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Research Article

Predictors of Breast Cancer Treatment Outcomes in Kenyan Women

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Background: Breast cancer is the most prevalent cancer among Kenyan women. Worldwide data show that diverse factors including socio-economic status, co-morbidities, and expression of hormonal receptors, have effect on disease recurrence or metastasis following treatment. Most studies on breast cancer treatment outcomes have been undertaken in developed countries, and there is scarcity of data on predictive indicators of breast cancer treatment outcomes in Africa.

Objective: This study was designed to determine the factors that predict the treatment outcomes in breast cancer patients in a Kenyan teaching and referral hospital.

Methods: This hospital based retrospective descriptive study was designed to evaluate the effect of the occurrence of estrogen receptor, progesterone receptor, human epidermal growth factor and cancer stage among other factors on the outcome of breast cancer treatment. Patients diagnosed with breast cancer and who had their first visit at the KNH in the period 2007-2008 were identified. Quantitative variables were described with medians or means. Association effects were determined by use of Chi-square test. Categorical variables were summarized using proportions. The time to event analysis was estimated using the Kaplan–Meier product limit method.

Results: The mean age of the 219 participants was 46.5 years (range 23 to 92 years), majority (36.1%) of whom were aged between 41 to 50 years. Most study participants had stage 2B (21.9%) cancer type, and the histological grade 3 breast cancer was predominant type (50.2%).

Nearly half of the patients (46.1%) developed metastases. In bivariate analyses, cancer stage 2A (OR 0.29, 95% CI 0.12 to 0.77) and stage 2B (OR 0.41, 95% CI 0.21- 0.77), presence of estrogen receptors (OR 0.24, 95% CI 0.12 to 0.77), presence of progesterone receptor (OR 0.26, 95% CI 0.09 to 0.72), human epidermal growth factors (OR 0.05, 95% CI 0.003 to 0.84), and those on hormonal treatment (OR 0.34, 95% CI 0.19 to 0.62) were factors less likely to be associated with development of metastasis after treatment. In multivariate analysis, HIV positive status (OR 0.004, 95% CI 0.002 to 0.75), presence of estrogen (OR 0.23, 95% CI 0.08 to 0.64) and human epidermal growth factors (OR 2.53, 95% CI 1.64 to 3.91) receptors and obesity (OR 2.53, 95% CI 1.64 to 3.91) were independent factors influencing development of metastasis after treatment.

Conclusion: This study showed that development of metastasis after breast cancer therapy has associations with the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor -2 (HER-2) as well as the stage of diagnosis. This study demonstrates the need for enhanced screening for breast cancer to improve early diagnosis and the testing of ER, PR and HER-2 are crucial as they predict outcomes of therapy.

Key words: Breast cancer, breast cancer treatment, cancer treatment outcomes, cancer treatment predictors.

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1. Introduction

Breast cancer is the most prevalent cancer among Kenyan women, and constitutes a major public health problem (Mutuma and Korir, 2006; WHO and IARC, 2008).

Although definite prevalence and incidence studies are lacking for Kenya, some estimates indicate that breast cancer accounts for about 23 % of all cancers, while cervical cancer and prostate cancer represent about 20 % and 9.4 % of all cancers respectively (Ministries of Health, 2011).

Breast cancer is a leading cause of death worldwide, and ranks as the fifth cause of death from cancer overall, and the most common cause of cancer death in women in both developing and developed countries (WHO, 2013).

However there is a more favourable survival of breast cancer following treatment in developed countries compared to sub-Saharan Africa (WHO and IARC, 2008).

The development of metastasis and local recurrence also vary for different treatments, and for different population groups (Youlden et al, 2012). Diverse factors are responsible for such variations, including demographics, ethnicity, disease stage of diagnosis, and co-morbidities. Nonetheless, most studies on predictors of breast cancer treatment outcome have been undertaken in developed countries, and there is paucity of data on predictive indicators of breast cancer treatment outcomes in Africa (Sant et al, 2004).

This study was therefore designed to determine the predictive factors of outcomes of breast cancer treatment in patients in a Kenyan teaching and referral hospital.

2. Methods

2.1 Study site

Kenyatta National Hospital (KNH) located in Nairobi, Kenya, is the largest national referral hospital in Kenya.

KNH has a Cancer Treatment Centre that offers comprehensive care and treatment to cancer patients. Treatment options offered include chemotherapy, radiotherapy and surgery.

2.2 Study Design

Patients of 18 years or above, diagnosed with breast cancer who first visited the KNH Cancer Treatment Centre in the period 2007 to 2008 were eligible for the study.

The design was an analytic retrospective hospital based cohort study that involved examination of records of patients undergoing breast cancer treatment.

A sample size of 219 patients was calculated to be sufficient to detect cancer recurrence or metastasis in patients at a two sided level of significance of 5 % and 95 % level of confidence.

Inclusion Criteria

Female breast cancer patients were eligible for inclusion in the study if they were adults aged at least 18 years. The patients had to have made their first visit to the KNH Cancer Treatment centre in period 2007 to 2008.

Exclusion Criteria

Patients were excluded if they were under 18 years of age or were male. Females were excluded if their medical record did not disclose date of diagnosis.

Outcomes

The primary outcome was development of metastasis in breast cancer patients undergoing treatment. Recurrence of the disease was a secondary outcome.

2.3 Statistical Analysis

Qualitative variables were described in frequencies or percentages, and chi-square test was used to test for the strength of association between categorical variables.

Quantitative variables were described with medians or means. Bivariate and multivariate analyses were used to determine the demographic, clinical and treatment types associated with the development of metastasis after treatment. In bivariate analyses, odds ratios (OR) and 95% confidence intervals (CI) for the association between development of metastasis and demographic, clinical or therapy characteristics was calculated using Poisson regression. In multivariate analyses, a manual backward elimination approach was used to reach the most parsimonious model including factors that were associated with the development of metastasis at the significance level of $p \leq 0.05$. The time to event analysis was estimated using the Kaplan–Meier product limit method. All statistical analyses were performed using STATA v 9.2 (StataCorp LP, Texas USA).

2.4 Ethical considerations

This study was approved by the Kenyatta National Hospital and University of Nairobi Ethics and Research Review Committee (KNH/UoN ERC, Approval Reference No. **P/403/11/2010**).

3. Results

Baseline characteristics of the study population

A total of 219 women were included in this study. The mean age of the participants was 46.5 years with median of 45 years [23- 92]. There were two main age group peaks: 36.1% were aged 41-50 years and 28.3% aged 31 to 40 years (**Table 1**).

The mean white blood cells (WBC) count was 6.6 x 10^9 cells/L, with a median of 12.7 x 10^9 cells/L [2 - 13.8]. Majority (59.8%) of the participants had WBC count within the normal ranges of 3.6 to 11.2 X 10^9 cells/L

The mean Hemoglobin (Hb) content was 12.45 (SD 1.93) g/dL and a median of 12.6 g/dL [2.9 - 17.7]. Majority (44.3%) of the participants had normal Hb ranges of 12 to 17 g/dL while 23.7% and 0.9% had

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abnormal Hb values in the lower and higher ranges respectively. The mean platelet count was 332.4 (SD 120.84) X 10^3/mm^3 and a median of 313 X 10^3/mm^3 [14 - 821 X 10^3]. Majority (51.6%) of the participants had normal platelets ranges of 140 to 440 X 10^3/mm^3 while 2.7% and 14.6 % had platelets values in the lower and higher ranges respectively.

The majority 18.3% of those whose HIV status was known were negative with only 3.7 % being positive ($p < 0.05$). 13.7% of patients tested for estrogen receptors (ER) had positive results compared to 15.5% whose results were negative. 12.8% had progesterone receptors (PR) positive results versus 16.4% whose results were negative ($p < 0.05$) (**Table 2**).

Table 1: Characteristics of study participants at study enrollment

Characteristic	Level	No. (n=219)	%
White Blood Cells count (* 10^9 cells/L)			
Mean (± SD 2.289)	6.6	151	68.9
Median (Range)	12.7 (2-13.8)	151	68.9
Haemoglobin (g/dL)			
Mean (± SD 1.93)	12.45	151	68.9
Median (Range)	12.6 (2.7 -17.7)	151	68.9
Platelets (* 10^3 /mm^3)			
Mean (± SD 120.84)	332.4	151	68.9
Median (Range)	313 (14-821)	151	68.9
Urea (mg/dL)			
Mean (± SD 7.07)	4.645	108	49.3
Median (Range)	3.9 (1.5-76)	108	49.3
Creatinine (µmol/L)			
Mean (± SD 29.67)	81.99	115	52.5
Median (Range)	80 (8.6-188)	115	52.5

Table 2: Participants HIV and Hormonal receptors characteristics

Characteristic	Sample size		$\chi 2$	df	P
	No	%			
HIV status					
Negative	40	18.3			
Positive	8	3.7	202.606	2	0.001
Not stated	171	78.1			
Estrogen receptor					
Negative	34	15.5			
Positive	30	13.7	138.274	2	0.001
Not stated	155	70.8			
Progesterone receptor					
Negative	36	16.4			
Positive	28	12.8	138.603	2	0.001
Not stated	155	70.8			
Human epidermal growth factor receptor					
Negative	35	16			
Positive	19	8.7	173.954	2	0.001
Not stated	164	74.9			

$\chi 2$ - Chi square; df- Degree of freedom; P- Level of significance

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Table 3: Clinical parameters and association with treatment outcomes

Clinical parameters	Total	Metastasis		Bivariate		Multivariate	
		Freq	Per	OR (95%CI)	P value	OR (95%CI)	P value
HIV status							
Positive	**8**	**2**	**25**	0.24(0.02-2.75)	0.258	**0.04(0.002-0.75)**	**0.031**
Negative	40	19	47.5	Referent	Referent	Referent	Referent
Presence of comobidities							
Yes	192	89	46.4	0.95(0.52-1.75)		NS	0.808
No	27	12	44.4	Referent	Referent		Referent
Cancer stage							
Stage 1	3	0	0	ND	ND		ND
Stage 2A	**27**	**6**	**22.2**	**0.29(0.12-0.77)**	**0.028**		0.153
Stage 2B	**46**	**14**	**30.4**	**0.41(0.21-0.77)**	**0.046**	NS	0.125
Stage 3A	48	23	47.9	0.64(0.37-1.11)	0.116		0.705
Stage 3B	44	23	52.3	0.71(0.41-1.21)	0.207		0.91
Stage 3C	12	6	50	0.67(0.28-1.61)	0.376		0.38
Stage 4	21	17	81	Referent	Referent		
Histological types							
Ductal carcinoma grade 1	6	1	16.7	Referent	Referent		Referent
Ductal carcinoma grade 2	62	21	33.9	0.69(0.3701.28)	0.243	NS	0.914
Ductal carcinoma grade 3	110	59	53.6	1.09(0.6601.82)	0.714		0.158
Body Surface Area (M^2)							
< 1.6	19	6	31.6	Referent	Referent	NS	Referent
?1.6	69	26	37.7	0.71(0.45-1.12)	0.146		0.174
Body Mass Index (Kg)							
<18.5kg (underweight)	2	1	50	1.12(0.15-8.26)	0.908		0.354
18.5-25 (normal)	58	28	48.3	Referent	Referent	NS	0.17
25-30 (overweight)	60	26	43.3	0.97(0.57-1.67)	0.926	1.97(0.99-3.91)	0.051
? 30(Obese)	**36**	**18**	**50**	1.13(0.62-2.03)	0.697	**2.24(1.09-4.57)**	**0.026**
ER Receptors							
Negative	34	14	41.2	Referent	Referent		
Positive	**30**	**4**	**13.3**	**0.24(0.09-0.67)**	**0.007**	**0.23(0.08-0.64)**	**0.005**
PR Receptors							
Negative	36	14	38.9	Referent	Referent		
Positive	**28**	**4**	**14.3**	**0.26(0.09-0.72)**	**0.01**	NS	0.289
HER-2 Receptors							
Negative	35	11	31.4	Referent	Referent		
Positive	**19**	**1**	**5.3**	**0.05(0.03-0.84)**	**0.037**	**0.027(0.001-0.61)**	**0.024**

NS-Not significant; ND-Not done; PR- Prevalence Ratio; CI-Confidence intervals; No.-Number; %-Percentage

The mean Hemoglobin (Hb) content was 12.45 (SD 1.93) g/dL and a median of 12.6 g/dL [2.9 - 17.7]. Majority (44.3%) of the participants had normal Hb ranges of 12 to 17 g/dL while 23.7% and 0.9% had abnormal Hb values in the lower and higher ranges respectively.

The mean platelet count was 332.4 (SD 120.84) X 10^3/mm^3 and a median of 313 X 10^3/mm^3 [14 - 821 X 10^3]. Majority (51.6%) of the participants had normal platelets ranges of 140 to 440 X 10^3/mm^3 while 2.7% and 14.6 % had platelets values in the lower and higher ranges respectively.

The majority 18.3% of those whose HIV status was known were negative with only 3.7 % being positive ($p < 0.05$). 13.7% of patients tested for estrogen receptors (ER) had positive results compared to 15.5% whose results were negative. 12.8% had progesterone receptors (PR) positive results versus 16.4% whose results were negative ($p < 0.05$) (**Table 2**).

8.7% whose human epidermal growth factors receptors (HER-2) tests were done had positive results compared to 16% whose results were negative. The mean body mass index (BMI) was 27.106 (SD 5.205) Kg/m^2 and a median of 26.76 Kg/m^2 [17.04 - 46.82]. Based on the BMI, 27.4% of the participants were overweight while 26.5% of patients had normal weight, with BMI of 18.5-25 Kg/m^2. About 0.9% and 16.4% were underweight (BMI < 18.5 Kg/m^2) and obese (BMI ≥30 Kg/m^2).

21.9% of the participants at the diagnostic stage were in cancer stage 3A, 21% in stage 2B, 20.1% in stage 3B, 1.4% in stage 1, and 9.6% in stage 4. The most common (50.2%) histological grade of the breast cancer was ductal carcinoma grade 3 followed by 28.3% ductal carcinoma grade 2 while 2.7% were ductal carcinoma grade 1.

Majority (75.8%) of the participants were on first line chemotherapy containing cyclophosphamide, doxorubicin and fluorouracil (CAF), 5.5% were on cyclophosphamide, methotrexate and fluorouracil

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(CMF), 3.2% on doxorubicin and cyclophosphamide (AC) while 0.5% were on cyclophosphamide, methotrexate, vincristine and fluorouracil (CMVF).

13.67% of the participants who did not respond to first line chemotherapy were subsequently put on second line chemotherapy. Second line therapy consisted of docetaxel and zoledronic acid (19.4%), docetaxel and vinorelbine (16.1%), docetaxel alone (12.9%), zoledronic acid (12.9%), fluorouracil (3.2%) and capecitabine (3.2%).

About 62.6 % of the participants were on hormonal therapy, with 54.8% on tamoxifen while 0.9% were on anastrozole. 35.6 % of the participants were on hormonal treatment for 1 - 3 years, 17.8 % for 4 - 6 years, while 0.9% were on treatment for seven years or longer.

Of the 219 participants, 24 (11%) had adverse effects during the course of hormonal treatment. Most (16.7%) of the adverse effects were joint pains. Other adverse effects included back pain (8.3%), chest pain (8.3%), and numbness (8.3%).

Treatment outcomes

Of 219 participants on treatment 101 (46.1%) had metastasis after treatment while 118 (53.9 %) had no evidence of metastasis disease or were lost to follow-up. Majority (10.5%) of the metastasis cases were to the bone. Others were lung metastasis (8.7%), local recurrence (10.5%), liver metastasis (1.8%), brain metastasis (1.8%), and lymphedema (0.5%).

Clinical factors influencing treatment outcome

Overall, in bivariate analyses, participants who were in breast cancer stage 2A were less likely to develop metastasis after treatment compared to participant who were in cancer stage 3 at the time of initiation of treatment (OR 0.29, 95% CI 0.12 to 0.77). Similarly, participants who were in breast cancer stage 2B were equally less likely to develop metastasis after treatment compared to participants who were in cancer stage 3 at the time of initiation of treatment (OR 0.41, 95% CI 0.21- 0.77) (**Table 3**).

In multivariate analyses, participants who were obese (BMI 25 - 30) were 24 % more likely to develop metastasis after treatment compared to those with normal BMI (OR 2.24, 95% CI 1.09 - 4.57). It was surprising to observe that HIV positive individuals were almost 3% less likely to develop metastasis after treatment compared to participants who were HIV negative (OR 0.04, 95% CI 0.002 - 0.75) (**Table 3**).

However, demographic factors, ethnicity and age groups were not associated with treatment outcomes in bivariate and multivariate analyses.

In bivariate analyses, participants who had estrogen receptors, progesterone receptors and human epidermal growth factors were less likely to develop metastasis after treatment compared to those who did not have these receptors (OR 0.24, 95% CI 0.09 - 0.67), (OR 0.26, 95% CI 0.09 - 0.72) and (OR 0.05, 95% CI 0.03 - 0.84) respectively.

In multivariate analyses, participants who had estrogen receptors were independently less likely to develop metastasis after treatment compared to those without these receptors (OR 0.23, 95% CI 0.08 - 0.64). Furthermore, participants with human epidermal growth factors were about 2% less likely to develop metastasis after treatment compared to participants who did not have these receptors (OR 0.027, 95% CI 0.0012 - 0.61).

Patients who experienced side effects of treatment were less likely to develop metastasis after treatment compared to those who did not experience any form of side effects (OR 0.34, 95% CI 0.12 - 0.91).

Overall, patients who were on hormonal treatment were less likely to develop metastasis after treatment compared to those who were not on hormonal treatment (OR 0.34, 95% CI 0.19 - 0.62) (**Figure 1**).

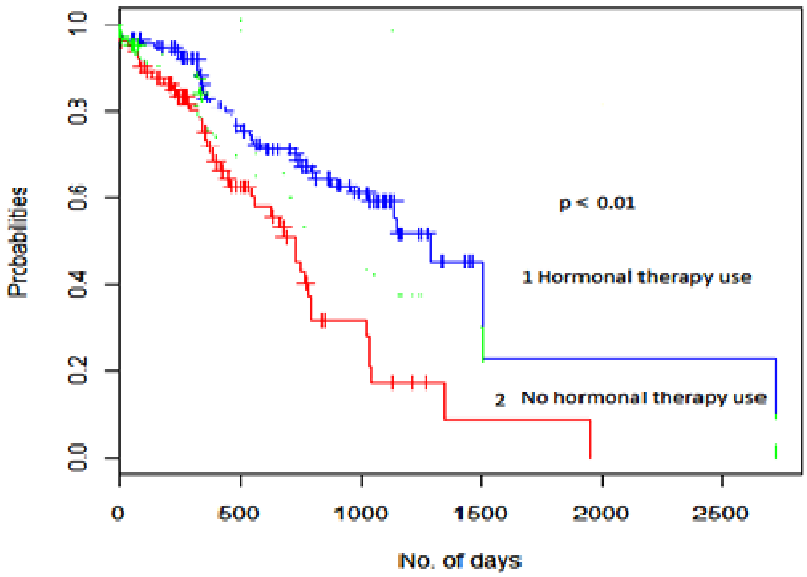

Figure 1: Survival curves for female breast cancer patients on hormonal therapy and non hormonal chemotherapy

4. Discussion

This study was conducted in female breast cancer patients to determine predictors of breast cancer treatment outcomes in Kenya's largest referral hospital.

On the basis of the results, ensuring that women are diagnosed early and put on treatment is one way of improving breast cancer treatment outcomes. According to our findings, women who at the time of initiation of treatment were in breast cancer stage 2 were less likely to develop metastasis compared to those who were in cancer stage 3. The impact of stage of diagnosis on treatment outcome was also reported to be associated by Porta et al (1991) who showed that the probability of survival decreased with increasing stage of breast cancer in Spanish women.

Our study further showed that metastasis after breast cancer therapy has associations with the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor -2 (HER-2). Women who expressed ER, PR or HER-2 were less likely to develop metastasis after treatment compared to those who did not express these receptors. Additionally, females with tissue biopsies positive for ER were independently less likely to develop metastasis after treatment compared to those who tested negative, and patients whose immunohistochemical tests were HER-2 positive were about 2% less likely to develop metastasis after treatment compared to those whose tests turned out negative.

Our findings agree with several studies in developed countries that have shown that patients who test negative for ER, PR or HER-2 have worse treatment outcomes and poorer survival (Colleoni et al, 2004; Bauer et al, 2007; Weigel and Dowsett, 2010). This shows that the expression of ER, PR and HER-2 can be biomarkers predictive of breast cancer treatment outcome in this group of patients.

Age was however not associated with risk of development of metastasis. This contrasts with other studies, where younger age was associated to higher risk of development of metastasis and older age had a lower risk (Adami et al, 1985). The difference could be due to social demographic and ethnicity differences between the studies undertaken in western countries and our study set in urban Kenya.

Another interesting finding in this study is that patients who tested positive for HIV were found to have a lower association with progression to stage 4 disease. This finding requires more research to investigate the relationship between HIV infection and breast cancer.

This study is not without limitations. The study findings should not be generalized, without further studies in more diverse study populations. Kenya has more than 40 ethnic communities, and for this study to be broadly valid all ethnic groups should be included in a broader study.

5. Conclusion

This study demonstrates the need for enhanced screening for breast cancer to improve early diagnosis and treatment as it is associated with better treatment outcomes. Testing of ER, PR and HER-2 are also crucial as they predicted the outcomes of breast cancer therapy in this group of patients. Moreover younger patients form a significant proportion of the population studied, and more effort should therefore be put in the early diagnosis and treatment of these patients as they have poorer prognosis.

Conflict of Interest declaration

The authors declare no conflict of interest

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