastectomy into prognostic risk categories using the NPI.

Address for correspondence:
Muonir *Edmund Der, MBChB, MGCP, FWACP*
*Address: Department of Pathology, School of Biomedical Sciences, Korle-Bu Teaching Hospita*l, Guggisberg Ave, Accra, Ghana
Tel: +233 30 267 4044
Email: *maadelle@yahoo.com, edmunder1869@gmail.com*

Methods

Study Design

This was a retrospective study covering the period from 2002 to 2014. Data were collected from the Department of Pathology, School of Biomedical

Sciences, College of Health Sciences of the University of Ghana located at Korle-Bu. This institution reports between 5 ,000 and 8 ,000 histology cases yearly.

Inclusion Criteria

1) All female BCs.

2) Well-fixed mastectomy specimens with axillary clearance.

Exclusion Criteria

1) All male breast cancers.

2) Poorly fixed female mastectomy specimens.

3) Receiving neoadjuvant chemotherapy prior to mastectomy without residual malignant cells.

Ethical consideration/informed consent

Permission to publish the data in this manuscript was granted by the head of the Department of Pathology.

Data Collection

Histopathology reports and slides of confirmed BC cases included in the study were reviewed. Of the total number, BC cases who had undergone mastectomy were selected and the clinicopathological characteristics of BCs were collected.

A positive tumor margin in this study was defined as the presence of malignant cells within 2 mm of the resection margins.

The study did not include the following prognostic factors: estrogen receptor, progesterone receptor, and HER2 expression, which are not routinely performed but on request, and proliferation indices, which are not performed at all in our institution.

BCs were classified according to the World Health Organization histology classification of breast tumors (WHO 2003).[12]

Histologic grading of breast tumors was performed according to the modification of the Bloom-Richardson system by Elston and Ellis.

The cancer stage was determined using the TNM system (pathological) developed by AJCC, which uses the size of the primary tumor (T), nodal involvement (N), and presence of metastasis (M).

Calculation of the Nottingham Prognostic Index(NPI)

The NPI is one of the most widely used prognostic indices for patients with invasive BC. The NPI was developed in 1982 to help in the management of primary operable BC.[13, 14] Multivariate analysis identified 3 factors to be significant: tumor grade, the number of lymph nodes involved, and the size of the tumor. These are viewed as the strongest independent predictors of outcome and make up the formula to calculate the prognostic score. Cutoff points were applied to divide patients into prognostic categories of excellent, good, moderate, and poor, and these correlate strongly with the survival rate.[15] Since the development of the NPI, attempts have been made by other researchers to improve its prognostic power, with limited success. Some people have suggested modifying the variables used to determine the index or combining additional markers with it, and others have used different statistical approaches.[15,16] However, to date, the original NPI remains the gold standard for stratifying BC patients into prognostic categories.

BCs that met the following criteria were included in the calculation of the NPI:

1. Must be graded using the modified Bloom-Richardson grading system.
2. Must have stated gross primary tumor size (cm).
3. Must have lymph nodes retrieved from the axillary content.

The NPI was calculated as follows:

Lymph node involvement (L) was scored as 1-3 (No nodes: 1, 1-3 nodes: 2, and > 3 nodes: 3).

The NPI was calculated using the formula: $NPI = G + L + (S \times 0.2)$.

BC cases were put into prognostic categories and 5-year survival rates based on their NPI scores.

Data Analyses

Data were entered into the SPSS software version 18 (IBM, Chicago, USA). Frequency distributions and descriptive statistics were calculated. The associations between tumor variables were determined using Spearman's correlation coefficient. Finally, BCs were categorized into prognostic groupings using the NPI. P values of < 0.05 were considered significant.

Results

Clinicopathological Characteristics of Bcs

During the period under review 4,175 BCs were diagnosed in our institution, of which 1,473 (35.3%) received a mastectomy. There was a gradual rise in the proportion of mastectomy-receiving BC cases over the period (Figure 1).

The age of patients ranged from 14 to 94 years (M = 51.9 y, SD = 12.5), with the modal age group of 40 to 49 years (27.9%) (Figure 2).

The most common primary presentation of BC was a painless palpable lump (N = 1467, 99.6%). A total of 669 (47.6%) women with palpable lumps had skin involvements. The duration of symptoms at presentation was available for 911 (61.8%) patients, of which 79.6% had reported after 3 months of illness (Table 1).

The size of primary tumors ranged from 0.5 to 24 cm, with a mean of 5.8 cm (SD = 3.9). Half of the tumors were larger than 5.0 cm (T3) in diameter. This was followed by 595 (40.4%) tumors that were larger than 2.0 cm, but less than or equal to 5.0 cm (T2), and 141 (9.6%) tumors that were 2.0 cm or less (T1).

The major categories of BCs in this study were epithelial (97.2%), mesenchymal (1.0%), and fibroepithelial (0.95%). The great majority of the BC

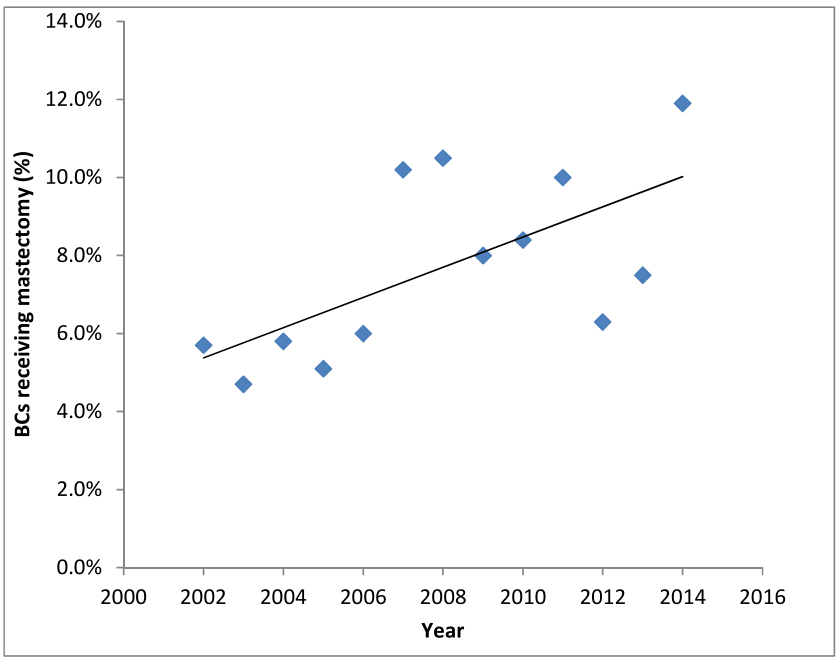

Figure 1. Trend in BC cases receiving mastectomy at Korle-Bu teaching hospital

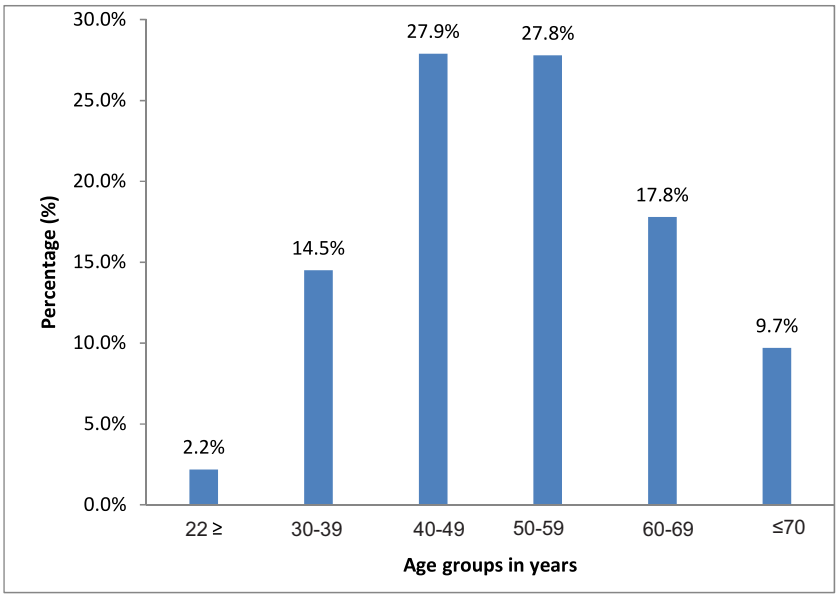

Figure 2. Age distribution of BCs during the period of review

Table 1. Symptoms and duration of BC at presentation

Variable			N (%)
Primary complaint	Nipple discharge		6 (0.4%)
	Palpable breast lump		1467 (99.6%)
	Laterality		
		Right breast	746 (50.9%)
		Left breast	713 (48.6%)
		Bilateral	8 (0.5%)
Additional symptoms	Skin involvement		699 (45.4%)
	Other		25 (1.7%)
Duration of symptoms at presentation (months)	1-3		186 (20.4%)
	4-6		172 (18.9%)
	7-9		108 (11.9%)
	10-12		224 (24.6%)
	13-24		134 (14.7%)
	>24		87 (9.5%)

Table 2. Histological types of BC

Histological types of breast cancers		N (%)
Epithelial		1432 (97.21%)
	Invasive ductal carcinoma, not otherwise specified (IDC-NOS)	1296 (87.98%)
	Mucinous	37 (2.51%)
	Lobular	31 (2.10%)
	Ductal carcinoma in situ (DCIS)	17 (1.15%)
	Papillary	17 (1.15%)
	Neuroendocrine	5 (0.33%)
	Medullary	9 (0.7%)
	Apocrine	5 (0.33%)
	Cribriform	4 (0.27%)
	Tubular	3 (0.20%)
	Squamous cell carcinoma	4 (0.27%)
	secretory	1 (0.06%)
	Inflammatory	1 (0.06%)
	Sweat gland	1 (0.06%)
Mesenchymal		15 (1.01%)
	Metaplastic	10 (0.67%)
	Sarcoma	3 (0.20%)
	Osteosarcoma	1 (0.06%)
	malignant peripheral nerve sheath tumor (MPNST)	1 (0.06%)
Fibroepithelial		14 (0.95%)
	Malignant phyllodes tumor	14 (0.95%)
Tumors of the nipple		11 (0.74%)
	Paget's disease	11 (0.74%)
Lymphoma		1 (0.06%)
Total		1473

subtypes were invasive ductal carcinoma, not otherwise specified (IDC-NOS) (88.0%) (Table 2).

A total of 1,458 (99%) cases undergoing mastectomy had Bloom-Richardson grading. Of this number, 42% were grade 2, 38.1% grade 3, and 19.9% grade 1. The number of cases with nodal involvement was 976 (66.3%), with the mean number of nodes involved being 3.4 (SD = 4.2, range: 1-42). Many (44%) of these cases had between 1 and 3 positive lymph nodes (Figure 3). In all, 56% had 4 or more positive lymph nodes.

A total of 1,426 (96.8%) BC cases undergoing mastectomy were pathologically staged. Of this number, 39.1% were stage III. The majority of cases were in stages III and IV combined (62.8%) (Figure 3). Only of 47 (3.2%) cases were residual cancers.

A total of 202 (13.7%) of the BC cases undergoing mastectomy were incompletely excised.

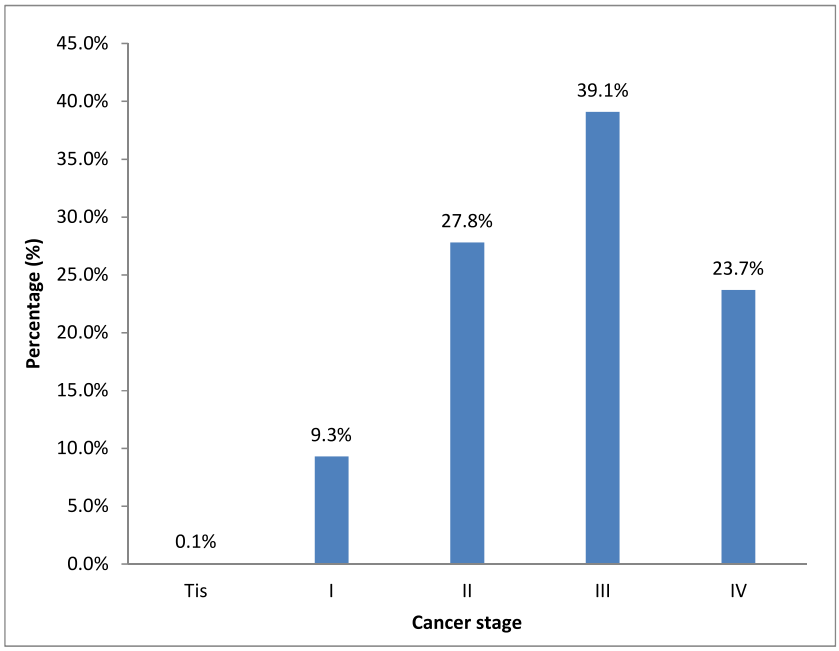

Figure 3. TNM staging of BC cases

Table 3. Association between BC prognosis indicators (By Spearman's Correlation)

	Tumor Size	Histologic type	Tumor grade	Positive LN	Tumor Stage	Positive margins
Tumor Size	-	**0.003**	**0.001**	**0.000**	**0.000**	0.027
Histologic type	**0.003**	-	0.441	0.300	0.503	0.350
Tumor grade	**0.001**	0.441	-	**0.002**	**0.000**	0.125
Positive LN	**0.000**	0.300	**0.002**	-	**0.003**	**0.003**
Tumor stage	**0.000**	0.503	**0.000**	**0.003**	-	**0.001**
Positive margins	0.027	0.350	0.125	**0.003**	**0.001**	-

Table 4. Stratification of breast cancer cases (N = 1,451) into prognostic categories using the NPI

NPI	N (%)	Prognosis	Expected 5-year survival rate
2.0-2.4	22 (1.5%)	Excellent	93%
2.4-3.4	157 (10.8%)	Good	85%
3.4-5.4	810 (55.8%)	Moderate	70%
> 5.4	462 (31.9%)	Poor	50%

Associations Between Tumor Variables

The size of the primary tumor was significantly correlated with histologic type (P = 0.002), tumor grade (P = 0.001), positive lymph nodes (P < 0.001), positive tumor margins (P = 0.027) and the tumor stage (P < 0.001). There were also significant positive associations between other tumor variables (Table 3).

Nottingham Prognostic Index Calculation

A total of 1,451 (98.5%) of the cases receiving mastectomy met the criteria for the calculation of the NPI.

More than half (55.8%) had NPIs within between 3.5 and 5.4, which translates into a moderate prognosis and an expected 5-year survival rate of 70%. Only 1.5% had an excellent prognosis and an expected 5-year survival rate of 93% (Table 4). The remaining 87.7% had moderate to poor prognosis.

Discussion

Breast cancer is the most common malignancy among women in developed and developing countries, such as Ghana.[1-3] In the current study, 35.3% of all histologically confirmed BCs had received mastectomy, with 51% of the women being younger than 50 years. This value seems to suggest that BC is still common among young Ghanaian women, as is the case with other African countries.[4-6] Patient's age at histological diagnosis is an independent prognostic factor: the younger the age the poorer the outcome after treatment.[7, 8] This have been the fate of the women in the current study.

Women commonly presented with palpable breast lumps, with 47.9% having skin involvements. This seems to suggest that women with BC in current study only present to a health facility when the disease is obvious. This may be due to the fact that there is no population-based BC screening program in the country, so lesions are not detected until they become palpable. BC women in our study are not used to self-examination of their breasts, therefore they detect their BC only when the tumor is obviously large to be felt accidentally. The current findings are in accord with some institution-based studies in Africa, which found that the disease was common in young women,[10] and that women with BC presented late,[6, 11] with large advanced tumors with skin involvement.[9,11]

The great majority (79.6%) of women with BC presented late (after 12 weeks) to health facilities, with advanced diseases. Late presentation of BC to health facilities in Ghana has been attributed to a prior visit to prayer camps, stigmatization of women with the disease, the wait-and-see attitude of patients, ignorance about the disease, financial hardship, and the hostile attitude of hospital workers and the hospital environment.[9,11] Studies in Nigerian,[17] Tunisian,[18] and South African women[19] similarly found the presentation of the disease to be late. Literature from other parts of the world for the past 30 years indicates that survival is worse for women with longer duration of symptoms.[20-23] Furthermore, the current findings are similar to the studies in the UK in the early 80s and late 90s (when routine BC screening was not commonplace), which found that most women with BC presented late with symptoms of the advanced disease and that there was a need for early detection and treatment.[24, 25] It is expected that early diagnosis and treatment would lead to a reduction in disease severity or mortality. For instance, Burgees *et al.,*[24] who defined patient delay as 12 weeks of symptoms before the first visit to the general practitioner (GP), found that 90% of their patients delayed ≥ 12 weeks in seeing the GP, and that patient delay was associated with clinical tumor sizes greater than 4 cm (P = 0.0002) and a higher incidence of locally advanced and metastatic disease (P = 0.001). There is evidence, however, that the duration of symptoms may not be associated with survival. Dennis et al and Fisher et al found that about 20% of the patients visited the GP at about 4 to 8 weeks after symptoms onset and concluded that survival after the symptoms have appeared is not related to the duration of the symptomatic period but

to established pathological criteria such as rate of growth, the tumor size, lymph node involvement, the number and location of lymph nodes involved, blood vessel invasion, and the presence of systemic metastases.[26, 27] These apparently conflicting results may be explained by differences in the cutoffs used to define delay.

The mean primary tumors size in our study was large (5.8 cm) and showed significant positive associations with the histological grade (P = 0.001), nodal involvement (P < 0.001), and the tumor stage (P < 0.001). The size of primary breast tumor is an independent prognostic factor and, together with nodal involvement, is used for staging BC.[28] Studies have shown that women with large primary are more likely to have positive lymph nodes and hence poor prognosis.[28,29] In the present study, 50% of the women had tumor sizes of greater than 5 cm, indicating that the majority of the women had a poor outcome and low survival rate. This, however, differs from Wo et al[30] who showed that very small tumors can equally have extensive lymph node involvement and hence poor survival rate.

Invasive ductal carcinoma, not otherwise specified (IDC-NOS) was the most common histological subtype of BC in this study similar to other studies.[31, 32] The grade of a breast tumor is directly related to prognosis,[33, 34] and the 5-year survival.[35, 36] The higher the tumor grade, the lower the 5-year survival rate. [35, 36] The great majority (80.1%) of the cases in this study were of high histological grade, and this may translate into a poor prognosis and a low 5-year survival rate. This finding is similar to the 76% prevalence of grade 3 tumors in Ghanaian women in the study of Stark et al,[37] who compared Ghanaian women with African American and white women diagnosed with BC.

The number of involved lymph nodes is a very important prognostic factor for invasive cancers.[38, 39] It is associated with a lower survival rate, high recurrence rate, decreased time to recurrence, and treatment failure.[38] Disease-free survival (DFS) and overall survival diminish with each additional positive axillary node.[40] It has been shown that about 70% of patients with nodal involvement will develop recurrence after mastectomy, and patients with 4 or more lymph nodes involved have a worse prognosis compared with those having fewer nodes involved.[41-43] Survival rate decreases with increased nodal involvement. With no nodal involvement, the 10-year DFS rate is between 70% and 80%. This rate declines to 35% to 40% when there are 1 to 3 positive nodes, and to 10% to 15% when ≥ 10 nodes are involved.[44] The current study found that 44% of the cases had 1 to 3 positive lymph nodes, while about 56% had 4 or more positive lymph nodes. This is consistent with Jatoi et al,[45] who found the hazard ratios for patients with 1 to 3 and ≥ 4 positive nodes to be 1.2 (95% CI, 0.8 to 1.9) and 2.5 (95% CI, 1.8 to 3.4), respectively. They concluded that patients with ≥ 4 involved nodes at diagnosis had a significantly poorer outcome after relapse compared with node-negative cases, regardless of the duration of the disease-free period. Our results suggest that nodal metastasis is a marker of an aggressive phenotype as well as being a diagnostic marker at a later point in the natural history of BC. Thus, the majority of women in this study are expected to be at increased risk for recurrence of the disease after mastectomy, treatment failure, and survival rates less than 40%.

The cancer stage at histological diagnosis showed strong positive associations with the histological grade (P < 0.001), and positive tumor margins (P = 0.001). The stage of BC determines the treatment option and the prognosis of tumors after the treatment.[46, 47] The higher the stage at diagnosis, the shorter the 5-year survival rate.[46] The majority of the BC patients in this study had stage III or IV cancers at the time of histological diagnosis and potentially a poor outcome of the disease, even with treatment, and a low 5-year survival rate.[48, 49] Furthermore, the large percentage of advanced-stage BCs in this study differs from the results of the study of Walters et al[45] in Canada, where they found that 82.9% of the BC patients were in stage I or II, while only 17.1% had stage III or IV cancer.

In this study, positive tumor margin frequency of 13.7% was found in mastectomy specimens. This value is close to the 12% for total mastectomies in Sheikh et al,50 but lower than the 20% in the study of Walters *et al.*[51] These women are therefore potentially at risk of developing local recurrence[52, 53] and systemic disease.[54,55]

The NPI is one of the most widely used prognostic indices for the management of patients with primary operable invasive BC.[13,14,56] It is the gold standard for stratifying BC patients into prognostic categories as excellent, good, moderate, and poor, which correlate strongly with the survival rate.[15] Data on the survival of BC patients after definitive diagnosis and treatment is nonexistent in Ghana. Available data from some African countries with limited resources for BC screening, diagnosis, and treatment showed varied results[16, 19, 57-59] compared with the United States of America and Canada,[60, 61] where effective screening and treatment and cancer registries are present. In the current study, based on the NPI scores, 31.9% of the women would have a poor prognosis, with an expected 5-year survival rate of 50%; 55.8% would have a moderate prognosis, with an expected 5-year survival of 70%; and only 1.5% would have an excellent prognosis, with an expected 5-year survival of 93%. The proportion of women with poor prognosis (31.9%) in this study is higher than the values observed in the Gambia (12.5%)[59] and Nigeria (24.5% and 25.6%),[58] but performs less than some African countries such as Uganda (56.4%) and South Africa (64%,

black women).[57] Furthermore, the finding from the current study also compared far less favorably with values such as 80% for South African white women,[60] 81% for the Republic of Korea,[62] 86% for Canada,[59] and 88% for the United States of America.[60,61]

In conclusion, the current study found that 87.7% of the BC cases had moderate to poor prognosis at the time of diagnosis. Patients were found to present late when the disease is advanced.

Acknowledgment

We would like to thank all the residents and the biomedical staff of the institution for their support.

Conflict of Interest

No conflict of interest.

References

1. Ghafoor A, Jemal A, Ward E, Cokkinides V, Smith R, Thun M. Trends in breast cancer by race and ethnicity. CA Cancer J Clin. 2003;53(6):342-55.
2. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013; 132(5):1133-45.
3. Calys-Tagoe BN, Yarney J, Kenu E, Amanhyia NAKO, Enchill E, Obeng I. Profile of cancer patients' seen at Korle Bu teaching hospital in Ghana (A cancer registry review). BMC research notes. 2014;7(1):577.
4. Quartey-Papafio J, Anim J. Cancer of the breast in Accra. 1980.
5. Ekanem VJ, Aligbe JU. Histopathological types of breast cancer in Nigerian women: a 12-year review (1993-2004). Afr J Reprod Health. 2006;10(1):71-5.
6. Clegg-Lamptey J, Hodasi W. A study of breast cancer in korle bu teaching hospital: assessing the impact of health education. Ghana Med J. 2007;41(2):72-7.
7. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? Journal of the National Cancer Institute Monographs. 1994(16):35-42.
8. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, *et al.* Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. J Clin Oncol. 1994;12(5):888-94.
9. Clegg-Lamptey J, Aduful H, Yarney J, Adu-Aryee N, Vanderpuye V, Kyereh M, *et al.* Profile of breast diseases at a self-referral clinic in Ghana. West Afr J Med. 2009;28(2):114-7.
10. Anyanwu SN. Breast cancer in eastern Nigeria: a ten year review. West Afr J Med. 2000;19(2):120-5.
11. Ohene-Yeboah MO. An audit of excised breast lumps in Ghanaian women. West African journal of medicine. 2005;24(3):252-5.
12. Eble JN, Tavassoli FA, Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs: Iarc; 2003.
13. Haybittle JL, Blamey RW, Elston CW, Johnson J, Doyle PJ, Campbell FC, *et al.* A prognostic index in primary breast cancer. Br J Cancer. 1982; 45(3):361-6.
14. Todd JH, Dowle C, Williams MR, Elston CW, Ellis IO, Hinton CP, *et al.* Confirmation of a prognostic index in primary breast cancer. Br J Cancer. 1987;56(4):489-92.
15. Rampaul RS, Pinder SE, Elston CW, Ellis IO, Nottingham Breast T. Prognostic and predictive factors in primary breast cancer and their role in patient management: The Nottingham Breast Team. Eur J Surg Oncol. 2001;27(3):229-38.
16. D'Eredita G, Giardina C, Martellotta M, Natale T, Ferrarese F. Prognostic factors in breast cancer: the predictive value of the Nottingham Prognostic Index in patients with a long-term follow-up that were treated in a single institution. Eur J Cancer. 2001;37(5):591-6.
17. Nggada HA, Yawe KDT, Abdulazeez J, Khalil MA. Breast cancer burden in Maiduguri, North eastern Nigeria. The breast journal. 2008;14(3):284-6.
18. Corbex M, Bouzbid S, Boffetta P. Features of breast cancer in developing countries, examples from North-Africa. European Journal of Cancer. 2014;50(10):1808-18.
19. Vorobiof DA, Sitas F, Vorobiof G. Breast cancer incidence in South Africa. J Clin Oncol. 2001;19(18 Suppl):125S-7S.
20. Machiavelli M, Leone B, Romero A, Perez J, Vallejo C, Bianco A, *et al.* Relation between delay and survival in 596 patients with breast cancer. Oncology. 1989;46(2):78-82.
21. Neave LM, Mason BH, Kay RG. Does delay in diagnosis of breast cancer affect survival? Breast cancer research and treatment. 1990;15(2):103-8.
22. DeVita VT, Hellman S, SA. R. Cancer: Principles & Practice of Oncology Review: Lippincott Williams & Wilkins; 2008.
23. NHSBSP. Annual review, expanding our reach-The extended age pilot scheme. 2009.
24. Macarthur C, Smith A. Delay in breast cancer and the nature of presenting symptoms. The Lancet. 1981;317(8220):601-3.
25. Burgess C, Ramirez A, Richards M, Love S. Who and what influences delayed presentation in breast cancer? British journal of cancer. 1998;77(8):1343.
26. Dennis CR, Gardner B, Lim B. Analysis of survival and recurrence vs. patient and doctor delay in treatment of breast cancer. Cancer. 1975;35(3):714-20.
27. Fisher ER, Redmond C, Fisher B. A perspective concerning the relation of duration of symptoms to treatment failure in patients with breast cancer. Cancer. 1977;40(6):3160-7.
28. Carter CL, Allen C, Henson DE. Relation of

tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989; 63(1): 181-7.
29. Fisher B, Slack N, Katrych D, Wolmark N. Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surgery, gynecology & obstetrics. 1975;140(4):528-34.
30. Wo JY, Chen K, Neville BA, Lin NU, Punglia RS. Effect of very small tumor size on cancer-specific mortality in node-positive breast cancer. Journal of Clinical Oncology. 2011;29(19):2619.
31. Adjei E. Breast cancer in Kumasi, Ghana. Ghana medical journal. 2012;46(1).
32. Edmund DM, Naaeder SB, Tettey Y, Gyasi RK. Breast cancer in Ghanaian women: what has changed? Am J Clin Pathol. 2013;140(1):97-102.
33. Bloom H. Histologic grading and prognosis in breast cancer. Br J Cancer. 1957;11:655-69.
34. Henson DE, Ries L, Freedman LS, Carriaga M. Relationship among outcome, stage of disease, and histologic grade for 22,616 cases of breast cancer. The basis for a prognostic index. Cancer. 1991;68(10):2142-9.
35. Bloom H. Further studies on prognosis of breast carcinoma. British journal of cancer. 1950;4(4):347.
36. Bloom H. Prognosis in carcinoma of the breast. British journal of cancer. 1950;4(3):259.
37. Stark A, Kleer CG, Martin I, Awuah B, Nsiah-Asare A, Takyi V, *et al.* African ancestry and higher prevalence of triple-negative breast cancer: findings from an international study. Cancer. 2010;116(21):4926-32.
38. Wilson R, Donegan W, Mettlin C, Natarajan N, Smart CR, Murphy G. The 1982 national survey of carcinoma of the breast in the United States by the American College of Surgeons. Surgery, gynecology & obstetrics. 1984;159(4):309-18.
39. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, *et al.* Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. Jama. 2011;305(6):569-75.
40. Vinh-Hung V, Burzykowski T, Cserni G, Voordeckers M, Van De Steene J, Storme G. Functional form of the effect of the numbers of axillary nodes on survival in early breast cancer. Int J Oncol. 2003;22(3):697-704.
41. Smith JA, 3rd, Gamez-Araujo JJ, Gallager HS, White EC, McBride CM. Carcinoma of the breast: analysis of total lymph node involvement versus level of metastasis. Cancer. 1977;39(2):527-32.
42. Russo J, Frederick J, Ownby HE, Fine G, Hussain M, Krickstein HI, *et al.* Predictors of recurrence and survival of patients with breast cancer. Am J Clin Pathol. 1987;88(2):123-31.
43. FishePathologic findings from the National Surgical r ER, Anderson S, Redmond C, Fisher B. Adjuvant Breast Project protocol B-06. 10-year pathologic and clinical prognostic discriminants. Cancer. 1993;71(8):2507-14.
44. Fisher B, Bauer M, Wickerham DL, Redmond CK, Fisher ER, Cruz AB, *et al.* Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer. 1983;52(9):1551-7.
45. Jatoi I, Hilsenbeck SG, Clark GM, Osborne CK. Significance of axillary lymph node metastasis in primary breast cancer. J Clin Oncol. 1999;17(8):2334-40.
46. Donegan WL. Cancer of the breast. Staging methods, primary treatment options and end results. Major Probl Clin Surg. 1979;5:221-301.
47. Merkel DE, Osborne CK. Prognostic factors in breast cancer. Hematology/Oncology Clinics. 1989;3(4):641-52.
48. Ferguson DJ, Meier P, Karrison T, Dawson PJ, Straus FH, Lowenstein FE. Staging of breast cancer and survival rates: an assessment based on 50 years of experience with radical mastectomy. Jama. 1982;248(11):1337-41.
49. Rosen PR, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. J Clin Oncol. 1989;7(3):355-66.
50. Sheikh F, Rebecca A, Pockaj B, Wasif N, McCullough AE, Casey W, *et al.* Inadequate margins of excision when undergoing mastectomy for breast cancer: which patients are at risk? Annals of surgical oncology. 2011;18(4):952-6.
51. Walters S,Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J, *et al.* Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. British journal of cancer. 2013;108(5):1195.
52. Clarke DH, Le MG, Sarrazin D, Lacombe MJ, Fontaine F, Travagli JP, *et al.* Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institut Gustave-Roussy. Int J Radiat Oncol Biol Phys. 1985;11(1):137-45.
53. Goldstein NS, Kestin L, Vicini F. Factors associated with ipsilateral breast failure and distant metastases in patients with invasive breast carcinoma treated with breast-conserving therapy. A clinicopathologic study of 607 neoplasms from 583 patients. Am J Clin Pathol. 2003;120(4):500-27.
54. Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. Semin Surg Oncol. 1992;8(3):161-6.
55. Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, *et al.* Significance

of ipsilateral breast tumour recurrence after lumpectomy. Lancet. 1991;338(8763):327-31.
56. Burke HB, Henson DE. Criteria for prognostic factors and for an enhanced prognostic system. Cancer. 1993;72(10):3131-5.
57. Gakwaya A, Kigula-Mugambe JB, Kavuma A, Luwaga A, Fualal J, Jombwe J, *et al.* Cancer of the breast: 5-year survival in a tertiary hospital in Uganda. Br J Cancer. 2008;99(1):63-7.
58. Kene TS, Odigie VI, Yusufu LM, Yusuf BO, Shehu SM, Kase JT. Pattern of presentation and survival of breast cancer in a teaching hospital in north Western Nigeria. Oman Med J. 2010;25(2):104-7.
59. Swaminathan R, Lucas E, Sankaranarayanan R. Cancer survival in Africa, Asia, the Caribbean and Central America: database and attributes. IARC Sci Publ. 2011(162):23-31.
60. National Cancer Institute of Canada (NCIC) Canadian cancer statistics 2006. NCIC. 2006.
61. American Cancer Society (ACS) Cancer facts and figures. 2006.