Drivers of Disparities in Stage at Diagnosis Among Women With Breast Cancer: South African Breast Cancers and HIV Outcomes Cohort

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Abstract

Objective

In low- and middle-income countries (LMICs), advanced stage diagnosis of breast cancer (BC) is common, and this contributes to poor survival. By understanding the determinants of the stage at diagnosis will aid in designing interventions to downstage disease and improve survival from BC in LMICs.

Methods

Within the South African Breast Cancers and HIV Outcomes (SABCHO) cohort, we examined factors affecting the stage at diagnosis of histologically confirmed invasive breast cancer at five tertiary hospitals in South Africa. The stage was assessed clinically. To examine the associations of the health system, socio-economic/household and individual factors, hierarchical multivariate logistic regression with odds of late-stage at diagnosis (stage III-IV), was used.

Results

The majority (59%) of the included 3497 women were diagnosed with late-stage BC disease (59%). The effect of health system-level factors on late-stage BC diagnosis was consistent and significant even when adjusted for both socio-economic- and individual-level factors. Women diagnosed in a tertiary hospital that predominantly serves a rural population were almost 3 times (OR=2.89 (95% CI: 1.40-5.97) likely to be associated with late-stage BC diagnosis when compared to those diagnosed at a hospital that predominantly serves an urban population. Taking more than 3 months from identifying the BC problem to first health system entry (OR=1.66 (95% CI: 1.38–2.00)), and receptor subtypes [luminal B (OR=1.49 (95% CI: 1.19–1.87)), HER2 enriched (OR=1.64 (95% CI: 1.16–2.32))] were associated with a late-stage diagnosis. Whilst having a higher socio-economic level (a wealth index of 5) reduced the probability of late-stage BC, OR=0.64 (95% CI: 0.47 – 0.85).

Conclusion

Advanced stage diagnosis of BC among women in SA who access health services through the public health system was associated with both modifiable health system-level factors and non-modifiable individual-level factors. These may be considered as elements in interventions to reduce the time to diagnosis of breast cancer in women.

Introduction

Breast cancer (BC) is currently the most diagnosed cancer in the world; among women, it accounts for close to 12% of all new cancers [1-3]. While survival is high in high-income countries (HICs), both incidence and mortality rates are increasing in low- and middle-income countries (LMICs) including South Africa (SA). These regions contribute over 53% of all new global BC cases and about 62% of global BC mortality

[4]. In sub-Saharan Africa (SSA), the estimated 3-year survival of women diagnosed with breast cancer is around 58% as compared to 90% in the United States (US) [5-6].

The high mortality rates among patients with BC are associated with a myriad of health system, patient, and environmental factors among the majority of the socioeconomically disadvantaged populations of SSA. This group is subject to structural vulnerability, which is also true for socioeconomically disadvantaged communities in HICs where disparities in BC survival rates are evident [7]. The socio-economically disadvantaged are more likely to experience poor general health status, disability, the simultaneous occurrence of more than one chronic condition or disease along with cancer (multimorbidity) and are less likely to access healthcare services [8-9].

Late-stage at diagnosis is a major contributing factor to low survival in SSA [10]. A later stage at BC diagnosis means, by definition, that the tumour is of a larger size or has spread beyond the breast to regional lymph nodes (stage III) or distant metastatic sites (stage IV) [11]. Cultural, socio-demographic and health system challenges associated with disparities in stage at BC diagnosis among SSA populations are beginning to be reported in the literature [12-15]. We aimed to contribute further to these findings by performing an in-depth analysis of health system, socio-economic, and individual-level factors that may be associated with disparities in stage at diagnosis of invasive BC in a cohort of socioeconomically disadvantaged women from urban and rural communities enrolled in the South African Breast Cancer and HIV-outcomes (SABCHO) cohort [16]. We also assessed the complex hierarchical inter-relationships among these (health system, socio-economic/household, and individual) factors to understand their roles in stage at BC diagnosis.

Methods

Study setting and data source

South Africa (SA) has a dual (public and private) healthcare system. Most of the population, approximately 84%, depend on the resource-constrained public health care system [17]. Within this group, there exists immense inequality, a wide range of economic levels including poverty and high unemployment rates [17-18]. The remaining 16% seek health services from the private sector, aided by their private health insurance which will at least partially cover cancer diagnosis and treatment.

The SABCHO cohort study [16] has enrolled women with newly diagnosed invasive breast cancers at 5 tertiary care hospitals in the Gauteng and KwaZulu-Natal (KZN) provinces of SA (Figure 1), with characteristics summarised in Table 1.

The Johannesburg hospitals serve predominantly urban and peri-urban communities, whereas the KZN sites serve both urban and rural communities. For the Chris Hani Baragwanath Academic Hospital (CHBAH) most BC patients are directly referred from local community-based primary care clinics in Soweto, Johannesburg. The other participating hospitals receive most of their patients from regional hospitals that receive symptomatic patients from their feeder district primary care clinics. In all these public sector

settings, BC is diagnosed at a symptomatic stage because there are no mammography-based nor clinical breast examination population-based screening programmes in SA. The Johannesburg tertiary hospital breast units perform the diagnostic assessments for BC including core biopsies for histopathological examination, immunohistopathology and receptor subtyping and provide multimodal cancer treatments, whereas, in KZN, core biopsies are performed mainly in regional hospitals where breast cancer surgical procedures are often also performed, particularly for rural patients. Chemo- and radiation therapy and endocrine treatments are provided in all the tertiary hospital sites. Details of each site are summarised in Table 1.

Table 1
Characteristics of study academic hospital

Tertiary academic hospitals	Chris Hani Baragwanath Academic Hospital (CHBAH)	Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)	Inkosi Albert Luthuli Central Hospital (Durban)	Grey's Hospital (Greys)	Ngwelezane Hospital (Ngwelezane)
Province	Gauteng		KwaZulu Natal		
Location	Johannesburg	Johannesburg	Durban	Pietermaritzburg	Empangeni
Catchment area population (N)	Soweto (3 million)	Johannesburg East and Central (1.5 million)	Durban Metropolitan, KZN province (3.5 million)	Western KwaZulu-Natal (3.5 million)	Uthungulu, Umkhanyakude, Zululand (3 million)
Urban / rural distribution	Urban	Urban	Urban	Urban and rural	Rural
Patients referred from	Mostly district primary care clinics; some regional hospitals	District primary clinics and regional hospitals	Regional hospitals	Regional hospitals	Regional clinics
Core biopsy diagnostic procedure locations	Mainly tertiary hospital	Mainly tertiary hospital	Mainly district secondary hospitals	Mainly district secondary hospitals	District secondary hospitals

Participants' recruitment and inclusion criteria

The SABCHO research team has prospectively collected data for more than 3,500 women with newly diagnosed invasive BC. Women were eligible to be recruited into the SABCHO study, if they were at least 18 years of age, were enrolled between July 1, 2015, and December 31, 2019, with a new diagnosis of stage I-IV invasive BC, had no prior history of cancer, received BC treatment at one of the study hospitals.

Participants were clinically staged at the time of diagnosis using the 7th edition of the American Joint

Committee on Cancer (AJCC) BC. Trained staff at the hospitals collected through face-to-face interviews and entered the following data: socio-demographic information (e.g., age, marital status, employment status, the highest level of education completed); reproductive history (number of full-term pregnancies, use of oral and injectable contraceptives), and behavioural factors (alcohol consumption, smoking). Household or socio-economic scores were calculated using patients' self-reported homeownership, home with indoor running water, car ownership, etc). Details of other collected variables and clinical data, their calculations including distances from the place of residence to the place of diagnosis and knowledge of BC, have been reported previously [9, 13].

Statistical analyses

We analysed the health system, socioeconomic and individual-level characteristics of the cohort grouped by stage at diagnosis: early (stages I and II) and late (stages III and IV). We used Pearson chi-squared and Fisher's exact tests to compare the distributions of values of categorical variables and student's t-test and the Wilcoxon rank-sum test to compare means and medians of continuous variables by stage group. We then conducted a hierarchical multivariate logistic regression analysis to examine the associations of individual, socio-economic, and health system-level characteristics with stage at diagnosis. This approach enabled us to investigate complex hierarchical inter-relationships among the three-broad individual, socio-economic, and health system variables. Figure 2 describes our approach to the analysis of the hierarchical relationship among the three broad variables. The labelled arrows represent the causal effect of the relevant variables. Health system factors (the distal determinants) may affect the stage at diagnosis directly ((c), Figure 2), or indirectly ((a & b), Figure 2), via the socio-economic and individual factors, which may, in turn, influence the stage at diagnosis. Health system-level factors are wider determinants of health, such as access and referral routes to health care services and geographical location. These factors are not directly under individual control but are considered part of the environment in which people live and work. Socio-economic-level factors include wealth index, employment status and education attainment. Lastly, individual-level factors are non-socioeconomic and include age, knowledge, genetics, disease and comorbidity clinical characteristics.

Model 1 of the hierarchical regression assessed the overall association of health system factors with the stage at diagnosis ((c), Figure 2). This model excluded the socio-economic/household and individual variables. In model 2, the socio-economic factors were added and their association with the stage at diagnosis was assessed, controlling for health-system factors ((a & e), Figure 2). The remaining effect of health system factors in model 2 thus reflected the part which was not confounded by socioeconomic factors.

The individual variables were added in model 3 to determine the association of personal and clinical characteristics with the stage at diagnosis, controlling for the health system, and socioeconomic variables ((a, d & f), Figure 2). The independent effects of the health system ((c), Figure 2), and socioeconomic factors ((e), Figure 2) were determined.

We pooled aggregate data using the meta-analysis common-effect inverse-variance model to estimate the overall association of the three variable levels with BC stage at diagnosis. We also conducted subgroup

analyses of the association of each of the three-block variables with the stage at diagnosis. We used Stata version 16 (StataCorp Ltd, Texas, US) to analyse these data.

Results

Health system and socio-economic-level factors of women with stages I-IV breast cancer

In 3497 women with BC, 2058 (58.9%) were diagnosed with late-stage (stage III-IV) disease. The health system and socio-economic characteristics of these women are summarised and compared by stage in Table 2. Tertiary hospital site appeared associated with stage at diagnosis and was included in subsequent hierarchical multivariate regression analyses. CHBAH had the greatest proportion of women presenting with early-stage disease (48.27%) as compared to Ngwelezane which had only 15.07%. In terms of late-stage disease, Ngwelezane had the greatest proportion (84.93%) as compared to CHBAH which had 51.73%. Overall, 63.86% (n=1242) of women who were indirectly referred had late-stage diagnoses ($p<0.001$). At the CHBAH site, 39.0% of patients had been indirectly referred, compared with 57.0% at CMJAH, 74.0% at Durban, 93.0% at Greys and 88.0% at Ngwelezane. Those directly referred from primary care facilities received their core biopsies at the tertiary hospital pathology sites.

Table 2
Health system and socio-economic-level characteristics of women with stages I-IV breast cancer in the SABCHO cohort by stage at diagnosis

	Early Stage		Late Stage		Total	p-value
	N	%	N	%	N (100%)	
Total	1439	41.1	2058	58.9	3497	
HEALTH SYSTEM-LEVEL CHARACTERISTICS						
Nearby tertiary hospital (where patients were diagnosed)						
CHBAH – Gauteng	656	48.27	703	51.73	1359	<0.001
CMJAH- Gauteng	332	38.16	538	61.84	870	
Durban	215	36.38	376	63.62	591	
Greys	225	37.25	379	62.75	604	
Ngwelezane	11	15.07	62	84.93	73	
Referral mode for diagnosis						
Direct from primary to tertiary	736	47.42	816	52.58	1552	<0.001
Indirect- primary to secondary to tertiary	703	36.14	1242	63.86	1945	
SOCIO-ECONOMIC-LEVEL CHARACTERISTICS						
Highest level of education attained						
Primary education or below	261	33.81	511	66.19	772	<0.001
Secondary education or higher above	1169	43.33	1529	56.67	2698	
Employment status						
Employed	402	42.05	553	57.95	956	<0.001
Unemployed	738	38.56	1176	61.44	1914	
Retired	295	47.81	322	52.19	617	
Homeownership						
Yes	899	42.09	1237	57.91	2136	0.158
No	536	39.67	815	60.33	1351	
Household possession wealth index						
1 (least wealthy)	201	28.76	498	71.24	699	<0.001
2	269	38.48	430	61.52	699	

	Early Stage		Late Stage		Total	p-value
3	290	41.43	410	58.57	700	
4	321	45.92	378	54.08	699	
5 (Wealthiest)	358	51.14	342	48.86	700	

Having less education (primary education and below) was associated with late-stage diagnosis as were unemployment and lack of household possessions (wealth index) ($p < 0.001$ for all the above).

Socioeconomic factors that appeared to be associated with stage at diagnosis and that were subsequently explored in hierarchical regression analyses were highest education level attained ($p < 0.001$), employment status and household possession wealth index ($p < 0.001$).

Individual-level factors of the women with stages I-IV breast cancer

As Table 3 shows, the mean age of the SABCHO participants was 55.7 (SD 14.3) years at diagnosis. Those women diagnosed at an early stage were older, than those diagnosed late ($p = 0.006$) and a larger proportion were postmenopausal ($p = 0.001$). Married women, those with a family history of cancer, and those with good knowledge of cancer were more likely than others to have been diagnosed at an early stage. Most women were diagnosed with hormone-responsive tumours, luminal A (ER/PR+/HER2-) (61.0%) and luminal B (ER/PR+/HER2+) (16.5%). The majority of women (70.6%) were diagnosed within 3 months from first recognising their breast symptoms and close to 58.7% ($n = 2051$) of women resided within 20km from their pathology diagnostic facility. Individual-level factors that initially appeared to be associated with later stage at diagnosis and that were subsequently explored in hierarchical regression analyses included younger age at diagnosis ($p = 0.006$), more full-term pregnancies ($p < 0.001$), single marital status ($p = 0.001$), self-reported family history of breast cancer ($p < 0.001$), less knowledge of breast cancer prior to diagnosis ($p = 0.034$), higher body mass index at diagnosis ($p = 0.016$), current cigarette smoker ($p < 0.001$) and regular alcohol intake ($p = 0.005$). Other individual factors that appeared to be associated with later stage at diagnosis were greater residential distance to histopathology diagnostic hospital ($p < 0.001$) and longer delay period from initial symptom detection to immunohistopathology confirmed diagnosis ($p < 0.001$). Clinical factors that initially appeared to be associated with later stage at diagnosis were self-reported comorbid diabetes ($p = 0.024$), hypertension ($p = 0.001$), HIV status ($p < 0.001$), BMI ($p = 0.016$) and BC receptor subtype ($p < 0.001$).

Table 3
Individual characteristics of women with stages I-IV breast cancer in the SABCHO cohort with stage at diagnosis

	Early Stage		Late Stage		Total	p-value
	N	%	N	%	N (100%)	
Total	1439	41.1	2058	58.9	3497	
INDIVIDUAL CHARACTERISTICS						
Age at diagnosis (mean(sd)), years						
	1439	56.65(13.71)	2058	54.95(14.69)	3497 [55.65(14.32)]	0.006
Age at menarche (mean(sd)), years						
	1332	15.94 (2.49)	1896	14.68 (2.29)	3228[15.20(2.38)]	0.2674
Number of complete/full-term pregnancies (median (IQR))						
	1307	3(2-4)	1907	3(2 - 4)	3214[3(2 - 4)]	<0.001
Menstrual status						
Pre-menopausal	499	37.55	830	62.45	1329	0.001
Post-menopausal	940	43.36	1228	56.64	2168	
Marital status						
Single	368	36.15	650	63.85	1018	0.001
Married/cohabiting	582	43.47	757	56.53	1339	
Divorced/widowed	485	42.92	645	57.08	1130	
Family history of cancer						
Yes	241	49.59	245	50.41	486	<0.001
No	1167	39.86	1761	60.14	2928	
Used contraception						
Yes	872	40.86	1262	59.14	2134	0.630
No	564	41.69	789	58.31	1353	
Knowledge of breast cancer						
Less/Intermediate knowledge	393	38.49	628	61.51	1021	0.034
Good knowledge	1049	42.37	1427	57.63	2476	

	Early Stage		Late Stage		Total	p-value
Body mass index (BMI) (kg/m ²)						
<25	198	36.07	351	63.93	549	0.016
25-29.9	368	43.60	476	56.40	844	
≥30	802	41.84	1115	58.16	1917	
Smoke cigarettes						
Yes	224	51.61	210	48.39	434	<0.001
No	1211	39.67	1842	60.33	3053	
Alcohol intake						
Yes	309	45.91	364	54.09	673	0.005
No	1126	40.00	1688	60.00	2814	
Diabetes						
Yes	208	46.02	244	53.98	452	0.024
No	1227	40.43	1808	59.57	3035	
Hypertension						
Yes	633	44.48	790	55.52	1423	0.001
No	802	38.86	1262	61.14	2064	
HIV						
Negative	1146	42.76	1534	57.24	2680	<0.001
Positive	273	35.73	491	64.27	764	
HIV positives on ARVs at time of breast cancer diagnosis						
Yes	228	37.38	382	62.62	610	0.082
No	45	29.80	104	70.20	151	
Receptor subtype						
ER/PR+/ HER2-	971	45.80	1149	54.20	2120	<0.001
ER/PR/ HER2+	202	35.25	371	64.75	573	
ER/PR-/HER2+ (HER2 Enriched)	69	29.61	164	70.39	233	
ER/PR/HER2- (Triple-Negative)	196	35.64	354	64.36	550	

	Early Stage		Late Stage		Total	p-value
Distance for the individual to travel to the closest diagnosis hospital						
<20 km	898	43.78	1153	56.22	2051	<0.001
20 to 59 km	358	37.41	599	62.59	957	
60 to 100 km	42	30.22	97	69.78	139	
>100 km	141	40.29	209	59.71	350	
Time (in months) from identifying the problem to histopathology-confirmed diagnosis						
<=3	1118	45.28	1351	54.72	2469	<0.001
>3	324	31.52	704	68.48	1028	

Health system-level characteristics, and later stage at diagnosis (Table 4, model 1)

As Table 4 shows, health system-level characteristics were the most important risk factors for late-stage BC diagnosis in the study population; both hospital where patients were enrolled in SABCHO and referral mode for diagnosis were associated with late-stage in all three hierarchical multivariate regression models. In the core health system level characteristics model 1, women diagnosed at Ngwelezane hospital, were more than 4 times (OR=4.40 (95% CI: 2.28 - 8.46)) more likely to have late-stage BC than women diagnosed at CHBAH hospital. Larger proportions of women diagnosed at the other hospitals had late-stage BC. Having been referred from feeder primary clinics to secondary hospitals and then to the tertiary hospitals was also associated (OR=1.49 (95% CI: 1.28 - 1.73)) with late-stage BC diagnosis.

Table 4

Hierarchical multiple logistic regression models of the associations between community, socio-economic, individual-level characteristics, and stage at diagnosis in the SABCHO cohort

Variables	Health system characteristics model	Health system + socio-economic/household model	Health system + socio-economic/household + individual model
	OR¹ (95% CI)	OR² (95% CI)	OR³ (95% CI)
HEALTH SYSTEM-LEVEL CHARACTERISTICS			
Tertiary hospital			
CHBAH – Gauteng	1	1	1
CMJAH- Gauteng	1.52 (1.28 – 1.81)	1.64 (1.37 – 1.97)	1.70 (1.37 – 2.11)
Durban	1.44 (1.71 – 1.77)	1.45 (1.17 – 1.79)	1.92 (1.39 – 2.66)
Greys	1.28 (1.03 – 1.58)	1.12 (0.90 – 1.40)	1.26 (0.94 -1.69)
Ngwelezane	4.40 (2.28 – 8.46)	3.00 (1.54 – 5.85)	2.89 (1.40 – 5.97)
Referral mode for diagnosis			
Direct from primary to tertiary	1	1	1
Indirect- primary to secondary to tertiary	1.49 (1.28 – 1.73)	1.36 (1.16 – 1.59)	1.32 (1.07 – 1.62)
SOCIO-ECONOMIC-LEVEL CHARACTERISTICS			
Highest level of education attained			
Primary education and below		1	1
Secondary education and above		0.78 (0.65 – 0.93)	0.82 (0.65 – 1.01)
Employment			
Employed		1	1
Unemployed		1.05 (0.89 – 1.24)	1.14 (0.94 – 1.40)
Retired		0.84 (0.68 – 1.04)	1.12 (0.84 – 1.50)
Homeownership			

Variables	Health system characteristics model	Health system + socio-economic/household model	Health system + socio-economic/household + individual model
	OR ¹ (95% CI)	OR ² (95% CI)	OR ³ (95% CI)
Yes		1	1
No		1.04 (0.90 – 1.21)	1.03 (0.85 – 1.25)
Wealth index			
1		1	1
2		0.77 (0.61 – 0.97)	0.83 (0.64 – 1.08)
3		0.69 (0.55 – 0.88)	0.84 (0.64 – 1.11)
4		0.55 (0.43 – 0.69)	0.72 (0.54 – 0.95)
5 (Wealthiest)		0.48 (0.38 – 0.62)	0.64 (0.47 – 0.85)
INDIVIDUAL CHARACTERISTICS			
Age at diagnosis			
			0.99 (0.98 – 1.00)
Age at menarche			
			1.02 (0.98 – 1.06)
Number of complete/full-term pregnancies			
			1.07 (1.02 – 1.13)
Menstrual status			
Pre-menopausal			1
Post-menopausal			0.99 (0.75 – 1.31)
Marital status			
Single			1
Married/cohabiting			0.88 (0.71 – 1.09)
Divorced/widowed			0.87 (0.69 – 1.09)
Family history of cancer			
No			1
Yes			0.77 (0.61 – 0.97)
Knowledge of breast cancer			

Variables	Health system characteristics model	Health system + socio-economic/household model	Health system + socio-economic/household + individual model
	OR¹ (95% CI)	OR² (95% CI)	OR³ (95% CI)
Less/Intermediate knowledge			1
Good knowledge			0.79 (0.66 – 0.95)
Body mass index (BMI)			
<25			1
25-29.9			0.82 (0.63 – 1.07)
≥30			0.93 (0.73 – 1.18)
Smoke cigarettes			
No			1
Yes			0.67 (0.52 – 0.87)
Alcohol intake			
No			1
Yes			0.84 (0.68 – 1.05)
Diabetes			
No			1
Yes			0.92 (0.71 – 1.19)
Hypertension			
No			1
Yes			0.86 (0.71 – 1.05)
HIV			
Negative			1
Positive			0.97 (0.78 – 1.22)
Receptor subtype			
ER/PR+/ HER2-			1
ER/PR+/ HER2+			1.49 (1.19 – 1.87)
ER/PR-/HER2+ (HER2 Enriched)			1.64 (1.16 – 2.32)

Variables	Health system characteristics model	Health system + socio-economic/household model	Health system + socio-economic/household + individual model
	OR ¹ (95% CI)	OR ² (95% CI)	OR ³ (95% CI)
ER/PR/HER2- (Triple-Negative)			1.36 (1.08 – 1.71)
Distance from residence to diagnostic hospital			
<20 km			1
20 to 59 km			1.11 (0.89 – 1.38)
60 to 100 km			1.00 (0.70 – 1.42)
>100 km			0.85 (0.63 – 1.15)
Time (in months) from identifying the problem to first health system entry			
<=3			1
>3			1.66 (1.38 – 2.00)

Health system- and socio-economic-level characteristics, and later stage at diagnosis (Table 4, model 2)

The associations of socio-economic-level factors with the stage at diagnosis were adjusted for confounding by health system factors in model 2. Two socio-economic variables, attaining secondary and higher level of education compared with primary or lower education (OR= 0.78 (95% CI: 0.65-0.93) and increasing wealth index (OR= 0.77 (95% CI: 0.61-0.97); OR= 0.69 (95% CI: 0.55-0.88); OR= 0.55 (95% CI: 0.43–0.69) and OR= 0.48 (95% CI: 0.38 – 0.62)) respectively for wealth indices 2-5 compared with poorest wealth index 1, were associated with earlier stage at BC diagnosis. The associations of health system-level factors with stage were attenuated but remained statistically significant in model 2. Notably, after adjusting for socioeconomic factors, the later stage at diagnosis originally seen in Greys and Ngwelezane hospitals was fully explained by these factors in Greys site (OR=1.12 (95% CI: 0.90 – 1.40)), and Ngwelezane site (OR=3.00 (95% CI: 1.54 – 5.85)).

Health system, socio-economic and individual-level characteristics, and later stage at diagnosis (Table 4, model 3)

In model 3, higher parity(number of complete or full-term pregnancies (OR=1.07 (95% CI: 1.02 – 1.13)), receptor subtype [luminal B (OR=1.49 (95% CI: 1.19 – 1.87)), HER2 enriched (OR=1.64 (95% CI: 1.16 – 2.32)) and Triple Negative subtypes OR= 1.36 (95% CI: 1.08-1.71)] and taking more than 3 months from identifying the BC problem to first health system entry (OR=1.66 (95% CI: 1.38 – 2.00)), were associated with late-stage diagnosis, even when both health system- and socio-economic-level factors were taken into

account. Other individual-level factors such as having a family history of cancer (OR=0.77 (95% CI: 0.61 – 0.97)), having good knowledge of BC (OR=0.79 (95% CI: 0.66 – 0.95)) and smoking cigarettes (OR=0.67 (95% CI: 0.52 – 0.87)) also were associated with an early-stage diagnosis of BC in the presence of both health system and socio-economic-level factors. The health system-level factors remained strongly associated with late-stage BC diagnosis.

The health system-level (tertiary hospitals) characteristics continued to be positively associated with late-stage BC diagnosis (percentage late-stage increased from hospitals that predominantly serve urban distribution to those that serve rural distribution, whilst wealth index characteristics showed a protective effect to being diagnosed with late-stage BC (percentage late-stage decreased with increase in wealth index) even when adjusted for each other and age at diagnosis (Figure 3).

Discussion

In this study, we examined the associations of the health system, socio-economic (household) and individual factors with BC stage in a cohort of women. We identified health system-level factors (tertiary hospital and referral route to diagnosis) and individual-level factors (having more full-term pregnancies and breast receptor subtypes) as important correlates of late-stage at BC diagnosis. We found that greater wealth was protective against late-stage at BC diagnosis. Overall, health system-level variables, tertiary hospital and referral mode for diagnosis, were the most important risk factors for late-stage BC diagnosis.

In the presence of both health system and individual-level factors, we found that women who were relatively wealthier, and better educated were more likely to be diagnosed with BC earlier. These findings are congruent with what was identified in other studies that have been conducted in LMIC settings [12-13, 20-22]. There is a high possibility that having higher education might mean having good knowledge of BC because in our study, having good knowledge of BC was found to be protective of later-stage diagnosis of BC. This link between higher education and having good knowledge of BC was also explained in a Nigerian study [21]. Increasing BC awareness through health promotion and education should be prioritised regardless of socio-economic status and such activities might be beneficial if introduced early in the mainstream education system and through sustained community-level health and cancer literacy interventions

In SSA the prevalence of prolonged delays of more than three months from symptom recognition to care-seeking can range up to 70% as compared to less than 17% in the USA and Europe [25]. Furthermore, BC progression is time-dependent [12, 26]. Our findings have shown the significance of delaying for more than 3 months, from identifying BC symptoms/problems to first health system entry, as a predictor of advanced-stage diagnosis. This finding is consistent with what has been reported in West Africa and in the ABC-DO cohort of 1795 women from SSA with breast cancer that included women from our Soweto site as well as women from Namibia, Uganda, Zambia and Nigeria [14, 27]. Reducing the interval between identifying the BC problem and first health system entry is crucial to downstaging disease at diagnosis and this can be facilitated by bringing BC diagnosis services into the community or primary care facilities with for example screening clinical breast examination, fine-needle aspiration point-of-care triaging diagnostic approaches

and by simplifying the referral process (as suggested by our findings). Such early detection strategies have been demonstrated to work in other parts of Africa [28-29] and in a 20-year Indian trial, proven to downstage disease among women of all ages and to increase survival among postmenopausal women [30].

In the model with health system and socioeconomic factors, luminal B, HER2 enriched, and triple-negative BC subtypes were found to be significantly associated with later-stage diagnosis of BC in our cohort when compared to luminal A. This is similar to what has been found elsewhere in Africa and high-income countries, for these more aggressive, faster-growing tumours [6,14,31].

Conclusion

Later stage diagnosis of BC among predominantly poor women in SA who access health services through the public health system is associated with modifiable health system-level factors as well as non-modifiable individual-level factors. Having shown the hierarchical interrelation between health system, socio-economic and individual factors, addressing community health systems barriers by introducing affordable evidence-based community and primary care screening and developing inexpensive point-of-care diagnostic tests may facilitate downstaging of BC in most poor resourced settings. The strong association of late-stage diagnosis with an indirect referral for diagnosis of women at regional secondary hospitals needs urgent examination. The CHBAH site that receives the majority of its patients directly referred from primary healthcare clinics in Soweto, had the greatest proportion of women presenting with early-stage disease, which suggests that secondary hospitals should not be involved in cancer diagnosis and management in South Africa. Before advocacy for any policy change is made, however, more research is required. We need to unpack in detail, the associations between referral mode and (i) women delay periods before accessing care and (ii) the number of visits and time spent within the referral facilities from date of first access to date of definitive diagnosis. Qualitative research with all stakeholders to understand in detail the reasons for patient and health system delays also need to be undertaken. We also need to understand how best to intervene in communities and in primary care settings to implement existing policy and guidelines for screening clinical breast examination.

Declarations

Ethical Approval and Consent to participate

The SABCHO study was approved by the University of the Witwatersrand Human Research Ethics Committee (Approval Number: M150351, dated: 6th May 2015, recertified M1911203 dated 28 January 2020), the University of KwaZulu-Natal Biomedical Research Committee, BF080/15, and the Institutional Review Board of Columbia University (protocol number AAAQ1359, dated 1st January 2016).

Consent for publication

The authors affirm that the research participants provided informed consent for publication of their de-identifiable data.

Availability of supporting data

This study contains confidential patient information; requests for de-identified data that support the results reported in this article may be made to the corresponding author.

Competing interests

The author(s) declare(s) that they have no competing interests.

Where authors are identified as personnel of the International Agency for Research on Cancer or World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of these organisations.

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Authors' contributions

WM - Made substantial contributions to the conception; design of the work; acquisition, analysis, and interpretation of data; drafted the work and substantively revised it.

SAN - Made substantial contributions to the conception; design of the work; acquisition, analysis, and interpretation of data; drafted the work and substantively revised it.

AC - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

OAA - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

WCC - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

JSJ - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

AIN - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

PR - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

HC - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

DSO - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

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SN - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

BP - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

TC - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

VAM - Made substantial contributions acquisition, analysis, and interpretation of data; and substantively revised the work.

MJ - Made substantial contributions to the conception; design of the work; acquisition, analysis, and interpretation of data; drafted the work and substantively revised it.

All the authors approved the submitted version and they agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Figures

Figure 1

Tertiary care hospitals participating in the SABCHO study

Figure 2

Conceptual hierarchical framework for factors potentially associated with breast cancer stage at diagnosis

Figure 3

Tertiary hospital and wealth index with a late-stage BC diagnosis