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Drivers of advanced stage at breast cancer diagnosis in the multicountry African breast cancer – disparities in outcomes (ABC-DO) study

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Breast cancer (BC) survival rates in sub-Saharan Africa (SSA) are low in part due to advanced stage at diagnosis. As one component of a study of the entire journey of SSA women with BC, we aimed to identify shared and setting-specific drivers of advanced stage BC. Women newly diagnosed in the multicountry African Breast Cancer–Disparities in Outcomes (ABC-DO) study completed a baseline interview and their stage information was extracted from medical records. Ordinal logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for advanced stage (I, II, III, IV) in relation to individual woman-level, referral and biological factors. A total of 1795 women were included from Nigeria, Uganda, Zambia, and the multiracial populations of Namibia and South Africa, 1091 of whom (61%) were stage III/IV. Stage was lower in women with greater BC knowledge (OR 0.77 (95% CI: 0.70, 0.85) per point on a 6 point scale). More advanced stage was associated with being black (4.00 (2.79, 5.74)), having attended <secondary education (1.75 (1.42, 2.16)), having never heard of BC (1.64 (1.31, 2.06)), an unskilled job (1.77 (1.43, 2.20)) and pregnancy in the past 3 years (30% of ≤45 year olds) (1.63 (1.15, 2.31)), and were mediated through delays to diagnosis: symptom duration of ≥1 year (OR 2.47 (1.93, 3.15)). These findings provide further evidence that late-stage BC in SSA is largely attributed to modifiable factors and strategies to improve BC education and awareness in women and the health system should be intensified.

Breast cancer (BC) is the most common cancer and the second most common cause of cancer death in women in sub-Saharan Africa (SSA).[1] In high-income countries, this cancer generally has a favorable prognosis, but unfortunately this is not the case in SSA. The few published five-year survival estimates are close to, or below, 50%,[2–7] and stand in marked contrast to 80% and 91% for US black and white women, respectively, diagnosed 2005–2011.[8] The reasons for poor

Key words: breast cancer, stage at diagnosis, survival, sub-Saharan Africa

Abbreviations: ABC-DO: African Breast Cancer–Disparities in Outcomes (study); BMI: body mass index; CI: confidence interval; ER: oestrogen receptor; FISH: florescent in-situ hybridization; HER2: human epidermal growth factor receptor 2; HIV: human immunodeficiency virus; IHC: immunohistochemistry; OR: odds ratio; PAF: population attributable fraction; PR: progesterone receptor; SD: standard deviation; SEP: socio-economic position; SSA: sub-Saharan Africa; TNM: tumor, node, metastasis classification

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What's new?

Breast cancer (BC) patients in sub-Saharan Africa (SSA) tend to have poor prognoses and low survival rates. This is largely because the majority of cases are not diagnosed until the disease has reached an advanced stage. In this study, the authors found that delayed diagnosis is associated with several modifiable factors, including limited schooling, low-wage jobs, and lack of awareness of BC. With incidence rates of BC steadily climbing in SSA, it is urgent that efforts to improve disease-specific education and awareness both among women and throughout the healthcare system be intensified.

survival in SSA are multifactorial, involving late presentation and stage at diagnosis, barriers to receiving and complying with appropriate treatment, and possibly, differences in tumor biology. Stage at diagnosis is a key prognostic factor for BC universally, including in SSA.[4,9] For example, in Ethiopia in 2005–10, 5-year distant metastases-free survival was 72% for stage I/II compared with 33% for stage III.[9]

As one of the multiple strategies needed to reduce BC deaths, the Breast Health Global Initiative (BHGI) recommends that the prevention of advanced symptomatic BC, using resource-appropriate strategies, should be regarded as a priority in low-income settings.[10] This priority is pertinent to SSA, where a recent systematic review revealed that between 45% and 90% of women are diagnosed at stage III and IV in different settings, none of which have organized screening programs.[11] This wide range of advanced stage tumors suggests that BC stage migration may be a realistic target within similarly resource-limited settings, for which an understanding of context-specific drivers of advanced stage at diagnosis is first needed.

Advanced stage at diagnosis is a function of a combination of the rate of tumor growth or spread, and the actions or reactions leading to the timing of diagnosis. The rate of tumor growth can be affected by biological determinants such as hormone receptor and/or environmental factors such hormone exposure during pregnancy. The likelihood of metastatic spread increases as cancers grow, meaning that delays to prompt diagnosis and treatment are associated with worsened prognosis, delays that can be attributed to both system- and woman-level (lifestyle, sociodemographic) factors.[12] In SSA, BC diagnosis typically concerns symptomatic disease, therefore the time interval between onset of symptoms and seeking help provides a critical time window of opportunity for achieving early diagnosis.[13,14] To react and seek help, however, patients must go through "symptom appraisal,"[14] a process which is likely to be heavily influenced by a woman's awareness of BC, and by the unique socio-cultural characteristics and belief systems prevalent in the SSA region.

The African Breast Cancer – Disparities in Outcomes (ABC-DO) study is a multicountry prospective study of BC outcomes in SSA. Among this BC cohort, we aimed to identify major shared and setting-specific drivers of advanced stage at BC diagnosis, including woman-level, referral-related and symptom duration and biological-level factors. We further attempted to examine whether the identified drivers operated mainly through changes in the rate of tumor growth or through time delays in BC diagnosis.

Methods

Study design and participants

ABC-DO is a prospective hospital-based study of outcomes after new BC diagnosis in adult (≥18 years old) women in five SSA countries, as described in detail previously.[15] The present analysis concerns 1939 women primarily recruited in tertiary hospitals: Windhoek Central Hospital, Namibia; Mulago Hospital and the Uganda Cancer Institute, Kampala, Uganda; the Federal Medical Centre, Owerri, Nigeria; University Teaching Hospital and the Cancer Diseases Hospital, Lusaka, Zambia; and the Chris Hani Baragwanath Academic Hospital, Soweto, South Africa (SA). In Aba, Nigeria, patients originated from Abia State University Teaching Hospital and the Maranatha private clinic hospital. The latter comprised a different patient profile and route to diagnosis than the other settings, and thus was considered as a distinct setting from the other Nigerian hospitals. Within the Nigerian healthcare system, private hospitals are utilized more than public, and waiting time is reported as the strongest determinant of facility choice,[16,17] meaning, in contrast to many other settings, private clinics are not restricted to the very rich and can have over representation of palliative care patients.

Recruitment started in September–December 2014, and had completed by April 2017, with the exception of Zambia (May 2016–September 2017), and SA which is ongoing for other purposes. For SA, women diagnosed until the last data extract (22 November 2016) were included. Participation involved a baseline interview, consent to access medical records and tumor tissue, and to be actively followed up telephonically at regular intervals.

ABC-DO was approved by ethics committees of all involved institutions: IARC (IEC 13–19, IEC15–18), LSHTM (6459), Federal Medical Centre Owerri, Abia State University Teaching Hospital, University of Zambia Biomedical Research Ethics Committee (004–08–15), University of Witwatersrand (M150345), Uganda National Council for Science and Technology (HS 1588) and the Ministry of Health and Social Services of Namibia (17/3/3).

Baseline questionnaire

The same face-to-face baseline questionnaire was utilized in all settings except SA where a pre-existing one was administered and harmonized to ABC-DO as outlined below. For the current analysis we included questions on age, marital and menopausal status at diagnosis (defined in Table 1 footnotes);

Table 1. Women and breast tumor characteristics in the ABC-DO cohort, overall and by stage at diagnosis[1]

Variable	Category or unit	Total ($n = 1795$)	Lower stage (0,I,II)[6]	Advanced stage (III,IV)[7]	
		Column %	*N*	*N*	Row %
All women	-	100	704	1091	61
Country and ethnic group	Namibia – black	22	143	256	64
	Namibia – non-black	6	78	26	25
	Nigeria – public	17	88	211	71
	Nigeria – private clinic	4	11	61	85
	South Africa – black	19	164	186	53
	South Africa – non-black	2	21	9	30
	Uganda	22	143	256	64
	Zambia	8	56	86	61
Age at diagnosis, years	Mean (SD)		53 (14)	50 (14)	
Woman-level					
Married	Yes	46	317	797	61
	No	54	384	588	60
Received secondary education	Yes	58	443	568	56
	No	42	230	488	68
Employment (current/past)	Skilled	28	243	258	52
	Unskilled	49	281	581	67
	N/A	23	170	243	59
SEP score	Low (0–3)	33	189	403	68
	Medium (4–6)	36	213	420	66
	High (7–9)	31	291	254	47
Parous	Yes	92	633	978	61
	No	8	57	89	61
Ever heard of BC	yes	81	608	838	58
	no	19	88	247	74
BC knowledge score	Low (0–2)	14	80	160	67
	Medium (3)	41	261	477	65
	High (4–5)	45	355	448	56
	missing		8	6	43
Referral-level					
Contacts with providers	1	13	73	144	66
	2	22	152	228	60
	3	27	186	275	60
	4	18	131	184	58
	5+	20	129	224	63
Resides in urban area	Yes	53	395	547	58
	No	47	309	543	64
Symptom duration (months)	<3	29	261	231	47
	3 to <6	18	123	184	60
	6 to <12	20	112	222	66
	12+	33	167	400	71
Biological-level					
HIV positive	Yes	10	62	116	65
	No/nk	90	642	975	60

Table 1. Women and breast tumor characteristics in the ABC-DO cohort, overall and by stage at diagnosis (Continued)

Variable	Category or unit	Total ($n = 1795$)	Lower stage (0,I,II)[6]	Advanced stage (III,IV)[7]	
		Column %	*N*	*N*	Row %
Receiving antiretrovirals[2]	Yes	89	39	78	67
Any other comorbidity	-	50	361	534	60
BMI, kg/m^2	Mean (SD)		28 (7)	27 (6)	
Post-menopausal at diagnosis[3]	Yes	53	397	548	58
	No	47	307	543	64
Recent pregnancy[4]	Yes	12	41	128	76
	No	88	478	768	62
Tumor size (mm)	Median (IQR)		35 (22–50)	70 (42–100)	
Grade	Well differentiated	11	81	115	59
	Moderately	29	232	280	55
	Poorly	21	154	230	60
	Unknown	39	237	466	66
Morphology[5]	Ductal	79	520	774	60
Receptor status	ER/PR+ HER2−	57	248	287	54
	ER/PR+ HER2+	19	86	98	53
	ER-PR-HER2+	7	29	40	58
	Triple negative	17	57	100	64
	Missing		284	566	67

[1]% lower/advanced amongst non-missing data. Missing data were few: marital status ($n = 9$), education ($n = 66$), employment ($n = 19$), SEP ($n = 25$), BC awareness ($n = 14$); BMI ($n = 108$); contacts with health providers ($n = 69$); delay time ($n = 95$); comorbidity ($n = 7$); morphology ($n = 153$); parity ($n = 38$).
[2]Among those listed HIV+ on medical records.
[3]Postmenopausal women had no menstrual periods in the previous 6 months, or had irregular periods or missing status and were over age 50; pre-menopausal had regular periods, or irregular/missing periods information and were under age 50 (median age at menopause within ABCDO was 49 years).
[4]Information not available for South Africa—% from Namibia, Nigeria, Uganda and Zambia.
[5]348 of which are lobular or other.
[6]Stage 0, I, IIA and IIB have 22, 102, 282 and 298 women, respectively.
[7]Stage IIIA, IIIB, IIIC and IV had 302, 415, 96 and 278 women, respectively. Metastatic site: bone ($n = 27$), liver (88), lung (62), brain (12), not specified (48).

detailed self-identified ethnic group was ascertained and dichotomized as black *versus* non-black. Employment was grouped into 3 categories: highly skilled/skilled, unskilled, and not applicable in ABC-DO and, respectively, employed, unemployed and retired in SA. Usual place of residence was defined as urban (city/town) or rural (village/rural) in ABC-DO and, in SA, as residing <10 km or ≥ 10 km straight-line distance to the diagnostic hospital. A score for socioeconomic position (SEP) ranging from 0 (low) to 9 (high) was generated from the sum of 9 equally-weighted (+1 each) possessions and facilities: home ownership; indoor water; flush toilet; electricity; vehicle; refrigerator; landline phone; gas or electric stove; and a bed. HIV infection (yes *vs*. no/not known) was based on self-reports (97% agreement with clinical records among those for whom the latter were available). Having other comorbidities (yes vs no) included any one of high blood pressure (the most common), heart disease, diabetes and history of any cancer and in all countries except SA it additionally included anemia, chronic obstructive pulmonary diseases, asthma, hepatitis, tuberculosis, other infections, and any other diseases. Measurements of height and weight at recruitment were used to calculate body mass index (BMI, kg/m^2), which was categorized into standard WHO groupings.[18] An indicator for recent pregnancy (yes vs no), defined as being pregnant at diagnosis or having given birth within 3 years of diagnosis, was created for all sites except SA where this information was not collected.

BC awareness prior to the current diagnosis was assessed at all sites. Indicators included whether the woman had ever heard of BC (yes vs no/do not know) and, in all sites except SA, whether BC is curable (yes vs no/do not know). A BC knowledge score (range 0–5 (highest)) was generated from the sum of positive answers (+1 each) to: (*i*) ever knowing anyone with BC; (*ii*) believing BC can be inherited; and negative responses (+1) to: believing BC could be (*iii*) caught from others; caused by (*iv*) an injury to the breast or (*v*) a curse or spiritual attack. Women were also asked to recall their journey to BC diagnosis. Two key features of this

journey were included in the present analysis: (*i*) the total number of pre-diagnostic contacts with health care providers, including traditional and alternative care providers, and (*ii*) symptom duration, as self-recalled from the date when the woman noticed the first symptom/sec to the date of BC diagnosis, with the later defined as per the European Network of Cancer Registries guidelines[19] and which typically coincided with the date of interview.

Stage at diagnosis and other tumor characteristics

BC stage at diagnosis, prior to the initiation of any treatment, was assessed using the American Joint Committee on Cancer (AJCC) TNM staging system.[20] Clinical staging and ultrasound were the primary methods used to ascertain stage, with <5% assessed using magnetic resonance imaging, computerized tomography or bone scan. Information on stage was available for 93% ($n = 1795$) of women overall; <1% was missing in Namibia, 1% in SA, 14% in Nigeria, 9% in Uganda, and 19% in Zambia due to ongoing data collection. Strike action that prohibited access to medical records led to higher proportions of missing stage information in Nigeria but likely in an unbiased fashion. Other tumor characteristics obtained were grade and morphology. Additionally, in SA and Namibia and occasionally at other sites, receptor status was determined (oestrogen-receptor (ER), progesterone-receptor (PR) and human epidermal growth factor receptor 2 (HER2)), by immunohistochemistry and, for HER2, florescent in situ hybridization. ER and PR were considered positive if >1% staining was present, and HER2 as positive if FISH was positive or HER2 score was 3.

Pathways to advanced stage at diagnosis

In an attempt to assess whether identified drivers of advanced stage at diagnosis were likely to act mainly through a time-to-diagnosis pathway or a tumor progression rate pathway, neither of which could be directly observed, the modeling strategy considered *a priori* confounders as core factors (age, ethnicity and country setting) and assumed that the total time-to-diagnosis, which is the sum of time from symptom onset to symptom recognition (unobserved) and symptom duration, is affected by determinants of the actions and reactions at the woman-level (marital status and family, education, employment and BC awareness) and by referral factors (contacts with health care providers, residential setting).[12] The modeling strategy also assumed that tumor growth rate is affected by biological factors (tumor subtype, grade and morphology, BMI, HIV and comorbidities, menopausal status, and recent pregnancy as such tumors tend to be more aggressive due to the pregnancy hormonal milieu).[21–23]

Statistical methods

The primary outcome was stage at diagnosis, which was analyzed using ordinal logistic regression models to estimate odds ratios (OR) for more advanced tumor stage, coded into 4 levels, 1 through 4, for stages 1 = 0 & I; 2 = IIA & IIB; 3 = IIIA, IIIB, & IIIC; 4 = stage IV. This model assumes a common OR for each ordered dichotomy of the 4 stages. ORs were first examined separately in relation to three groups of factors: woman-level, referral and biological factors (as defined above). For each, ORs were first estimated adjusting for age at diagnosis (categorical), country setting, and black/non-black ethnicity ("core models"), before simultaneously adjusting for all indicators within the same group of factors, and then adjusting for covariates from other groups. Finally, amongst the majority black women, we estimated population attributable fractions (PAFs) for advanced stage BC (stage III/IV v 0/I/II) in public hospital settings, from logistic regression models regressed on variables that were significant in ordinal models. All analyses were performed using STATA version 14.2. All p values are two-sided.

Results

A total of 1795 women with BC were included with nonmissing stage information: 503 (28%) from Namibia; 399 (22%) from Uganda; 380 (21%) from SA; 371 (21%) from Nigeria and 142 (8%) from Zambia (Table 1). Hereafter, sample-wide descriptions and associations are provided in tables, and where setting-specific information adds extra insight—this is provided in the text. At diagnosis, approximately half of women were premenopausal, half were married and half had attended secondary education or higher. In total, 178 (10%) were HIV positive, predominantly women from Namibia (11% HIV-prevalence), SA (14%) and Uganda (10%). Of the 1415 non-SA women, 169 (12%) had had a recent pregnancy. From the 945 tumors examined to date, most were ER/PR + HER2− (57%), 19% were ER/PR + HER2+ and 17% were triple negative. Overall, 1091 women (61%) were diagnosed at advanced stage (stage III or IV), of which 15% were stage IV with lung and liver being the most common metastatic sites. Among stage 0–II cancers, stages IIA and IIB predominated; *in situ* and stage I, that is, tumors <2 cm were rare (7% overall). The most common symptoms reported by women (not mutually exclusive) were a lump or thickening of the breast (87%) followed by pain (26%), and swelling or lump in the armpit (15%, data not shown).

Ethnic group, country and age at diagnosis

The lowest proportions of advanced stage cancer occurred in non-black women in Namibia (25%) and in SA (30%), and the highest in women recruited at the private clinic in Nigeria (85%), followed by public hospital patients in Nigeria (71%), in Namibian black women (64%) and Ugandan women (64%) (Table 1). Consequently, among core variables, being black as opposed to non-black emerged as the strongest determinant of more advanced stage (OR 4.00), which was partly but not fully explained by woman-level and referral factors (OR = 2.56; 95% CI 1.69–3.86) (Table 2). This association arises from lower stage in the multi-racial populations in Namibia (where 13% were white and 7% mixed-ancestry) and SA (5% mixed-ancestry), and was stronger in older than

Table 2. Associations between woman-level factors, referral indicators and symptom duration with advanced stage at breast cancer diagnosis, ABC-DO cohort

Variable	Adjustment→	Core[1], $n = 1795$		Core[1] + woman-level[2] $n = 1669$		Core[1] + woman[2] + referral[3] + symptom duration $n = 1594$	
	Category↓	OR	95% CI	OR	95% CI	OR	95% CI
			Core				
Country	South Africa	1					
	Namibia	1.43	1.11–1.83	1.39	1.01–1.92	1.22	0.86–1.73
	Nigeria – public	1.73	1.30–2.29	1.76	1.23–2.53	2.41	1.54–3.78
	Nigeria – private clinic	2.68	1.68–4.26	3.04	1.81–5.11	4.47	2.46–8.11
	Uganda	1.55	1.18–2.03	1.27	0.86–1.87	1.02	0.67–1.54
	Zambia	1.21	0.85–1.72	1.18	0.79–1.79	1.22	0.77–1.92
Ethnicity	Non-black	1					
	Black	4.00	2.79–5.74	2.67	1.79–3.97	2.56	1.69–3.86
Age	60+ years	1					
at diagnosis	50–59	0.98	0.77–1.25	1.14	0.88–1.49	1.12	0.86–1.47
	40–49	1.16	0.91–1.47	1.40	1.07–1.83	1.36	1.03–1.80
	<40	1.25	0.97–1.61	1.58	1.17–2.13	1.48	1.08–2.03
			Woman-level				
Marital status	Married	1					
	Not married	1.19	0.99–1.44	1.11	0.91–1.35	1.03	0.84–1.27
Education	Secondary	1					
	<Secondary	1.75	1.42–2.16	1.32	1.04–1.69	1.27	0.98–1.63
Employment	Skilled	1					
	Unskilled	1.77	1.43–2.20	1.38	1.08–1.77	1.34	1.03–1.73
	n/a	1.49	1.14–1.94	1.10	0.81–1.49	1.10	0.80–1.51
SEP	Continuous score	0.88	0.84–0.92	0.95	0.90–1.01	0.98	0.92–1.04
Ever heard	Yes	1					
of BC	No/unsure	1.64	1.31–2.06	1.24	0.96–1.59	1.26	0.97–1.63
BC knowledge	Continuous score	0.77	0.70–0.85	0.83	0.74–0.92	0.86	0.77–0.96
			Adjustments as above				
Symptom	<3	1		1		1	
duration	3 to <6	1.47	1.13–1.93	1.36	1.03–1.80	1.33	1.00–1.77
(months)	6 to <12	1.91	1.45–2.52	1.72	1.29–2.29	1.65	1.24–2.20
	12+	2.47	1.93–3.15	2.15	1.66–2.77	2.03	1.56–2.63

Referral-level	Adjustment→ Category↓	Core[1]		Core[1] + referral-level[3] $n = 1725$		Core[1] + woman[2] + referral[3] + symptom duration n=1594	
No. contacts	1	1					
with care	2	1.43	1.00–2.03	1.39	0.98–1.98	1.35	0.93–1.95
providers	3	1.97	1.34–2.89	1.87	1.27–2.74	1.85	1.23–2.77
	4	1.97	1.31–3.05	1.92	1.25–2.93	1.98	1.26–3.10
	5+	2.41	1.58–3.68	2.32	1.52–3.55	2.04	1.30–3.20
Residence	Urban	1					
	Rural	1.44	1.19–1.73	1.37	1.13–1.67	1.07	0.85–1.34

Abbreviations: BC: breast cancer; CI: confidence interval; n/a: not applicable; OR: ordinal odds ratio; SEP: socio-economic position.
[1]Basic model: Adjusted for age at diagnosis (<40, 40–49, 50–59, ≥60 years), country and black versus non-black ethnicity, estimated by ordinal logistic regression on stage 0, I, IIA, IIB, IIIA, IIIB, IIIC and IV.
[2]Woman-level factors are marital status, education, employment, socioeconomic position, BC awareness and knowledge.
[3]Referral factors are place of residence, number of contacts with providers.

younger women (p interaction 0.006, not in tables), reflecting a greater excess of advanced stage disease in black than non-black women over age 50 (61% vs 20%) than under (67% vs 40%). Country-specific ethnic differences were also examined, but were generally underpowered. Nevertheless, in Namibia, compared to the majority Ovambo women (29% of the sample), Nama (8%, OR 2.0 (1.0–4.0)) and Angolan (9%, OR 1.7 (1.0–3.1)) women had advanced stage, whilst Damara (11%), Herero (10%) and Kavango (5%) had raised, albeit not statistically significant, ORs of 1.3 to 1.6 (not shown). All settings, except Zambia, had a more advanced stage at BC diagnosis than SA, including after taking age and ethnic group into account. The increase in odds of more advanced BC in Namibia and Uganda, compared to SA, were fully attenuated upon adjustment for referral-related, symptom time and woman-level factors (Table 2). In contrast, compared to SA, advanced stage at diagnosis in the Nigerian settings could not be explained by woman-level or reported symptom duration. Younger age at diagnosis was not associated with more advanced stage in core models but became significant when adjusted for women-level factors (OR 1.58 for <40 years: Table 2); the magnitude of this association increased further upon adjustment for women-level plus biological variables in the subset with these available (OR 2.02 for <40 years: Table 3).

Woman-level factors

Lower SEP and lower general educational level were associated with more advanced stage, as indicated by not having secondary education (OR 1.75) and holding an unskilled job (OR 1.77) (Table2). Another indicator (not in Tables) of lower education, illiteracy, showed similar findings: in the one in five women who were illiterate in both their mother tongue and English, 76% had advanced stage compared to 60% of literate women. These associations remained after adjusting for BC-awareness indicators, which were themselves independently predictive of more advanced stage: never having heard of BC (OR 1.64) and poor knowledge of the disease (OR 0.77 per unit increase in knowledge score). Similarly, in non-SA sites, not knowing that BC is curable was also associated with advanced stage (OR 1.27 (1.02–1.59), not in Tables). These associations were all attenuated upon adjustment for referral-related factors, especially symptom duration, showing that their associations arise, at least partially, through a delay in time-to-diagnosis pathway. No associations were found between stage and parity or marital status at the time of diagnosis.

Further analyses were conducted to investigate why woman-level factors were not fully attenuated when adjusting for symptom duration. Differences persisted when adjustment for time was continuous as opposed to categorical. Additionally, within each delay stratum, mean tumor size was smaller among the more educated women (e.g., for symptom duration of <3 months: 52 mm; 12+ months: 65 mm) than among their less educated counterparts (<3 months: 55 mm; 12+ months: 69 mm). Similarly results held for indicators of poor BC awareness (not shown). Together these findings suggest that the length of women's prerecognition intervals may also have been inversely associated with their educational level and BC awareness.

Symptom duration and referral factors

The distribution of symptom duration for each setting, overall and by advanced stage is shown in Figure 1. The symptom duration was, as expected, strongly associated with more advanced stage (OR 2.5 for ≥12 vs <3 month symptom duration) and was not majorly attenuated upon adjustment for any factors (Table 2). More prediagnostic contacts with health care providers or living in rural areas were associated with longer duration of symptoms (e.g., 18% of women with one contact reported ≥12 months with symptoms, vs 45% of women with ≥5 contacts, and 30% of urban *vs*. 37% of rural-residing women), thus these factors were also associated with advanced stage, but residential setting was fully attenuated upon adjustment for time with symptoms.

Adjusting for the biological factors listed in Table 3, within the subset of participants for whom such data were available, minimally affected the woman-level, referral and delay associations described above. In particular, the advanced stage associations with having less than secondary education (OR 1.57 (1.06–2.31), being in unskilled employment (OR 1.62 (1.09–2.39) having more BC knowledge (OR 0.79 (0.67–0.92), and having a delay time longer than 3 months (3–<6 months 1.45 (0.96–2.19); 6–<12 months OR 2.21 (1.40–3.51); 12+ months OR 2.61 (1.77–3.84)), remained significant, and were in fact even stronger in the biological subset of women (not in Tables).

Biological factors

Associations between biological factors and more advanced stage diagnosis are provided in Table 3, based on available data primarily from Namibia and SA. Compared to those with well differentiated tumors, women with moderately (OR 1.7) or poorly differentiated (OR 2.1) tumors were more likely to be diagnosed at a more advanced stage, and this strong association was, as expected, not confounded by woman-level or referral factors. Black women still had advanced stage at diagnosis, compared with non-black women, after adjusting for both woman-level, and referral indicators (Table 2) as well as tumor characteristics (Table 3). In this study, there was no suggestion of any association between HIV status, having other comorbidities or high BMI with advanced stage. Having had a recent pregnancy within 3 years was independently associated with more advanced stage at diagnosis in the core model (OR 1.65; 1.15–2.37) and after adjustment for woman-level and referral factors. Recent pregnancy tended to occur in younger women: with little between-country variation; 30% of women under age 45 were within 3 years of pregnancy, of which 13% were currently pregnant, 18% within 1 year, 33% 1 to 1.9 years, and 36% 2

Table 3. Associations between biological factors and advanced stage diagnosis of breast cancer in the ABC-DO cohort

Variable	Adjustment→	Core model[1] $n = 869$		Core[1] + all biological $n = 869$		Core[1] + biological +woman-level[2] $n = 792$		Core[1] + biological + woman[2] + referral[3] + symptom duration $n = 734$	
	Category↓	OR[1]	95% CI	OR[2]	95% CI	OR[3]	95% CI	OR[5]	95% CI
Core									
Country	South Africa	1							
	Namibia	1.34	1.02–1.78	1.43	1.04–1.97	1.37	0.92–2.06	1.17	0.75–1.82
Nigeria—public		1.06	0.55–2.03	1.19	0.57–2.49	1.59	0.71–3.58	1.65	0.67–4.11
	Uganda	0.98	0.53–1.84	1.09	0.55–2.16	1.23	0.56–2.70	1.08	0.47–2.52
	Zambia	0.80	0.43–1.50	0.81	0.42–1.54	0.93	0.47–1.87	0.69	0.32–1.47
Ethnicity	Non-black	1							
	black	5.33	3.55–8.01	5.15	3.41–7.77	3.16	1.99–5.01	3.15	1.94–5.10
Age	60+ years	1							
at diagnosis	50–59	1.08	0.77–1.52	1.10	0.78–1.57	1.40	0.95–2.05	1.39	0.93–2.07
	40–49	1.36	0.97–1.90	1.40	0.97–2.02	1.90	1.25–2.89	1.84	1.18–2.87
	<40	1.34	0.92–1.94	1.40	0.93–2.10	2.02	1.26–3.23	2.07	1.25–3.42
Biological									
HIV	Negative/NK	1							
	Positive	0.97	0.65–1.44	0.94	0.63–1.41	0.88	0.56–1.38	1.03	0.63–1.67
Other	No	1							
comorbidity	Yes	1.02	0.77–1.34	1.02	0.77–1.36	1.02	0.75–1.39	1.00	0.73–1.38
BMI	<18.5	1.53	0.86–2.72	1.54	0.87–2.72	0.98	0.53–1.79	0.90	0.47–1.69
(kg/m2)	18.5–<25	1							
	25–<30	1.05	0.74–1.48	1.04	0.74–1.47	1.06	0.73–1.53	1.09	0.75–1.61
	30+	1.03	0.75-1.42	0.98	0.72–1.38	1.06	0.74–1.52	1.13	0.77–1.66
Subtype	ER/PR+HER2-	1							
	ER/PR+HER2+	0.93	0.67–1.03	0.91	0.65–1.28	0.86	0.60–1.23	0.86	0.58–1.25
	HER2-enriched	1.24	0.75–2.06	1.27	0.77–2.12	1.40	0.82–2.38	1.62	0.93–2.80
	Triple negative	1.34	0.95–1.90	1.29	0.90–1.85	1.15	0.77–1.67	1.14	0.76–1.71
Grade	Well	1							
	Moderately	1.51	0.96–2.39	1.53	0.96–2.41	1.76	1.09–2.85	1.65	1.01–2.72
	Poorly	1.69	1.04–2.74	1.63	1.00–2.67	1.92	1.15–3.21	2.11	1.23–3.60
	Unknown	1.29	0.79–2.11	1.24	0.76–2.05	1.30	0.77–2.17	1.43	0.84–2.44
Morphology	Ductal	1							
	Other	1.02	0.74–1.41	1.10	0.79–1.53	1.00	0.70–1.43	0.89	0.61–1.30
Recent pregnancy[4]			$n = 540$		$n = 450$		$n = 444$		$n = 435$
	>3 years	1							
	≤3 years	1.65	1.15–2.37	1.58	1.05–2.39	1.88	1.21–2.91	2.00	1.27–3.15

Abbreviations: BMI: body mass index; CI: confidence interval; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; HIV: human immunodeficiency virus; NK: not known; OR: ordinal odds ratio; PR: progesterone receptor; SEP: socio-economic position.
[1]Basic model: Adjusted for age at diagnosis (<40, 40–49, 50–59, ≥60 years), country (SA $n = 300$; Namibia $n = 460$; Uganda $n = 42$; Zambia $n = 35$; Nigeria $n = 32$, Nigeria private not included) and black versus non-black ethnicity, estimated by ordinal logistic regression on stage 0–I, IIA–IIB, IIIA–IIIC, IV.
[2]Woman level factors are marital status, education, employment, socioeconomic position, BC awareness and knowledge.
[3]Referral factors are place of residence, number of contacts with providers.
[4]Model excludes South Africa and women over 45 years, is adjusted for age as continuous variable and uses all variables in table except tumor subtype.

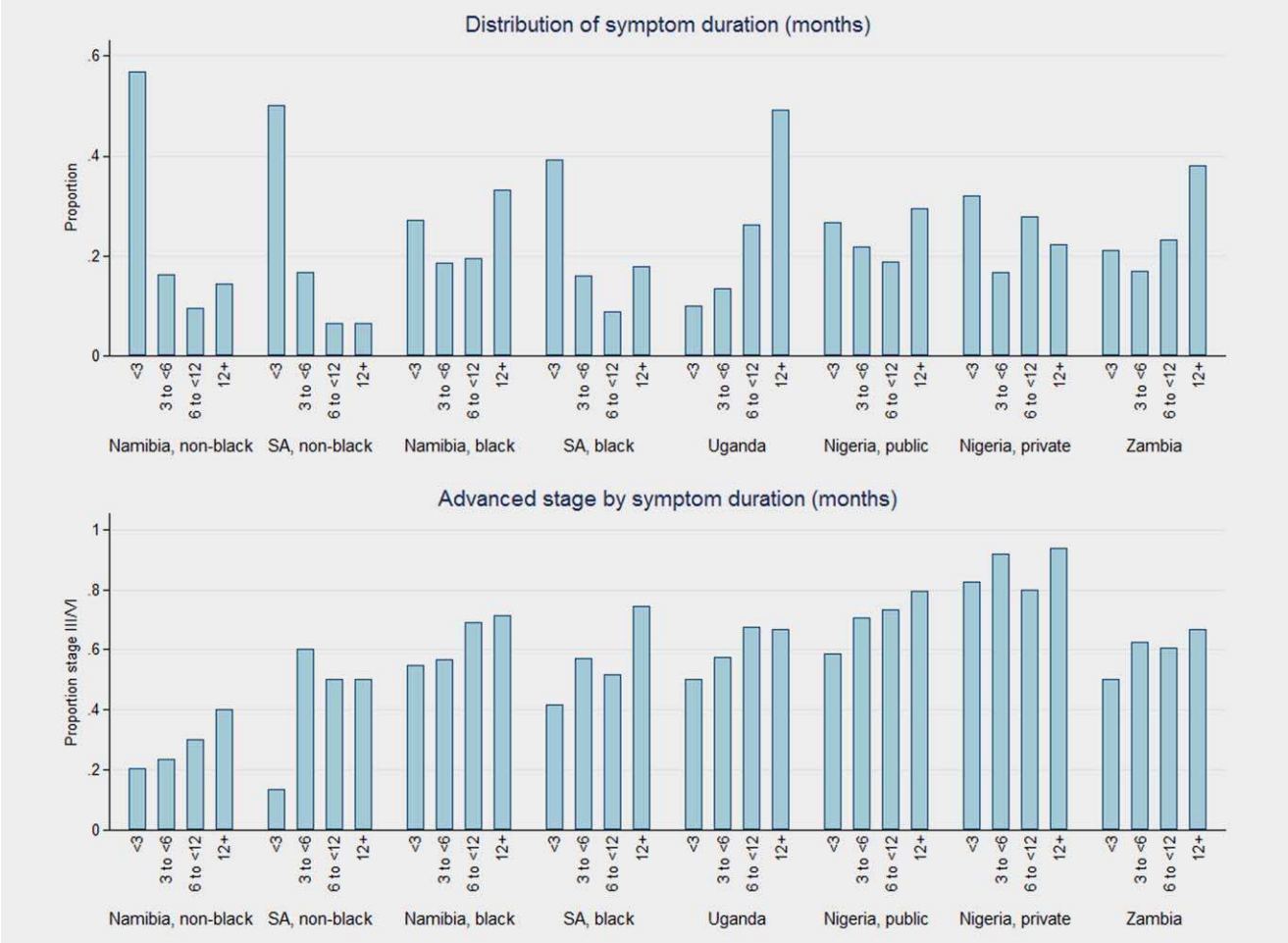

Figure 1. Symptom duration: self-reported time from symptom to diagnosis. (*a*) Distribution of time overall for each country/setting. (*B*) Distribution of time by advanced stage diagnosis for each country/setting. [Color figure can be viewed at wileyonlinelibrary.com]

to 2.9 years since last pregnancy. For women having had a pregnancy within 1 year the association was not significant (core model OR 1.39; 0.83–2.34, not in Tables). There was some evidence that younger women were at increased odds of being diagnosed at a more advanced stage; however, similar to the age associations shown in Table 2, these only became significant upon adjustment for woman-level factors and were not driven my triple negative tumor subtypes.

PAFs

The proportion of BCs (PAFs) in each country that hypothetically would **not** have been diagnosed at an advanced stage (stage III/IV) if all women had experienced a time to diagnosis within 3 months of symptoms, had at least secondary education, worked in skilled employment, had heard of BC and scored the highest on the BC knowledge score was estimated overall at 42% (95% CI 30–52%), and ranged from 34% in Nigeria to 49% in Uganda. The advanced stage contribution associated with recent pregnancy was estimated at 6% (2–10%) among women ≤45 years of age, and ranged from 4% in Uganda to 7% in Namibia and Zambia. The contribution of tumor aggressiveness was 12% in Namibia and 13% in SA; these were estimated for the two countries where receptor status assessment is done routinely by hypothesizing the scenario whereby all women were diagnosed in the favorable categories of having well-differentiated and non-triple-negative tumors.

Discussion

Main findings

This study identified key determinants of stage at BC diagnosis across five countries in SSA. Advanced stage (stage III/IV) at diagnosis constituted the majority of BC in all black populations but the extent differed between countries, and contrasted starkly to a majority stage 0/I/II disease in non-black women in Namibia and SA. In addition, younger age and a recent pregnancy were independently associated with more advanced stage, as were several amenable factors: low education and socioeconomic position, working in unskilled employment, and poor BC awareness. These factors were mediated at least in part through a time-to-diagnosis pathway, as one-third of SA black women, half of Nigerian and

Namibian women and three-quarters of Ugandan women reported having had symptoms for over 6 months, making this the largest contributor to advanced stage at diagnosis. Higher grade and triple-negative tumors also tended to be more advanced stage tumors.

Comparisons with other studies

Many of these findings are consistent with previous work in SSA. Low levels of education have, not surprisingly, been found to be associated with advanced stage BC in many studies in the region.[24–26] Long delays between first symptom recognition and diagnosis are also consistent with previous SSA research,[24] and were associated with more visits to health care provider facilities.[25] Reducing delays to three months is a reasonable target in SSA, as it is difficult to show any worsening of outcome when treatment is initiated after that time; delays longer than one year should be considered extreme in any system. Previous studies have found that women who were not married at the time of BC diagnosis were more likely to be advanced stage or have long delays before seeking help[24,26]; in this study, this association was accounted for by their lower SEP. Overweight and obesity did not emerge as being related to more advanced stage, in contrast to other Western settings,[27,28] even though the prevalence of overweight and obesity was relatively high in the ABC-DO study (60%).

As expected, there was an association between higher grade tumors and more advanced stage; however, no association emerged for tumor morphological subtype. Several studies have highlighted more aggressive BC subtypes (e.g. triple negative tumors) in SSA,[29,30] but a recent systematic review and meta-analysis demonstrated a predominance of better prognosis oestrogen-receptor (ER)-positive tumors in SSA.[31,32] The ABC-DO findings confirm that triple negative tumors are diagnosed later, but they made up less than one-fifth of tumors, thus of the factors studied, nonbiological factors were the main drivers of advanced stage BC. Biological factors were limited, however, both in sample size and to immunohistochemical markers, thus molecular studies of BC in SSA are needed and may identify stronger additional drivers of diagnostic stage. Further, although the study population was primarily black, lower stage in the minority non-black women in Namibia and SA, who were diagnosed in the same settings as their black counterparts, highlights the prospect for downstaging. While the ethnic differential in advanced tumors is likely to partially be due to less aggressive tumors in non-black women, it is likely additionally driven by a complex combination of BC awareness, education, culture, financial means and privilege.[25,32–34]

Strengths and limitations

This study was conducted primarily in tertiary hospital settings, with the latter being often the only cancer treatment centers in the country. Although participation rates were very high (~99%), the cohort may not be representative of all BC patients as women who never seek health care or are never referred to a diagnostic hospital will not be represented. For example, during the study conduct, strike action from different groups of health professionals severely interrupted diagnosis during prolonged periods, yet a catch-up was not observed; women may have travelled abroad or sought treatment in the rapidly expanding private sector. The study benefitted from highly complete questionnaire data, aided by m-Health implementation (described in detail in the ABC-DO study protocol).[15] However, symptom recognition and, therefore, estimations of delays were dependent on patient recollection, and therefore may not be entirely accurate. Information on stage and other tumor characteristics were extracted from medical records and the quality may be variable. Furthermore information on receptor status was not available for most women outside Namibia and SA, which is a problem inherent to SSA that prevents women from benefitting from optimal treatments for their type of tumor.

Implications

The findings help to identify which groups of women are vulnerable to advanced stage disease and strategies to improve early presentation and diagnosis. The breast cancer patients identified in this study as more likely to be diagnosed with advanced disease, such as black women, women with low levels of literacy and education, and working in unskilled employment, are not women of privilege. The fact that the associations found for woman-level factors such as working in unskilled employment remained after accounting for recognized delay time, suggest that they may be also reflecting the 'uncaptured' time from detectable symptoms to symptom recognition. Help seeking behavior depends heavily on the way a woman views herself, her status, and her roles within her community (as wife, mother, daughter, etc.), and looking at the wider scope, empowerment also plays a key role in SSA BC disparities.[34,35] The current study was only able to capture part of the pre-diagnostic journey, that is, it was unable to measure the symptom-onset to symptom recognition interval.[36] A common theme in symptom appraisal models is that, for a bodily change or symptom, to be detected it must be of sufficient significance,[14] meaning the likelihood of symptoms going unnoticed is greater among those with external competing demands,[37,38] and such kinds of demands have been associated with lower socioeconomic demographics.[39]

Greater BC awareness was associated with lower stage disease, independently of educational level. This finding suggests that although stage migration in SSA may be achieved in the long-term through improvements in the general education level of women, it raises the prospect that it may also benefit in the short-term from specifically-tailored BC awareness interventions, such as community education on BC symptoms, breast self-examination, where to seek help and of the potential to cure BC. Of relevance in this context is the fact that in this population overall, one in five women were

illiterate, therefore print materials would not be solely effective and awareness campaigns via the radio, in markets, churches, schools and community places, are needed to be inclusive.[40,41] Such activities have increased in SSA in recent years, especially by cancer associations, including of the important efforts of cancer survivors to tackle stigma. Methods currently seen across SSA include education using pamphlets, cancer walks, wear pink days and advocacy. In addition to increasing awareness in communities, awareness in health professionals has also been tackled in successful down-staging interventions.[42,43] Clinical breast examination has been associated with shorter delays to diagnosis and may also be of value as an educational tool for breast awareness in resource limited settings.[44]

More advanced stage at diagnosis in recently pregnant women has been found internationally,[21,45,46] but this study is the first such report from SSA and was consistent across its countries. It may indicate a common hormonal-driver of proliferation and more diagnostic challenges within lactating breasts, or it may simply reflect greater time demands of raising infant children, as the majority were women who had given birth 2–3 years ago. Under age 45, 30% of women with a recent or current pregnancy had more advanced BCs and somewhat surprisingly, this group made up 30% of BC patients diagnosed under age 45. In this age group, this group largely reflected recent (27% of BCs) rather than current pregnancies (3%), as the latter is a similar percentage to very different settings.[47] Thus, although women had their first pregnancies early (median 21 years), the reproductive period from first to last pregnancy was often long. Of the BC patients, 25% had their last pregnancy at or over 40 years of age, similar to historical values in western countries.[48] Although BC risk is small during/postpregnancy, the contact with the health system during and postpregnancy offers an ideal opportunity for educating women on breast health and women's cancers both for the near and distant future. Linking BC early detection efforts to reproductive health clinics would be a sensible targeting educational opportunity, regardless of the association driver.

Finally, HIV-positive women did not have more advanced stage at BC diagnosis; nevertheless, their contact with the health system could also offer an opportunity for earlier diagnosis. Ideally being diagnosed HIV positive, or diagnosed with any comorbidity that requires regular contact with health professionals, should be associated with a lower stage diagnosis. Within this study, 89% of HIV positive women were receiving antiretroviral therapy, and while these women were diagnosed at earlier stages than their counterparts not on therapy, they were still later stage than HIV negative women. Once again this highlights the importance of education for both women and health professionals and the opportunities that arise when they interact.

Conclusion

There is an urgent need to improve breast cancer survival rates in SSA as the incidence burden increases over the coming decades. Downward stage migration, followed by timely treatment, is essential to this. This study has identified groups of women who are vulnerable to delays in diagnosis, for whom downward stage migration may be achievable through a combination of strategies that improve breast cancer awareness and promote timely help-seeking behavior with improvements in access to health care.

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