Treatment guideline concordance, initiation, and abandonment in patients with non-metastatic breast cancer from the African Breast Cancer–Disparities in Outcomes (ABC-DO) cohort in sub-Saharan Africa: a prospective cohort study

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Summary

Background Comprehensive breast cancer management is essential to achieve high breast cancer survival; however, detailed reports of the treatment regimens received by patients are scarce in sub-Saharan Africa where survival is low. We aimed to examine treatment initiation, guideline concordance, and abandonment in patients with non-metastatic breast cancer in sub-Saharan Africa from the African Breast Cancer–Disparities in Outcomes (ABC-DO) prospective cohort.

Methods The ABC-DO prospective cohort study recruited women (aged ≥18 years) with newly diagnosed invasive breast cancer in eight hospitals across five sub-Saharan African countries (Namibia, Nigeria, Uganda, South Africa, and Zambia). We analysed treatments received by women who were classified as non-metastatic (M0) at the initial presentation. Data on surgery, radiotherapy, and systemic therapies were obtained from medical records and a self-reported follow-up questionnaire at 6 months after the diagnosis, follow-up calls every 3 months, and a baseline questionnaire. Initiation, completion, and abandonment of treatment modalities and combined therapy regimens were examined overall, by country-specific groups, and by clinical factors relevant for guideline-based treatment.

Findings Of 2313 women recruited into the ABC-DO study between Sept 10, 2014, and Dec 31, 2017, 2226 had histologically or clinically confirmed breast cancer. Of these 2226 women, 510 were excluded from the present analysis because 378 had metastatic disease, 37 were prevalent cases (defined as those previously diagnosed with breast cancer >2 years before baseline), 82 had unknown TNM stage, and 13 were White or Asian women in South Africa (number was too small for analysis). After a median follow-up of 5·2 years (IQR 4·6–5·9), 1163 (68%) of 1716 women underwent breast cancer surgery. Surgery and systemic therapy (ie, multimodality treatment) with radiotherapy was initiated in 370 (36%) of 1028 women with localised tumours versus 156 (23%) of 688 women with locally advanced tumours, whereas multimodality treatment without radiotherapy was initiated in 386 (38%) versus 167 (24%) women, respectively. Of 1530 patients requiring chemotherapy (which excludes 105 who died within 6 months after baseline), 1013 (66%) initiated treatment of neoadjuvant chemotherapy or surgery within 3 months after baseline, which was adequately completed by 359 (35%) of 1013 women, marginally completed by 284 (28%), abandoned by 200 (20%), and unknown in 151 (15%). 19 (2%) women died within 6 months after chemotherapy initiation. Of 1375 women in whom endocrine therapy was indicated, this treatment was initiated in 920, and lasted at least 3 years in 367 (40%) women. Treatment disparities between country-specific groups were substantial for all therapy regimens.

Interpretation A high proportion of patients with non-metastatic breast cancer did not initiate, did not fully complete, or abandoned treatment with surgery, systemic therapy, radiotherapy, or an appropriate combination of these, highlighting the need for improved treatment access and completion in sub-Saharan Africa to potentially prevent premature breast cancer deaths.

Funding National Institutes of Health (National Cancer Institute), Susan G Komen, and the International Agency for Research on Cancer.

Lancet Oncol 2022; 23: 729–38

Published **Online** May 9, 2022 https://doi.org/10.1016/S1470-2045(22)00198-X

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Introduction

Breast cancer is the most common cancer and cause of cancer death among women worldwide, with almost 2·3 million new cases and 700 000 deaths globally in 2020.[1] Survival is particularly low in sub-Saharan Africa, where only 40–70% of women are alive 3 years after diagnosis, compared with nearly 90% being alive after 5 years in high-income countries.[2–4] To reduce global breast cancer mortality, in 2021 WHO launched the Global Breast Cancer Initiative (GBCI).[5] One of its

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Research in context

Evidence before this study

We searched PubMed and Google Scholar from database inception to Nov 1, 2021, with no language restrictions, using the search terms "breast cancer" in combination with "SSA" or "sub-Saharan Africa", or each country in sub-Saharan Africa individually, and "treatment", "management", "resources", "care", and "abandonment". We found 12 studies that published unbiased percentages of multimodality breast cancer treatment initiation (surgery and systemic therapy), of which seven also reported on completeness of treatment. Of these, five studies analysed data from earlier than 2010. The other two were hospital-based studies from Nigeria and Rwanda. Although crude treatment percentages were similar across studies, treatment completion was defined by only four cycles of chemotherapy in the Rwandan study and the Nigerian study did not report on combined therapies. Also, both were single country analyses and thus, not suitable to detect regional differences within sub-Saharan Africa.

Added value of this study

In 2021, WHO launched the Global Breast Cancer Initiative to improve breast cancer survival worldwide. One of its strategic pillars was to improve breast cancer management, specifically to promote multimodality treatment and reduce treatment abandonment. Although these areas are widely known to need improvement in sub-Saharan Africa, there is a scarcity of high-quality detailed data on breast cancer management and its concordance with resource-stratified treatment guidelines (ie, the NCCN Harmonized Guidelines for sub-Saharan Africa). We provide data on treatment initiation, guideline adherence, and completion that were collected for female patients with breast cancer in the African Breast Cancer-Disparities in Outcomes (ABC-DO) study, which was done in five countries. ABC-DO is the first multicentric, prospective, breast cancer cohort in sub-Saharan Africa. We found large between-country differences in the initiation of multimodal breast cancer treatment. Around 50% of women presenting with localised tumours (T1–3, N0–1, M0) in Nigeria initiated multimodality treatment compared with more than 90% in South Africa and Namibia; however, almost one-fifth of these Namibian women did not receive surgery. Our results further emphasise the need to overcome treatment abandonment: only a third of women requiring chemotherapy and initiating timely treatment adequately completed the scheduled treatment cycles (ie, >85% of cycles). This finding is worrying, because marginally completed or abandoned chemotherapy will provide the patient with only minimal or no survival benefit, but not without the side-effects of the treatment. In the participating hospitals in Nigeria, Zambia, and Uganda, immunohistochemistry is not routinely available, making adherence to breast cancer management guidelines unfeasible, and radiotherapy facilities are few and overstretched, which substantially hampers treatment quality.

Implications of all the available evidence

We found a high proportion of patients with non-metastatic breast cancer who did not undergo surgical tumour removal and who did not initiate, or abandoned, systemic therapy. Sub-Saharan Africa has the lowest breast cancer survival worldwide; thus, alongside early detection efforts to shift the tumour stage at presentation towards an earlier stage and thus better prognosis, timely high quality treatment is needed to fulfil the goal of improving survival. Our results also highlight the need to improve oncology infrastructure in sub-Saharan Africa, such as radiotherapy and pathology services, to enable guideline-concordant cancer treatment and to ensure that patients and health workers have good understanding of breast cancer and the treatment options.

three strategic pillars is comprehensive breast cancer management, with a goal of at least 80% of patients completing stage-appropriate multimodal treatment without abandonment. Crucially, the GBCI emphasises that the concept of treatment abandonment is two sided; responsibility for incomplete treatment is not only down to the patient, but also the system in which the patient is being treated. Assessment of the causes for abandonment needs to begin with the collection of detailed data on treatment and its quality for benchmarking and priority setting; in sub-Saharan Africa, these data are scarce.

Early diagnosis coupled with stage appropriate treatment were identified as the major factors that could improve survival in the African Breast Cancer–Disparities in Outcomes (ABC-DO) study,[2] a prospective breast cancer cohort recruited from hospitals in five countries in sub-Saharan Africa. Our first report on treatment data in ABC-DO showed that 20% of patients with newly diagnosed breast cancer did not initiate treatment (systemic therapy, surgery, or radiotherapy) within 12 months of diagnosis;[6] however, a more detailed assessment on the completion of treatment is required. If less than 85% of the total cumulative chemotherapy regimen is completed, patients might have adverse side-effects with minimal or no survival benefit.[7,8]

To provide guidance for the treatment of patients with breast cancer in sub-Saharan Africa, the National Comprehensive Cancer Network (NCCN) Harmonized Guidelines define tailored strategies adapted to the available treatment in each region, but concordance to these guidelines remains underevaluated.[9]

Here, we provide a comprehensive profile of non-metastatic breast cancer management in sub-Saharan Africa using the ABC-DO cohort. Specifically, we describe receipt of breast cancer surgery and initiation of systemic therapy (chemotherapy or endocrine therapy), or their combination, and observe patterns of treatment completion and abandonment in a hospital setting. We also compare the concordance of such treatments with NCCN Harmonized Guideline recommendations, and

identify treatment gaps and opportunities for systematic improvements in care.

Methods

Study design and participants

The ABC-DO prospective cohort study recruited women (aged ≥18 years) with newly diagnosed histologically confirmed, clinically confirmed or suspected invasive breast cancer in eight hospitals across five sub-Saharan African countries (Namibia, Nigeria, Uganda, South Africa, and Zambia; appendix p 3). A baseline interview at first presentation to hospital and a follow-up call thereafter occurred once every 3 months. The baseline questionnaire collected data on education, relationship status, residential status, socioeconomic status, HIV status, and other comorbidities (appendix p 4). Treatment, histology, pathology, and cancer staging data were recorded by trained fieldworkers into a tailor-made mHealth application, which automatically uploaded encrypted data to a Cloud server.[10] To capture the actual breast cancer journey of patients in sub-Saharan Africa, ABC-DO was intentionally observational without additional capacities for diagnosis and treatment provided. The ABC-DO South African participants are the Sowetan subset of the ongoing SABCHO cohort.[11]

In the present analysis, we analysed the treatments received by women who were classified as non-metastatic (M0) at the initial presentation. The absence of any metastasis mentioned was considered as M0. Because non-metastatic disease management was the focus, if progression to a metastatic stage occurred subsequent to recruitment, only treatments received before the date of known metastatic spread were included. The ABC-DO study was approved by the relevant institutional ethics committees (appendix p 2), and all patients provided written or thumbprint informed consent. The protocol has previously been published.[12]

Procedures

To account for ethnic and sociodemographic differences, patients were categorised into seven groups: two in Namibia (Black or non-Black), two in South Africa (Black or mixed-race), Nigeria (all), Uganda (all), and Zambia (all). Breast cancer stage according to the American Joint Committee on Cancer TNM staging system (8th edition) and histologically confirmed tumour grade were entered into the mHealth application (appendix pp 5, 6).[13] To assess concordance with NCCN Harmonised Guidelines, TNM stage was dichotomised into localised (T1–3, N0–1, M0) versus locally advanced or inoperable tumours (T4, N2–3, M0).

Immunohistochemistry for oestrogen receptor, progesterone receptor, and HER2 status were routinely done in Namibia and South Africa, but not in the other countries. Oestrogen receptor and progesterone receptor status were considered positive if at least 1% of tumour cells had positive nuclear staining with the corresponding assay and HER2 was considered positive if the immunohistochemistry HER2 score was 3, and for the equivocal score of 2, if fluorescent in-situ hybridisation (FISH) was positive. Receptor-defined subtypes were classified into hormone receptor-positive (positive for oestrogen receptor or progesterone, or both) or hormone receptor-negative; and by HER2 status (positive or negative). Patients with distant metastasis (imaging or clinical confirmation) were excluded from the analysis, but not the cohort.

Treatment data were obtained from hospital medical records; a self-reported follow-up questionnaire at 6 months after diagnosis; follow-up calls every 3 months, using the question "are you currently receiving any medical treatment for breast cancer?"; and in case of any treatment before presentation at the recruiting hospital, in the baseline questionnaire. As treatment was analysed for women with non-metastatic breast cancer, any treatment received after progression of cancer from non-metastatic at baseline interview to metastatic during the course of follow-up, was not included in the present analysis. The following data were extracted for surgery: date, surgery type (mastectomy or breast-conserving surgery), and lymph node dissection (axillary sampling, sentinel node biopsy, or complete axillary node dissection); for chemotherapy: first and last cycle dates, therapy timing (adjuvant or neoadjuvant), number of cycles, and drug regimen (combination or monotherapy with cyclophosphamide, doxorubicin, fluorouracil, methotrexate, and taxanes and targeted therapy with trastuzumab); for oral endocrine therapy: first and last treatment dates, therapy timing (neoadjuvant or adjuvant), and drugs prescribed (tamoxifen or aromatase inhibitor); and for surgical oophorectomy: whether or not an ovarian ablation was performed and the date. If multiple treatment dates were available, the earliest date was chosen. For radiotherapy, only basic information (yes or no) was extracted because radiotherapy is unavailable in most participating hospitals, and in sub-Saharan Africa in general.

See Online for appendix

To judge adherence to NCCN Harmonized Guidelines, chemotherapy completion and abandonment was calculated only for women who started treatment (including surgery before adjuvant chemotherapy) within 3 months after study initiation (ie, baseline interview at presentation to hospital) and were still alive at 6 months after study initiation. Palliative care was beyond the scope of this Article and will be reported separately.

Chemotherapy was considered indicated for women who had at least one of the following factors: HER2-positive tumours, hormone receptor-negative tumours, positive lymph nodes (two or more nodes affected), T2 or higher TNM staging, grade 3 breast cancer, and were younger than 35 years at diagnosis. Chemotherapy initiation was considered guideline concordant if breast cancer treatment was started within 3 months after baseline. To account for differences in completion of the chemotherapy

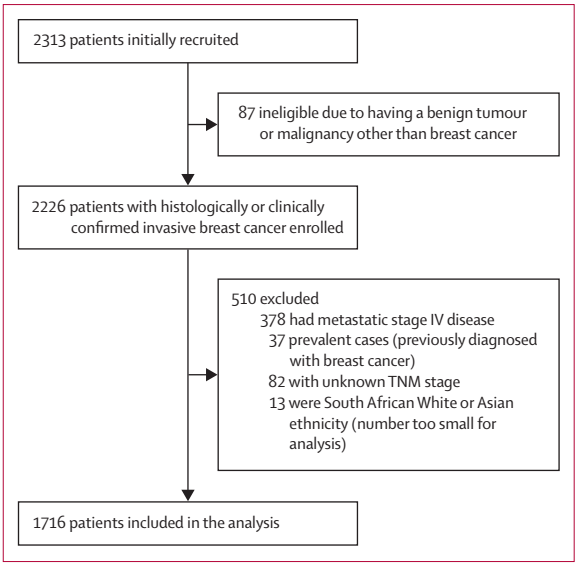

Figure 1: **Study profile**

regimen, we included two levels of completion: marginally completed or adequately completed. Marginally completed was defined as at least five cycles of fluorouracil, doxorubicin, and cyclophosphamide therapy (or an equivalent regimen) administered within 20 weeks from the first dose or cycle (the recommended timeframe is within 15 weeks from the first dose or cycle) or four cycles of doxorubicin and cyclophosphamide (evidence category 2B, according to NCCN Harmonized Guidelines) within the recommended 12 weeks. Adequately completed (ie, >85% of the total cumulative chemotherapy completed) was defined as at least five cycles of fluorouracil, doxorubicin, and cyclophosphamide therapy (or an equivalent regimen) administered within 15 weeks after chemotherapy initiation, or seven to eight cycles of fluorouracil, doxorubicin, cyclophosphamide, and taxane therapy within 28 weeks, after the first dose or cycle (the recommended timeframe is within 24 weeks of diagnosis). Endocrine therapy was considered indicated for women with known hormone receptor-positive or missing hormone receptor status.

We descriptively analysed initiation of monotherapy and combined therapies, and concordance (initiation, completion, and abandonment) of treatment by patient risk factors to the NCCN guidelines.

Statistical analysis

Descriptive statistics were used for all analyses. Binary data (yes or no) of treatment ever initiated for each treatment method were created. Crude monotherapy and combined therapy initiation frequencies and percentages were calculated overall, by population group, and by localised or locally advanced tumours. Treatment quality assessment was guided by NCCN Harmonized Guidelines for sub-Saharan Africa. Absolute cumulative initiation and abandonment of multimodality treatment (ie, surgery and systemic therapy) were plotted over 1 year after baseline for each study population. Data were analysed using Stata (version 15.0) and R Studio (version 3.6.1).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 2313 women recruited into the ABC-DO study between Sept 10, 2014, and Dec 31, 2017, 2226 had histologically or clinically confirmed breast cancer (figure 1). Of these 2226 women, for the present analysis 510 were excluded because 378 had metastatic disease, 37 were prevalent cases, 82 had unknown TNM stage, and 13 were White or Asian women in South Africa (number was too small for analysis). This approach was also applied in a previous 3-year survival analysis.[2] The absence of any metastasis mentioned was considered as M0, according to TNM classification (415 [24%] of 1716 patients). Thus in total, we included 1716 patients with non-metastatic breast cancer in the analysis. The sociodemographic profile of all included women is given in the appendix (p 4).

In the analysis of treatment data from Oct 13, 2013, to July 15, 2021, the median duration of follow-up was 5·2 years (IQR 4·6–5·9). Of 1716 patients, 256 (16%) died within 1 year after hospital presentation (all-cause mortality; data not shown). Most of these women (181 [71%] of 256) had initiated treatment; nine (4%) had only surgery, 101 (39%) initiated only systemic treatment, 71 (28%) initiated both, and 75 (29%) did not initiate treatment. 137 (8%) of 1716 women died before starting any treatment, with a median time between hospital presentation and death of 10·1 months (IQR 3·1–21·8).

In total, 1163 (68%) of 1716 women underwent breast cancer surgery, ranging from 53% (79 of 150) in Zambia to 90% in Namibia (82 of 91 non-Black women; table 1). Among these women, 909 (78%) received a mastectomy. The proportion of patients who underwent breast-conserving surgery was highest in Nigeria (76 [49%] of 156). Among 255 women receiving breast-conserving surgery overall, subsequent radiotherapy was initiated by 107 (42%), but only two of these women were from Nigeria. In South Africa, the only setting with complete information on this procedure, complete axillary node dissection was performed in 361 (87%) of 415 Black women and 26 (93%) of 28 mixed race women, with similar results between women with localised and locally advanced tumours (appendix p 7).

1232 (72%) of 1716 patients initiated chemotherapy, with the lowest percentage in Nigeria (143 [49%] of 292), 973 (57%) initiated endocrine therapy (109 [37%] in Nigeria and 70 [77%] of 91 non-Black women in Namibia; table 1).

	Total (all patients)	Namibia		Nigeria (all)	South Africa		Uganda (all)	Zambia (all)
		Black	Non-Black		Black	Mixed race		
Breast cancer surgery performed*	1163/1716 (68%)	221/309 (72%)	82/91 (90%)	156/292 (53%)	415/544 (76%)	28/34 (82%)	182/296 (61%)	79/150 (53%)
Mastectomy performed†	909/1163 (78%)	205/221 (93%)	66/82 (80%)	80/156 (51%)	297/415 (72%)	18/28 (64%)	167/182 (92%)	76/79 (96%)
Received consecutive radiotherapy‡	426/909 (47%)	160/205 (78%)	43/66 (65%)	7/80 (9%)	127/297 (43%)	12/18 (67%)	45/167 (27%)	32/76 (42%)
Breast-conserving surgery†	255/1163 (22%)	16/221 (7%)	16/82 (20%)	76/156 (49%)	119/415 (29%)	10/28 (36%)	15/182 (8%)	3/79 (4%)
Received consecutive radiotherapy§	107/255 (42%)	13/16 (81%)	15/16 (94%)	2/76 (3%)	67/119 (56%)	6/10 (60%)	4/15 (27%)	0/3
Lymph nodes dissected†								
Not done	45/1163 (4%)	11/221 (5%)	0/82	4/156 (3%)	6/415 (1%)	0/28	23/182 (13%)	1/79 (1%)
Sentinel or sampling	44/1163 (4%)	26/221 (12%)	15/82 (18%)	3/156 (2%)	0/415	0/28	0/182	0/79
Complete axillary node dissection	456/1163 (39%)	40/221 (18%)	11/82 (13%)	6/156 (4%)	361/415 (87%)	26/28 (93%)	8/182 (4%)	4/79 (5%)
Unknown	618/1163 (53%)	144/221 (65%)	56/82 (68%)	143/156 (92%)	48/415 (12%)	2/28 (7%)	151/182 (83%)	74/79 (94%)
Additional systemic therapy†¶								
Neoadjuvant	475/1163 (41%)	132/221 (60%)	45/82 (55%)	69/156 (44%)	157/415 (38%)	9/28 (32%)	23/182 (13%)	40/79 (51%)
Adjuvant	851/1163 (73%)	143/221 (65%)	61/82 (74%)	76/156 (49%)	332/415 (80%)	25/28 (89%)	167/182 (92%)	47/79 (59%)
No systemic therapy	84/1163 (7%)	6/221 (3%)	2/82 (2%)	35/156 (22%)	19/415 (5%)	1/28 (4%)	12/182 (7%)	9/79 (11%)
Chemotherapy initiated*	1232/1716 (72%)	245/309 (79%)	65/91 (71%)	143/292 (49%)	415/544 (76%)	27/34 (79%)	228/296 (77%)	109/150 (73%)
Neoadjuvant‖**	714/1232 (58%)	187/245 (76%)	44/65 (68%)	89/143 (62%)	226/415 (54%)	13/27 (48%)	75/228 (33%)	80/109 (73%)
Adjuvant‖**	518/1232 (42%)	58/245 (24%)	21/65 (32%)	54/143 (38%)	189/415 (46%)	14/27 (52%)	153/228 (67%)	29/109 (27%)
Chemotherapy regimen**								
Doxorubicin and cyclophosphamide or cyclophosphamide, methotrexate, and fluorouracil	172/1232 (14%)	36/245 (15%)	16/65 (25%)	22/143 (15%)	75/415 (18%)	7/27 (26%)	8/228 (4%)	8/109 (7%)
Fluorouracil, doxorubicin, and cyclophosphamide	238/1232 (19%)	63/245 (26%)	6/65 (9%)	56/143 (39%)	31/415 (7%)	1/27 (4%)	44/228 (19%)	37/109 (34%)
Fluorouracil, doxorubicin, cyclophosphamide, and taxane	486/1232 (39%)	131/245 (52%)	34/65 (52%)	6/143 (4%)	253/415 (61%)	16/27 (59%)	6/228 (3%)	40/109 (37%)
Non-standard††	49/1232 (4%)	6/245 (2%)	5/65 (8%)	7/143 (5%)	28/415 (7%)	1/27 (4%)	0/228	2/109 (2%)
Unknown	287/1232 (23%)	9/245 (4%)	4/65 (6%)	52/143 (36%)	28/415 (7%)	2/27 (7%)	170/228 (75%)	22/109 (20%)
Trastuzumab received*	47/1716 (3%)	36/309 (12%)	9/91 (10%)	1/292 (<1%)	1/544 (<1%)	0/34	0/296	0/150
Endocrine therapy initiated*	973/1716 (57%)	233/309 (75%)	70/91 (77%)	109/292 (37%)	309/544 (57%)	26/34 (76%)	161/296 (54%)	65/150 (43%)
Neoadjuvant‡‡§§	312/973 (32%)	97/233 (42%)	15/70 (21%)	66/109 (61%)	42/309 (14%)	3/26 (12%)	56/161 (35%)	33/65 (51%)
Adjuvant‡‡	645/973 (66%)	131/233 (56%)	55/70 (79%)	43/109 (39%)	267/309 (86%)	23/26 (88%)	95/161 (59%)	31/65 (48%)
Unknown timing‡‡	16/973 (2%)	5/233 (2%)	0/70	0/109	0/309	0/26	10/161 (6%)	1/65 (1%)
Type of endocrine therapy‡‡								
Tamoxifen	883/973 (91%)	196/233 (84%)	46/70 (66%)	107/109 (98%)	304/309 (98%)	25/26 (96%)	145/161 (90%)	60/65 (92%)
Aromatase inhibitor	31/973 (3%)	5/233 (2%)	17/70 (24%)	0/109	5/309 (2%)	1/26 (4%)	3/161 (2%)	0/65
Tamoxifen followed by aromatase inhibitors	50/973 (5%)	27/233 (12%)	7/70 (10%)	1/109 (1%)	0/309	0/26	11/161 (7%)	4/65 (6%)
Unknown	9/973 (1%)	5/233 (2%)	0/70	1/109 (1%)	0/309	0/26	2/161 (1%)	1/65 (2%)
Ovarian ablation*	14/1716 (1%)	12/309 (4%)	2/91 (2%)	0/292	0/544	0/34	0/296	0/150

Data are n/N (%). *Denominator is the whole study sample. †Subsample (n=49) of those who received surgery. ‡Subsample of those who received mastectomy. §Subsample of those who received breast-conserving surgery. ¶Percentages do not add up to 100% because 247 women received neoadjuvant and adjuvant systemic therapy. ‖Including 287 women who did not receive surgery after chemotherapy was initiated. **A subsample with medical chemotherapy records (n=975). ††Among 50 patients with a non-standard regimen: 41 received only taxane, two received only capecitabine, five received carboplatin, and one received cyclophosphamide and carboplatin. ‡‡Subsample of those who initiated endocrine therapy. §§Includes 185 women not receiving surgery after they initiated endocrine therapy.

Table 1: **Breast cancer management in women with non-metastatic breast cancer in the ABC-DO cohort**

In total, 569 (33%) initiated radiotherapy (nine [3%] in Nigeria and 60 [66%] non-Black women in Namibia; figure 2). Chemotherapy was mostly neoadjuvant (714 [58%] of 1232 women; table 1). The most common drug regimen was fluorouracil, doxorubicin, cyclophosphamide, and taxane (in 486 [39%] of 1232 women who received chemotherapy). The endocrine therapy received by patients was mostly tamoxifen (883 [91%] of 973).

Of 1716 women, 1028 (60%) had localised tumours (T1–3, N0–1, M0) and 688 (40%) had locally advanced tumours (T4, N2–3, M0; table 2; appendix p 5). Surgery and systemic therapy (ie, multimodality treatment) with radiotherapy was initiated by 370 (36%) of 1028 women with localised tumours versus 156 (23%) of 688 women with locally advanced tumours (appendix p 8); whereas multimodality treatment without radiotherapy was initiated by 386 (38%)

versus 167 (24%) women, but with notable variations across country-specific groups (table 2; appendix p 9). Initiation of multimodality treatment with or without radiotherapy was lowest in Nigeria for localised tumours (58 [46%] of 127) and locally advanced tumours (63 [38%] of 165), and highest in Namibia for women with localised tumours (67 [89%] of 75 non-Black women) and those with locally advanced tumours (13 [81%] of 16 non-Black women). Systemic therapy with or without radiotherapy and with no surgery was received by 135 (13%) of 1028 women with localised versus 236 (34%) of 688 with locally advanced tumours, and no treatment was received by 77 (7%) versus 104 (15%) women, respectively. Concerning the timing of treatment commencement, 1349 (88%) of 1535 women who initiated any treatment did so within 3 months from baseline (including 456 women starting treatment before baseline or on the day).

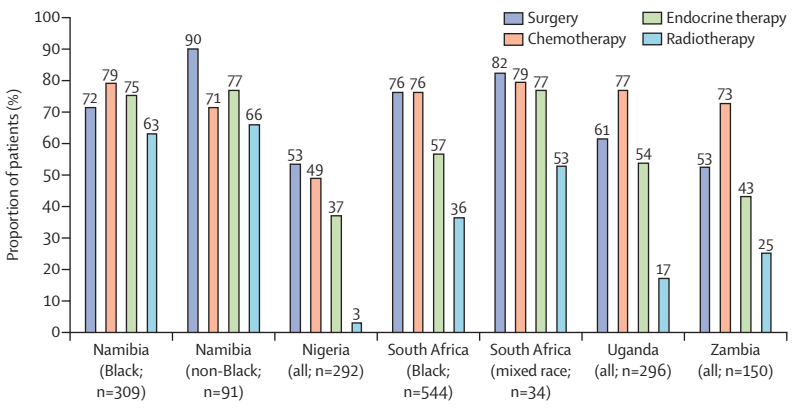

Figure 2: **Treatment initiation in women with non-metastatic breast cancer and known TNM stage in the African Breast Cancer–Disparities in Outcomes cohort**

The initiation, abandonment, and completion of multimodality treatment for all women and by country-specific groups is shown in figure 3 (because of x-axis censoring at 12 months, endocrine therapy completion was set to 9 months for all women who had at least 3 years of continued endocrine treatment). According to the NCCN Harmonized Guidelines, 1530 (95%) of 1611 patients (excluding 105 who died within 6 months after baseline) should have received chemotherapy (table 3). Of these 1530 patients, 1013 (66%) initiated treatment of neoadjuvant chemotherapy or surgery within 3 months after baseline (exemplary treatment trajectories of 15 women per population group are displayed in appendix p 10), with more than 60% of women initiating chemotherapy in all population groups except Nigeria (97 [39%] of 251;

	Total (all patients)	Namibia		Nigeria (all)	South Africa		Uganda (all)	Zambia (all)
		Black	Non-Black		Black	Mixed race		
Localised tumours*								
Number of women†	1028/1716 (60%)	178/309 (58%)	75/91 (82%)	127/292 (43%)	344/544 (63%)	26/34 (76%)	191/296 (65%)	87/150 (58%)
Surgery and systemic therapy with radiotherapy	370/1028 (36%)	111/178 (62%)	46/75 (61%)	6/127 (5%)	126/344 (37%)	14/26 (54%)	41/191 (21%)	26/87 (30%)
Surgery and systemic therapy without radiotherapy	386/1028 (38%)	30/178 (17%)	21/75 (28%)	52/127 (41%)	171/344 (50%)	9/26 (35%)	78/191 (41%)	25/87 (29%)
Surgery with or without radiotherapy	60/1028 (6%)	3/178 (2%)	2/75 (3%)	25/127 (20%)	14/344 (4%)	1/26 (4%)	8/191 (4%)	7/87 (8%)
Systemic therapy with or without radiotherapy	135/1028 (13%)	32/178 (18%)	6/75 (8%)	12/127 (9%)	20/344 (6%)	2/26 (8%)	47/191 (25%)	16/87 (18%)
No treatment	77/1028 (7%)	2/178 (1%)	0/75	32/127 (25%)	13/344 (4%)	0/26	17/191 (9%)	13/87 (15%)
Locally advanced tumours*								
Number of women†	688/1716 (40%)	131/309 (42%)	16/91 (18%)	165/292 (57%)	200/544 (37%)	8/34 (24%)	105/296 (35%)	63/150 (42%)
Surgery and systemic therapy with radiotherapy	156/688 (23%)	60/131 (46%)	11/16 (69%)	3/165 (2%)	65/200 (33%)	3/8 (38%)	8/105 (8%)	6/63 (10%)
Surgery and systemic therapy without radiotherapy	167/688 (24%)	14/131 (10%)	2/16 (13%)	60/165 (36%)	34/200 (17%)	1/8 (13%)	43/105 (41%)	13/63 (21%)
Surgery with or without radiotherapy	25/688 (4%)	3/131 (2%)	0/16	10/165 (6%)	6/200 (3%)	0/8	4/105 (4%)	2/63 (3%)
Systemic therapy with or without radiotherapy	236/688 (34%)	50/131 (38%)	2/16 (13%)	44/165 (27%)	65/200 (33%)	4/8 (50%)	42/105 (40%)	29/63 (46%)
No treatment	104/688 (15%)	4/131 (3%)	1/16 (6%)	48/165 (29%)	30/200 (15%)	0/8	3/105 (3%)	13/63 (21%)
All women with non-metastatic breast cancer								
Any treatment initiated	1535/1716 (89%)	303/309 (98%)	90/91 (99%)	212/292 (73%)	501/544 (92%)	34/34 (100%)	271/296 (92%)	124/150 (83%)
Initiated treatment within 3 months from baseline‡	1349/1535 (88%)	300/303 (99%)	87/90 (97%)	131/212 (62%)	467/501 (93%)	31/34 (91%)	235/271 (87%)	98/124 (79%)

Data are n/N (%). *Dichotomised variable derived from tumour size, nodes, and metastases. †Denominator is the whole study sample. ‡Subsample of those who initiated treatment.

Table 2: **Treatment initiation in women with localised or locally advanced breast cancer in the ABC-DO cohort**

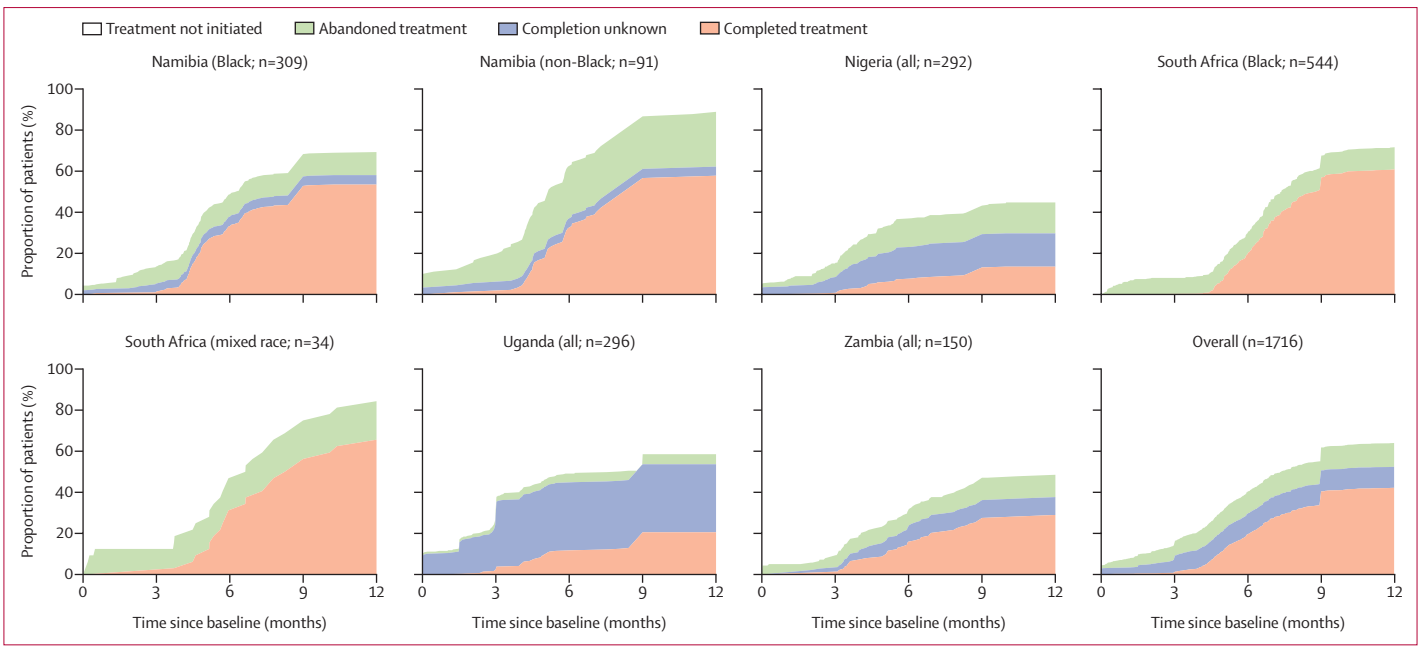

Figure 3: **Multimodal treatment use (surgery and systemic therapy) in the ABC-DO cohort**
The cumulative percentages represent the crude percentage among all women per site, unadjusted for death. ABC-DO=African Breast Cancer–Disparities in Outcomes.

appendix p 9). Initiated chemotherapy was adequately completed by 359 (35%) of 1013 women, marginally completed by 284 (28%), and abandoned by 200 (20%). Completion was unknown in 151 (15%) of 1013 women, of whom 114 were from Uganda, and 19 (2%) of 1013 women died within 6–9 months after chemotherapy initiation. Chemotherapy abandonment was particularly frequent in Nigeria (37 [38%] of 97), Zambia (25 [29%] of 85), and Black women in Namibia (56 [24%] of 232).

In most women, endocrine therapy was indicated (1375 [85%] of 1611) because of hormone receptor-positive tumours (n=828) or unknown hormone receptor status (n=631). Of these 1375 women, 920 (67%) initiated treatment. Endocrine therapy duration lasted at least 3 years in 367 (40%) of 920 patients. Most women in South Africa and Namibia had hormone receptor-positive tumours or HER-negative tumours.

Compliant with guidelines, 658 (79%) of 828 women with hormone receptor-positive tumours initiated endocrine therapy. In women with unknown hormone receptor, a scenario not considered in the NCCN Harmonized Guidelines, 273 (43%) of 631 initiated endocrine therapy and 385 (61%) initiated chemotherapy. Targeted therapy (trastuzumab) was received by only 42 (16%) of 259 women with HER2-positive tumours, all of whom were in Namibia (nine [50%] of 18 non-Black women and 33 [33%] of 99 Black women).

Discussion

Our analysis of the ABC-DO cohort provides a detailed profile of breast cancer treatment in a public-sector hospital settings in sub-Saharan Africa, comprehensive benchmark estimates to inform the third pillar of the GBCI, and quantifies the needs to enhance treatment quality and reduce treatment abandonment in sub-Saharan Africa. Our results highlight the unacceptably high proportion of patients with localised tumours who did not receive surgical tumour resection, or abandoned or did not initiate guideline-concordant systemic therapy, leading to impaired survival chances of a potentially curable cancer. Our data also emphasise that the necessary infrastructure for guideline-compliant treatment is insufficient in most settings—particularly the availability of radiotherapy, immunohistochemistry, and diagnostic imaging—highlighting the need for overall health system improvements and government investment in assuring equitable access to quality cancer care.

Breast cancer treatment requires multimodal treatment (surgery and systemic therapy, often with the addition of radiotherapy), which was initiated by around 70% of women with localised tumours and around 50% with locally advanced tumours in the ABC-DO cohort, which is predominantly made up of women attending major public hospitals in each country. Moreover, treatment abandonment was common, particularly in Nigeria, Namibia, and Zambia while data on abandonment in Uganda were largely missing. The observed treatment initiation rates can be compared with those reported in three publications[14–16] from sub-Saharan Africa. The first report analysed population-based, retrospective registry data from the African Cancer Registry Network (AFCRN) in 11 countries and found an overall treatment initiation rate (surgery and systemic therapy) of 45% among women with non-metastatic breast cancer.[14] This lower

	Total (all)	Namibia		Nigeria (all)	South Africa		Uganda (all)	Zambia (all)
		Black	Non-Black		Black	Mixed race		
Women alive at 6 months after baseline (number of women with non-metastatic breast cancer)*	1611/1716 (94%)	298/309 (96%)	90/91 (99%)	256/292 (88%)	517/544 (95%)	32/34 (94%)	281/296 (95%)	137/150 (91%)
Chemotherapy indicated†	1530/1611 (95%)	292/298 (98%)	71/90 (79%)	251/256 (98%)	487/517 (94%)	29/32 (91%)	266/281 (95%)	134/137 (98%)
Treatment initiated within 3 months after baseline‡	1013/1530 (66%)	232/292 (79%)	57/71 (80%)	97/251 (39%)	355/487 (73%)	22/29 (76%)	165/266 (62%)	85/134 (63%)
Adequately completed§	359/1013 (35%)	97/232 (42%)	25/57 (44%)	9/97 (9%)	198/355 (56%)	14/22 (64%)	8/165 (5%)	8/85 (9%)
Marginally completed§	284/1013 (28%)	74/232 (32%)	18/57 (32%)	21/97 (22%)	99/355 (28%)	6/22 (27%)	20/165 (12%)	46/85 (54%)
Abandoned§¶	200/1013 (20%)	56/232 (24%)	11/57 (19%)	37/97 (38%)	54/355 (15%)	1/22 (5%)	16/165 (10%)	25/85 (29%)
Died 6 to 9 months after baseline§	19/1013 (2%)	0/232	0/57	5/97 (5%)	4/355 (1%)	1/22 (5%)	7/165 (4%)	2/85 (2%)
Completion unknown§	151/1013 (15%)	5/232 (2%)	3/57 (5%)	25/97 (26)	0/355	0/22	114/165 (69%)	4/85 (5%)
Endocrine therapy indicated†	1375/1611 (85%)	224/298 (75%)	72/90 (80%)	246/256 (96%)	412/517 (80%)	30/32 (94%)	269/281 (96%)	122/137 (89%)
Endocrine therapy initiated‖	920/1375 (67%)	213/224 (95%)	69/72 (96%)	98/246 (40%)	297/412 (72%)	26/30 (87%)	155/269 (58%)	62/122 (51%)
Duration ≥3 years**	367/920 (40%)	112/213 (53%)	37/69 (54%)	30/98 (31%)	104/297 (35%)	8/26 (31%)	53/155 (34%)	23/62 (37%)
Duration <3 years**	215/920 (23%)	31/213 (15%)	17/69 (25%)	10/98 (10%)	106/297 (36%)	11/26 (42%)	32/155 (21%)	8/62 (13%)
Died within 3 years after initiation**	177/920 (19%)	42/213 (20%)	3/69 (4%)	23/98 (23%)	59/297 (20%)	3/26 (12%)	38/155 (25%)	9/62 (15%)
No information on duration**	161/920 (18%)	28/213 (13%)	12/69 (17%)	35/98 (36%)	28/297 (9%)	4/26 (15%)	32/155 (21%)	22/62 (35%)
Hormone receptor-positive tumour*								
Endocrine therapy initiated	658/828 (79%)	213/223 (96%)	68/71 (96%)	15/23 (65%)	300/428 (70%)	26/31 (84%)	15/25 (60%)	21/27 (78%)
Chemotherapy initiated	625/828 (75%)	172/223 (77%)	47/71 (66%)	21/23 (91%)	315/428 (74%)	24/31 (77%)	23/25 (92%)	23/27 (85%)
Hormone receptor-negative tumour*								
Endocrine therapy initiated	43/257 (17%)	17/79 (22%)	1/19 (5%)	6/13 (46%)	9/114 (8%)	NA	7/13 (54%)	3/16 (19%)
Chemotherapy initiated	222/257 (86%)	68/79 (86%)	17/19 (89%)	12/13 (92%)	99/114 (87%)	NA	11/13 (85%)	12/16 (75%)
Hormone receptor status unknown*	631/1716 (37%)	7/309 (2%)	1/91 (1%)	256/292 (88%)	2/544 (<1%)	0/34	258/296 (87%)	107/150 (71%)
Endocrine therapy initiated	273/631 (43%)	NA	NA	88/256 (34%)	NA	NA	140/258 (54%)	41/107 (38%)
Chemotherapy initiated	385/631 (61%)	NA	NA	110/256 (43%)	NA	NA	194/258 (75%)	74/107 (69%)
HER2-positive tumours*	259/1716 (15%)	99/309 (32%)	18/91 (20%)	4/292 (2%)	119/544 (22%)	7/34 (21%)	6/296 (2%)	6/150 (4%)
Trastuzumab received	42/259 (16%)	33/99 (33%)	9/18 (50%)	NA	0/119	NA	NA	NA

Data are n/N (%). NA=not applicable (n ≤10). *Whole study sample. †Women alive at 6 months after baseline. ‡Alive at 6 months and chemotherapy indicated. §Women alive at 6 months, chemotherapy indicated, and treatment initiated. ¶Including 24 patients with a non-standard regimen (taxane alone, carboplatin or monotherapy of adriamycin, cyclophosphamide, or ftorafur). ‖Alive at 6 months and endocrine therapy indicated. **Alive at 6 months, endocrine therapy indicated, and treatment initiated.

Table 3: **Treatment initiation, abandonment, and completion in women with non-metastatic breast cancer from the ABC-DO cohort**

percentage in AFCRN could be due to the study time period (2009–15) or nature of data collection (population-based and retrospective). A higher initiation percentage (57%) than in the ABC-DO cohort was reported in a small patient sample from a cancer centre in Rwanda in 2012–13,[15] with a chemotherapy completion rate of 74% (at least four cycles) compared with 35% for adequate completion and 28% for marginal completion in our study. The third study, conducted by the African Research Group of Oncology (ARGO) in Nigeria, reported separate percentages for surgery, chemotherapy, and endocrine therapy and combined women with non-metastatic and metastatic disease.[16] The proportion of women undergoing surgery in ARGO (50%) was similar to Nigerian patients in the ABC-DO cohort (53%), but chemotherapy initiation was higher in our study (39% *vs* 49%), whereas abandonment was around 40% in both studies. Some heterogeneity between studies was probably due to the more specialised cancer centres in ARGO.

Nearly a third of patients did not undergo surgery. This treatment course might have been recommended in women with locally advanced large tumour masses (40%) whose neoadjuvant therapy course was not successful and they developed metastasis. In this case, not proceeding to a futile surgical resection would be guideline concordant. Contrarily, metastatic spread could have already occurred during the longer delay to treatment initiation. We measured TNM stage only once at baseline (and women were possibly understaged because of the absence of diagnostic imaging) and, unfortunately, we were not able to systematically and routinely assess disease progression in all women, thus the complete reasons for changes in treatment plans could not be assessed at the individual level. Other reasons for women not receiving surgery and conveyed to us by the study

team in Namibia, was frailty or other comorbidities. In Namibia, such women are usually given tamoxifen or radiotherapy, or both. However, approximately 20% of women with localised tumours did not receive surgery. The precise reasons were not documented, but are likely to include costs, reliance on traditional medicine, fear of a mastectomy, and psychological distress.[6,17]

Among women receiving surgery, the predominant type in Namibia, Uganda, and Zambia was a mastectomy, which is a guideline recommendation in the absence of radiotherapy facilities, for large tumour masses, or both.[9] The proportion of women undergoing breast-conserving surgery—the recommendation for localised or small tumours if radiotherapy is provided—was highest in Nigeria, but, worryingly, only two of these patients initiated radiotherapy, whereas almost all patients in Namibia who received breast-conserving surgery initiated consecutive radiotherapy.

Almost all women in the ABC-DO cohort (95%) would have needed chemotherapy, as is indicated for advanced or aggressive tumours, independently of their hormone receptor or HER2 status. However, only 66% of these patients initiated timely treatment and of those, only a third adequately completed chemotherapy. In low-income countries (such as Nigeria, Uganda, and Zambia) without universal health coverage, treatment is often abandoned because of financial barriers.[6,18,19] Additionally, long travel times and insufficient transport are known barriers to health-care access in the countries in the ABC-DO cohort.[20] Side-effects from chemotherapy could have also contributed to the high abandonment rates, especially in women positive for HIV, but the side-effects could not be evaluated because of incomplete data.

Systemic and targeted therapy for breast cancer is tailored to the tumour's receptor status. Patients with hormone receptor-positive tumours receive endocrine therapy; those with hormone receptor-negative tumours and, to a lesser extent, those with hormone receptor-positive tumours require chemotherapy; and patients with HER2-positive tumours tend to respond to additional targeted therapy. Therefore, knowledge of receptor status is a minimal requirement for treatment planning, which is also mentioned in the NCCN Harmonized Guidelines.[9] As is the case in many countries in sub-Saharan Africa, the pathology infrastructure in Nigeria, Uganda, and Zambia is poor and immunohistochemistry testing needs to be arranged personally and paid out-of-pocket (appendix p 3).[21,22] Thus, for nearly 90% of women with unknown receptor status in these countries, evidence-based systemic treatment decisions cannot be provided. However, in Namibia and South Africa, immunohistochemistry testing is standard and we showed that almost all women with hormone receptor-positive tumours started endocrine therapy, with the exception of Black women in South Africa among whom 30% did not initiate endocrine therapy despite substantial survival benefits and fewer side-effects than chemotherapy.[23,24] Another indication of scarce resources is longer time to treatment initiation that should not exceed 3 months, which is a crucial cutoff for improved survival, but we showed that a substantial proportion of patients in Nigeria (61%), Uganda (38%), and Zambia (37%) had not initiated treatment within this 3-month period, but commenced at a later time.[5,25] Moreover, nearly 10% of patients with non-metastatic breast cancer did not initiate any treatment. Determinants of limited treatment access in the ABC-DO cohort have been described previously.[6]

A unique strength of the ABC-DO study was the mHealth-based prospective design that allowed assessment of timing, composition, and completeness of breast cancer therapy, and reduced missing data and loss to follow-up, which are common problems in cohort studies in sub-Saharan Africa.[10,26] One of the study's limitations was that chemotherapy completion could not account for the dose intensity because documentation of the actual dose received was not precise (only included the regimen in some hospitals) and exact treatment dates for every cycle were not always documented. Nevertheless, we were able to extract the planned regimen, total number of cycles, and the start and end date of chemotherapy. Based on this information, we accounted for different treatment schedules and treatment quality by stratifying the treatment completion time and chemotherapy regimen. Additionally, we introduced a category of marginal treatment completion to capture any treatment benefits in a hospital setting, where various issues might hinder planned optimal treatment schedules. Several medical records were missing and for some patients results relied entirely on a small amount of self-reported data (limited to whether or not treatment was received, side-effects, and reasons for treatment abandonment), resulting in difficulties when judging treatment completion in Uganda. However, the concordance of medical records and self-reported treatment data at 6 months after baseline was high, as we had published previously.[6] For example, 86% (460 of 533) of chemotherapy and 83% (357 of 428) of surgery medical treatment records that were recorded within 6 months after baseline had corresponding self-reported data.[6] Finally, results cannot be generalised to all patients in the respective countries, since many patients will not reach a specialised oncology centre. For example, the catchment population for the Nigerian hospitals, FMC Owerri and Aba, were local and most often these hospitals were the patients primary care contact (appendix p 3).[27] We excluded White or Asian women in South Africa, because the number of patients was too small for analysis, and this group is expected to have better treatment access than Black women in the country, reflecting their higher educational level.[28]

Effective interventions are needed to improve breast cancer survival in sub-Saharan Africa.[2] In addition to programmes aimed at achieving earlier diagnosis, shifting the stage at diagnosis distribution favourably will only deliver long-awaited survival gains if they are

accompanied by comprehensive treatment. Investments into professional training, diagnostic services (including pathology expertise and laboratories) and therapeutic management are needed at the health-system level and support in terms of finance, transport, accommodation, and education is needed at the patient level, to achieve the much needed improvements in breast cancer survival in the region.

Contributors

MF statistically analysed the data and drafted the manuscript. EJK and VM verified the treatment data. BOA, EJK, VM, IdSS, AZ, HC, MJ, AA, SO, MG, GP, LFP, and JS designed the study. All authors contributed to the interpretation of results and writing of the manuscript. EJK and VM advised on the statistical analyses. All authors had full access to all data in the study and all authors accept responsibility to submit for publication. MF and VM have accessed and verified all the data in the study.

Declaration of interests

MG is a THRiVE-2 fellow (supported by DELTA African initiative DEL-15–011). LFP is supported by the University of Washington T32 Fellowship (5T32CA009515–34). We declare no competing interests.

Data sharing

The protocol from the ABC-DO study has been published.[12] Data will be made available upon reasonable request to the principal investigators (VM and IdSS). Reasonable access criteria include research proposals for stand-alone analysis within the scope of this study. Such proposals will be evaluated and supported if deemed relevant. Proposals from researchers and doctoral students in low-income and middle-income countries are encouraged. Relevant data will be shared with a signed data access agreement.

Acknowledgments

The ABC-DO study was funded by the US NIH National Cancer Institute (1R01CA244559) and Susan G Komen (IIR 13264158, GSP18IARC001, and GSP19IARC001), and as part of "Implementing breast cancer care efficiency in Zambia through specialized health provider training and mHealth evaluation of patient outcomes" for the Zambian site, and by the International Agency for Research on Cancer. We thank all patients who participated in the ABC-DO study and the original principal investigator at Aba, our friend and colleague Charles Adisa. We also thank the research assistants and nurses who interviewed women in the ABC-DO cohort. Where authors are identified as personnel of the International Agency for Research on Cancer or WHO, the authors alone are responsible for the views expressed in this Article, which do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer or WHO.

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