Breast Cancer Diagnostics, Therapy, and Outcomes in Sub-Saharan Africa: A Population-Based Registry Study

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ABSTRACT

Background: Breast cancer (BC) is the most common cancer in sub-Saharan Africa (SSA). However, little is known about the actual therapy received by women with BC and their survival outcome at the population level in SSA. This study aims to describe the cancer-directed therapy received by patients with BC at the population level in SSA, compare these results with the NCCN Harmonized Guidelines for SSA (NCCN Harmonized Guidelines), and evaluate the impact on survival. **Methods:** Random samples of patients with BC (≥ 40 patients per registry), diagnosed from 2009 through 2015, were drawn from 11 urban population-based cancer registries from 10 countries (Benin, Congo, Cote d'Ivoire, Ethiopia, Kenya, Mali, Mozambique, Namibia, Uganda, and Zimbabwe). Active methods were used to update the therapy and outcome data of diagnosed patients ("traced patients"). Excess hazards of death by therapy use were modeled in a relative survival context. **Results:** A total of 809 patients were included. Additional information was traced for 517 patients (63.8%), and this proportion varied by registry. One in 5 traced patients met the minimum diagnostic criteria (cancer stage and hormone receptor status known) for use of the NCCN Harmonized Guidelines. The hormone receptor status was unknown for 72.5% of patients. Of the traced patients with stage I–III BC ($n=320$), 50.9% received inadequate or no cancer-directed therapy. Access to therapy differed by registry area. Initiation of adequate therapy and early-stage diagnosis were the most important determinants of survival. **Conclusions:** Downstaging BC and improving access to diagnostics and care are necessary steps to increase guideline adherence and improve survival for women in SSA. It will also be important to strengthen health systems and facilities for data management in SSA to facilitate patient follow-up and disease surveillance.

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Background

Breast cancer (BC) is the most common cancer among women in sub-Saharan Africa (SSA) and is the second leading cause of cancer death after cervical cancer.¹ Approximately 7 in 10 women diagnosed in SSA present with advanced stages of disease (stages III–IV).² Survival among these patients is relatively poor; however, there are survival differences between African countries.^{3–6}

BC treatment is resource-intensive. For nonmetastatic BC, the main pillars of therapy are surgery, radiotherapy (RT), chemotherapy, endocrine therapy (if hormone receptor-positive), and targeted therapies. In SSA, all of these recommended treatment modalities are available in only a few state-of-the-art cancer facilities. Typically, accessibility to such institutions is limited to residents of these areas, those who are covered by health insurance schemes, or those who can afford to pay out-of-pocket. Few African nations have country-specific treatment recommendations, and most often, clinicians offer therapy options based on available local resources. NCCN developed resource-stratified therapy recommendations for

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SSA for the most common cancers⁷ to facilitate therapeutic decision-making for clinicians in resource-constrained settings. There is limited information, however, on whether BC therapy in SSA is concordant with these resource-stratified therapy recommendations.

Most information on BC therapy and survival in SSA is from hospital-based reports, and these describe the survival of patients treated in cancer referral centers. Although these patients receive the best therapy locally available, survival is generally poor. However, what is not known is the experience of the general population of patients with BC in different SSA countries (not only those reaching specialist treatment centers) by way of the therapy received and how this influences survival. To address this knowledge gap, we performed this study including random samples of women from 11 population-based cancer registries (PBCRs) in SSA to describe the cancer-directed therapy (CDT) received at the population level, compare these results to recommended guidelines, and evaluate the impact on survival.

Methods

Study Design, Population, and Data Source

This was a retrospective population-based registry study. The sampling frame was the database of the African Cancer Registry Network (AFCRN).⁸ After excluding patients registered based on a death certificate only, we drew random samples of at least 40 patients with BC (per ICD-10, code C50) per registry of patients diagnosed from 2009 to 2015 from 10 PBCRs: Abidjan (Côte d'Ivoire), Bamako (Mali), Brazzaville (Congo), Bulawayo (Zimbabwe), Cotonou (Benin), Eldoret (Kenya), Kampala (Uganda), Maputo (Mozambique), Namibia, and Nairobi (Kenya). In Addis Ababa (Ethiopia), we included all patients diagnosed from January to March 2012. All included patients were African women who were residents of the registry area. The number of randomly selected patients per registry was determined by the practical feasibility of retrospectively tracing health records across multiple centers. All of these PBCRs cover a city, except for the Namibian cancer registry, which covers the national territory. All the registries use the CANREG software developed by the International Agency for Research on Cancer for data entry and for verification checks. Records were traced from the registry to the source of registration, and information on the date of diagnosis and stage was verified or updated and any duplicates excluded (see supplemental eFigure 1, available with this article at JNCCN.org). The registry records were updated with information on diagnostic procedures, treatment received, and patients' vital status from clinical records. However, if this information could not be found in clinical records, then as a last resort the

patients or relatives were contacted by registry staff when a contact number was available.

Patients for whom we succeeded in obtaining additional information that was not routinely available in the registry records, from either the source health facilities and/or from reaching patients or their next of kin, are subsequently referred to as "traced patients."

Data management was conducted using SPSS Statistics, version 25 (IBM Corp) and data analyses were performed with STATA, version 14.2 (StataCorp, LP).

Explanatory and Outcome Measures

The main explanatory variable was the therapy received. The outcome measure was the patients' vital status at the closing date of the study. This measure was ascertained by active follow-up methods as described earlier. The observational time was the time from diagnosis to death, date of last contact, or until the end of the study (December 31, 2017), whichever occurred first. Patients not found to have died, using the active methods as described, were counted as being alive.

Ethical Considerations

This study used anonymized and encrypted data from the AFCRN database. The study protocol was approved by the Research Committee of the AFCRN, by the individual registries, and by the Martin-Luther-University Halle-Wittenberg Review Board (votum number 2019-009). The study complied with the Declaration of Helsinki.

Data Management and Assessing Therapy

We used the NCCN Harmonized Guidelines for Sub-Saharan Africa (NCCN Harmonized Guidelines for SSA) for Breast Cancer, version 2.2017,⁹ as a guide for therapy evaluation. Information on stage at diagnosis, hormone receptor status (HRS), and tumor histology are required to use these guidelines for therapy evaluation effectively. To use the same classification categories as the NCCN Harmonized Guidelines for SSA and based on the anatomic stage groupings of the AJCC, we categorized patients into 3 stage groups for therapy evaluation: early BC (stages I, II, and T3N1M0), locally advanced BC (stage IIIA [except T3N1M0], IIIB, and IIIC), and metastatic disease (stage IV, M1).¹⁰ Patients with early and locally advanced BC are subsequently referred to as "patients with curable or non-metastatic disease."

For chemotherapy, RT, hormonal therapy, surgery, and targeted therapy, we assessed whether there was documented evidence that the patient had initiated treatment. To assess chemotherapy completeness, we evaluated what proportion of patients received the prescribed chemotherapy regimen. We categorized chemotherapy received as >85% complete if the patient received all but one prescribed chemotherapy session, as ≤85% com-

plete¹¹ if the patient had ≥ 2 missed chemotherapy sessions, and unknown if there was no record of chemotherapy found. We were unable to assess the completeness of RT because the total dose received was not recorded for most patients. Completeness of endocrine therapy could not be assessed because we could not ascertain therapy adherence and completion until year 5. For surgery, we categorized patients as having received surgery (either a mastectomy or a lumpectomy) or not.

We used a simplified schema based on these guidelines to evaluate the therapy received. Among traced patients with curable BC, we used the categorization below for therapy evaluation:

1. Initiated adequate therapy (the patient received as a minimum): surgery (mastectomy or [lumpectomy + RT]) and systemic therapy (chemotherapy and/or endocrine therapy) and/or RT
2. Inadequate therapy (with no curative potential): surgery with no systemic therapy, a therapy combination without surgery, or a monotherapy
3. No therapy: traced patients with no evidence of receiving any CDT

For patients with metastatic disease, we described the therapy they received (see Table 1 for therapies).

Assessing Loss to Follow-Up

We assessed the proportion of patients lost to follow-up by registry at year 1, 3, and 5, and used a Cox regression model with loss to follow-up (LTFU) as the outcome, and age and stage at diagnosis as exposure variables to determine whether LTFU was random or associated with either age or stage at diagnosis.

Survival Analyses

For survival analyses, we excluded patients for whom the date of last contact was the same as the date of diagnosis and who thus had no additional follow-up information. We estimated the all-cause Kaplan-Meier survival for patients by therapy received at year 1, 3, and 5, and estimated relative survival by age, stage at diagnosis, therapy modality, and country-level Human Development Index (HDI).

Modeling Excess Mortality

We modeled the excess hazards of death from BC in a framework of generalized linear models using a piecewise Poisson regression model with smoothing splines. We split time into monthly time bands, and adjusted for age, stage at diagnosis, HRS, tumor grade, therapy, and country-level HDI. Registries were grouped by country-level data for parsimony and to improve the power of the multivariable model. All patients with at

least 30 days follow-up and with nonmetastatic BC were included. We estimated the relative excess risk of death from curable BC, after considering background mortality. We obtained data on background mortality from 5-year-age abridged WHO Global Health Observatory life-tables, which we expanded from 5-year ages (eg, ages 0–4, 5–9, and 10–14 years) to single-year ages (eg, ages 0, 1, 2, and 3) using a Poisson regression model with a flexible function. We performed sensitivity analyses limiting the analyses to traced patients and to registries with <50% LTFU in the first year.

Results

Patient and Tumor Characteristics

A total of 809 patients from 11 PBCRs were included; these patients represented one-fifth of all patients registered with BC during the study period (Table 2). Median age at diagnosis was 48 years. Approximately 16% of the cohort was aged <35 years at diagnosis, with 53% aged <50 years. Additional information on stage, therapy, or vital status was obtained for 63.9% (517 records) of patients using active methods (traced patients), and this proportion varied by registry (Table 2). Half of the registry records were traced to public hospitals, 14.7% were traced to private hospitals, and 35.2% could not be traced to a treatment facility (Table 3). We found that 65.0% of tumors were ductal carcinomas. Of the 809 patients, stage at diagnosis was known for 53.5% ($n=433$; supplemental eFigure 2). Of those with known stage, 20.8% had metastatic disease at time of diagnosis and 46.4% were diagnosed with stage III disease (ie, 67.2% in stages III and IV), with <2% of patients diagnosed with stage I disease. When limited to the traced patients, stage at diagnosis was known for 405 patients, 320 of whom had nonmetastatic BC.

Regarding imagery for staging, imaging type was recorded in all registries apart from Addis Ababa. Less than 7% of patients had a record of using either a CT scan, an MRI, or bone scintigraphy for staging. Abdominal ultrasounds and chest and bone radiographs were the most commonly used means of screening for metastases. The HRS was recorded for 17.5% of all women and for 27.5% of traced patients.

Therapy Characteristics

Therapy Received and Guideline Adherence

In the population-based cohort, there was no record of any CDT for 48.7% of patients (12.6% of these patients were traced but without any therapy, and 36.1% of records were not traced) (Table 1). Patients from registries in regions with medium HDI (Eldoret, Nairobi, and Namibia) had better access to therapy and/or records of therapy compared with those from registries in regions with low

Table 1. Therapy Characteristics for Patients With BC by Stage at Diagnosis

	Population-Based Cohort n (%)	Traced Cohort (n=517)				
		n (%)	Early-Stage BC ^a %	Locally Advanced BC ^b %	Metastatic BC %	Unknown Stage %
Total, N	809	517	163	153	85	112
Chemotherapy						
Anthracycline-based regimen (without a taxane)	149 (18.4)	149 (28.8)	36.8	26.8	27.1	21.4
Anthracyclines and taxanes	94 (11.6)	94 (18.2)	18.4	25.5	18.8	8.0
Others	41 (5.1)	41 (7.9)	6.1	4.6	10.6	12.5
CMF	5 (0.6)	5 (1.0)	1.8	0.6	0.0	0.9
None recorded	228 (28.2)	228 (44.1)	36.8	42.5	43.5	57.1
Not traced	292 (36.1)	—	—	—	—	—
Neoadjuvant chemotherapy						
Yes	92 (11.4)	92 (17.8)	22.1	22.2	12.9	8.9
None recorded	425 (52.5)	425 (82.2)	77.9	77.8	87.1	91.1
Not traced	292 (36.1)	—	—	—	—	—
Surgery						
Mastectomy	277 (34.2)	277 (53.6)	66.3	57.5	37.6	42.0
Lumpectomy	43 (5.3)	43 (8.3)	10.4	3.3	5.9	14.3
None recorded	197 (24.4)	197 (38.1)	23.3	39.2	56.5	43.7
Not traced	292 (36.1)	—	—	—	—	—
Radiotherapy						
Yes	135 (16.7)	135 (26.1)	28.8	30.1	23.5	19.6
None recorded	382 (47.2)	382 (73.9)	71.2	69.9	76.5	80.4
Not traced	292 (36.1)	—	—	—	—	—
Hormone therapy						
Yes and HR+	74 (9.3)	74 (14.3)	22.7	13.7	7.1	8.9
Yes and HRS unknown	70 (8.6)	70 (13.5)	15.3	13.1	14.1	11.6
Yes and HR–	4 (0.5)	4 (0.8)	0.6	0.0	1.2	1.8
No and HR+	23 (2.7)	23 (4.4)	4.9	4.6	2.3	4.5
No and HR–	41 (5.1)	41 (7.9)	8.6	8.5	12.9	2.7
No and HRS unknown	305 (37.7)	305 (59.0)	47.9	60.1	62.4	70.5
Not traced	292 (36.1)	—	—	—	—	—

(continued on next page)

HDI (Figure 1). There was no statistical association between age at diagnosis and therapy receipt, although there were lower proportions of women who initiated adequate therapy among patients aged 20 to 34 years and ≥ 65 years (supplemental eFigure 3).

When we limited the analyses to the traced cohort (n=517), there was no record of any form of CDT for 19.7% of patients (Table 3). Of these traced patients, 104 (20.1%) had recorded the diagnostic information (stage at diagnosis and HRS) necessary for assessing therapy according to the NCCN Harmonized Guidelines for SSA⁹ (supplemental eFigure 4); the main characteristic unknown was the HRS for 72.5% of traced patients. We

also found that 40.5% of traced patients with early BC and 58.2% of traced patients with locally advanced BC received inadequate therapy with no curative potential or had no record of therapy (Table 1). In total, of all traced patients with curable BC, 50.9% had inadequate or no CDT.

Surgery

Surgery was the most available form of therapy, with a surgical intervention documented for 41% of all women and 64.2% of traced patients (Table 3). Of those who had surgery recorded, 86.6% had a mastectomy. However, the type of mastectomy (simple, modified

Table 1. Therapy Characteristics for Patients With BC by Stage at Diagnosis (cont.)

	Population-Based Cohort n (%)	Traced Cohort (n=517)				
		n (%)	Early-Stage BC ^a %	Locally Advanced BC ^b %	Metastatic BC %	Unknown Stage %
Targeted therapy						
Yes and HER2+	8 (1)	8 (1.5)	2.4	0.7	2.3	0.9
No and HER2+	35 (4.3)	35 (6.8)	11.7	3.9	9.4	1.8
No and HER2–	87 (10.7)	87 (16.8)	20.9	19.6	7.1	14.3
No and HER2 status unknown	387 (47.8)	387 (74.9)	65.0	75.8	81.2	83.0
Not traced	292 (36.1)	—	—	—	—	—
All CDT received						
Surgery + systemic therapy ± radiotherapy	234 (28.9)	234 (45.3)	59.5	41.8	36.5	36.6
Surgery without systemic therapy/monotherapies/therapy combination without surgery	181 (22.4)	181 (35.0)	27.0	39.2	42.3	34.8
No therapy	102 (12.6)	102 (19.7)	13.5	19.0	21.2	28.6
Not traced	292 (36.1)	—	—	—	—	—

Stages classified for therapy assessment following the NCCN Harmonized Guidelines for Sub-Saharan Africa for Breast Cancer⁹ recommendations. For 4 patients the stage at diagnosis was recorded as stage III, without additional details, and thus could not be dichotomized for this table and was not included.

Abbreviations: BC, breast cancer; CDT, cancer-directed therapy; CMF, cyclophosphamide/methotrexate/5-fluorouracil; HR, hormone receptor; HRS, hormone receptor status.

^aStages I, II, T3N1M0.

^bStage IIIA apart from T3N1M0, IIIB, IIIC.

radical, or radical) was not always specified, and neither were details on surgical axillary node staging and dissection.

Systemic Therapy

We found that 55.9% of traced patients had a record of chemotherapy (Table 3). Of those, 51.6% had an anthracycline-based regimen, 32.5% had an anthracycline regimen with a taxane, and the others received different combinations of drugs.

In addition, 28.6% of traced patients received endocrine therapy (Table 3). In the traced cohort, 13.5% of patients with tumors of unknown receptor status received endocrine therapy (Table 1). However, 4.4% of patients who had hormone receptor–positive disease had no record of receiving endocrine therapy. More patients diagnosed at early stages of disease had a record of receiving endocrine therapy (Table 1).

Radiotherapy

Approximately 1 in 4 traced patients received RT as part of their treatment regimen (Table 1). The proportion of patients who received RT varied by registry.

Targeted Therapy

Of traced patients, 35 (6.8%) who had HER2-positive disease received no therapy with monoclonal antibodies,

such as trastuzumab (Table 1). Use of trastuzumab was recorded for 8 patients in the entire cohort, 5 of them from Namibia.

Long-Term Follow-Up

LTFU was highest in the first year after diagnosis (supplemental eTable 1), and the proportion varied by registry. Namibia had the lowest fraction of patients with LTFU after diagnosis. Median follow-up time ranged from <1 year in Brazzaville, Bulawayo, and Cotonou to almost 5 years in Namibia. LTFU was not differential by age or stage at diagnosis among patients with a known stage. However, for patients without stage recorded, there was a more than 2-fold increased risk of LTFU compared with patients diagnosed at an early stage.

Survival

The overall observed survival in this cohort was 84.0% (95% CI, 80.5%–86.9%) at year 1, 58.9% (95% CI, 54.0%–63.5%) at year 3, and 47.2% (95% CI, 41.1%–53.1%) at year 5 (Figure 2). Patients with curable BC who received adequate therapy had better overall survival compared with those who received inadequate or no therapy (Figure 2). Figure 2 also shows overall survival for patients with metastatic disease, showing the poorest survival rates irrespective of the therapy received.

Table 2. Population-Based Registries Included in the Study

Registry	Country-Level HDI 2015	Period of Diagnosis	Patients With BC During Study Period n	DCO During Study Period Excluded n (%)	Population-Based Cohort n	Sampling Fraction	Traced Cohort ^b n (%)	Included for Survival Analyses n (%)
Abidjan, Cote d'Ivoire	Low	2012–2013	531	23 (4.3)	66	12.4%	50 (75.8)	53 (80.3)
Addis Ababa, Ethiopia	Low	2012	437	0 (0.0)	114	26.1%	51 (44.7)	93 (81.6)
Bamako, Mali	Low	2012–2013	639	5 (0.8)	90	14.1%	48 (53.3)	47 (52.2)
Brazzaville, Congo	Low	2012–2013	212	0 (0.0)	75	35.4%	19 (25.3)	75 (100)
Bulawayo, Zimbabwe	Low	2012–2013	167	16 (9.6)	56	33.5%	35 (62.5)	53 (94.6)
Cotonou, Benin	Low	2013–2014	132	0 (0.0)	92	69.7%	85 (92.4)	92 (100)
Eldoret, Kenya	Medium	2009–2014	379	17 (4.5)	81	21.4%	62 (76.5)	69 (85.2)
Kampala, Uganda	Low	2012–2013	283	8 (2.8)	58	20.5%	35 (60.3)	41 (70.7)
Maputo, Mozambique	Low	2014–2015	81	14 (17.8)	43	53.1%	34 (79.1)	41 (95.4)
Nairobi, Kenya	Medium	2012–2013	722	38 (5.3)	57	7.9%	37 (64.9)	55 (96.5)
Namibia	Medium	2012–2013	454	0 (0.0)	77	17.0%	61 (79.2)	64 (83.1)
Total		2009–2015	4,037	121 (3.0)	809	20.0%	517 (63.9)	684 (84.6)

Abbreviations: BC, breast cancer; DCO, death certificate–only patients; HDI, Human Development Index.

^bAdditional data on diagnostics, therapy, and/or outcome revealed after active record-finding.

Excess Mortality From Nonmetastatic BC

We assessed the excess mortality rate ratio among women with nonmetastatic disease and with at least 30 days of follow-up. Age at diagnosis was not an independent prognostic factor after adjusting for the effects of stage, tumor grade, therapy, and registry country-level HDI ($P=.389$). Being diagnosed with stage III BC compared with stages I and II BC was associated with a more than 3-fold increased risk of death rate ratio (risk ratio [RR], 3.83; 95% CI, 1.81–6.11; Figure 3). Patients who received inadequate or no therapy had more than double the risk of death compared with patients who initiated adequate therapy (Figure 3). Mortality risk did not differ by registry HDI (low vs medium).

Concerning specific therapy modalities (supplemental eFigure 5), not receiving oncologic surgery was associated with an increased risk of death compared with receiving surgery (RR, 1.67; 95% CI, 1.06–2.65). Having suboptimal chemotherapy was associated with a more than 2-fold increased risk of death (RR, 2.38; 95% CI, 1.24–4.57) compared with receiving >85% of the prescribed chemotherapy regimen. Receipt of RT was not associated with a difference in mortality risk. Nonreceipt of endocrine therapy was associated with an approximately 3-fold increased mortality risk (RR, 3.11; 95% CI, 1.50–6.10). When we

conducted sensitivity analyses, limiting the analyses just to traced patients and excluding Brazzaville (with >50% LTFU at year 1), these observed associations remained unchanged.

Discussion

Main Findings in the Context of Previous Studies

BC is a curable disease when diagnosed early and treated according to guidelines. This study shows the tenuous situation of women with BC in SSA; most patients are diagnosed at an advanced stage and only a small proportion receive guideline-concordant therapy. Of 809 women from 11 PBCRs in 10 countries, we traced 517 patient records (63.9%) and obtained detailed therapy information. Two in 3 patients (67.2%) with known stage were diagnosed with stage III or IV BC; however, given the limited access to advanced radiologic tools such as CT scans, bone scintigrams, and MRIs, this proportion may be even higher. Of traced patients with curable BC, 50.9% received inadequate or no CDT. Of all traced patients, the HRS was known for 27.5% of patients, making the use of current therapy guidelines challenging. The proportion of patients who received adequate therapy varied by registry (with patients in relatively richer countries receiving

Table 3. Cohort Characteristics

Characteristic	Population-Based Cohort n (%)	Traced Cohort n (%)
Total, N	809	517
Age at diagnosis		
20–34 y	129 (15.9)	78 (15.1)
35–49 y	300 (37.1)	196 (37.9)
50–64 y	273 (33.8)	175 (33.9)
≥65 y	107 (13.2)	68 (13.1)
Additional information found		
Yes (traced cohort)	517 (63.8)	—
No additional information except registry data	292 (36.2)	—
Hospital type		
Public hospital	405 (50.1)	385 (74.5)
Private hospital	119 (14.7)	94 (18.2)
Unknown	285 (35.2)	38 (7.3)
ECOG performance status		
0/1	144 (17.8)	144 (27.8)
2	31 (3.8)	31 (6.0)
3	19 (2.4)	19 (3.7)
4	4 (0.5)	4 (0.8)
Unknown	611 (75.5)	319 (61.7)
Tumor size		
≤5 cm (T1–T2)	120 (14.8)	110 (21.3)
>5 cm (T3–T4)	257 (31.8)	252 (48.7)
Unknown	432 (53.4)	155 (30.0)
Nodal involvement		
Present	89 (11.0)	85 (16.4)
Absent	256 (31.6)	248 (48.0)
Unknown	464 (57.4)	184 (35.6)
TNM stage		
I	12 (1.5)	10 (1.9)
II	130 (16.1)	119 (23.0)
III	201 (24.8)	191 (36.9)
IV	90 (11.1)	85 (16.4)
Unknown	376 (46.5)	112 (21.7)
Tumor grade		
1	32 (4.0)	32 (6.2)
2	124 (15.3)	124 (24.0)
3	85 (10.5)	85 (16.4)
Unknown	568 (70.2)	276 (53.4)
HRS		
ER/PR-negative	45 (5.5)	45 (8.7)
ER/PR-positive	97 (12)	97 (18.8)
Unknown	667 (82.5)	375 (72.5)

(continued)

Table 3. Cohort Characteristics (cont.)

Characteristic	Population-Based Cohort n (%)	Traced Cohort n (%)
HER2 status		
Positive	43 (5.3)	43 (8.3)
Negative	87 (10.8)	87 (16.8)
Unknown	679 (83.9)	387 (74.9)
Therapy received		
Surgery	332 (41.0)	332 (64.2)
Chemotherapy	289 (35.7)	289 (55.9)
Radiotherapy	135 (16.7)	135 (26.1)
Endocrine therapy	148 (18.3)	148 (28.6)
None recorded	102 (12.6)	102 (19.7)
Unknown	292 (36.1)	—

Abbreviations: ER, estrogen receptor; HRS, hormone receptor status; PR, progesterone receptor.

more comprehensive therapy), accounting for some of the differences in survival observed across different SSA countries.

Adequate BC therapy requires a multidisciplinary approach and is resource-intensive. Many of the women in our cohort received only fragmented care or none at all. Limited access to these main forms of therapy has been described for SSA,¹² linked to both geographic and financial inaccessibility, with most women having to pay out-of-pocket for healthcare.^{13,14} In this study, surgery was the most available therapy option, with 64.2% of women in the traced cohort having a record of surgery. Still, many women never received surgery because of either

Figure 1. Recorded therapy received by patients (A) in the population-based cohort (n=809) and (B) by registry area.

Figure 2. Overall survival (A) in the population-based cohort and (B) by therapy received.

inoperable or stage IV disease, fear of disfigurement, lack of access to surgery, or options to use neoadjuvant chemotherapy.¹⁵ Initiatives to task-share surgical BC care in primary and secondary healthcare facilities (vs tertiary healthcare facilities) have been proposed to increase the accessibility of this essential intervention.¹⁶ The main type of surgery received was mastectomy, in line with recommendations for areas with limited access to RT. However, in terms of emotional and social coping, mastectomy is often difficult for patients,¹⁷ particularly young patients in the absence of counseling and with limited access to reconstructive surgery.

Systemic treatment of BC requires specialists. In a review of the oncologic workforce worldwide, it was estimated that in 25 of the 32 African countries represented, there was approximately 1 clinical oncologist per 1,000 incident patients.¹⁸ Of the countries included in this study, this number ranged from 1 clinical oncologist per 325 incident patients in Namibia to 1 per 10,167 incident patients in Ethiopia. In the United States, there is approximately 1 clinical oncologist per 137 incident patients. Chemotherapy is not readily available; of traced patients, >40% of those with locally advanced cancer received no chemotherapy. This led to decreased survival; receiving suboptimal or no chemotherapy was associated with a poorer

prognosis compared with completing the treatment regimen. These results must be interpreted with care because reverse causation is possible (see “Limitations”).

Concerning RT, in 2010, it was estimated that in Africa there was <1 RT machine per million people, compared with almost 15 RT machines per million people in North America.¹⁹ Even within Africa, there are significant disparities in access: 60% of RT facilities are found in southern and northern Africa, with 23 countries without any RT facilities.¹⁹ The NCCN Harmonized Guidelines for SSA⁹ acknowledge this deficit in the therapy recommendations, and provide therapy guidelines that could be followed in the absence of RT facilities. Most of the patients in our cohort were candidates for RT, but only 1 in 4 traced patients received it. Of the 10 countries included, RT was available in only 5 of these countries at the time of the study: Ethiopia, Kenya, Namibia, Uganda, and Zimbabwe. A few patients from registries without in-country RT facilities had traveled abroad to receive the treatment. RT is necessary not only for curative purposes but also for palliation; approximately 70% of patients present at advanced stages with limited access to opioid analgesics in the region.^{20, 21} RT further decreases the risk of locoregional recurrence and mortality for women with stage III BC.²²

Figure 3. Three-year RS and excess risk of death from breast cancer among women in the population-based cohort without known metastases and with at least 30 days of follow-up ($n=525$) adjusted for therapy, stage, age, and country-level HDI. Abbreviations: HDI, Human Development Index; HR, hazard ratio; RR, risk ratio; RS, relative survival.

Endocrine treatment is effective for hormone receptor-positive tumors, has few adverse effects, and could be available at comparatively low costs. However, the HRS was unknown for 72.5% of the traced patients. In some of the registry areas included in this study, there was only 1 (Addis Ababa, Cotonou) or no (Bamako) laboratory with immunohistochemistry facilities for HRS testing.²³ The NCCN Harmonized Guidelines for SSA⁹ present the standard-of-care situation with the availability of HRS and do not make recommendations for treatment when the HRS is unknown. Previous recommendations have suggested giving endocrine therapy to women with locally advanced BC even with unknown HRS.²⁴ Patients who did not initiate endocrine therapy in this study had a more than 2-fold increased hazard of death compared with those who did initiate endocrine therapy, after accounting for the effect of stage and other therapy modalities.

Access to these different treatment modalities varied by registry, as seen in Figure 1. Of the registries included in our study, the Namibian national healthcare system provides free therapy for patients with cancer,⁶ including transport service to and from remote areas. This level of access seemed to be reflected in physicians actually seeing

the highest proportion of patients who initiated adequate therapy (Figure 1). Such government policies may serve as an example for best practices in access to “oncology health service for all” for patients who most likely otherwise fall out of the system. There was less comprehensive or nonexistent health coverage at public hospitals for all the other registries at the time of this study, leading to high disparities within countries. Even where government subsidies exist, medication stock-outs, indirect medical costs, and breakdowns of RT machines make completing therapy challenging,²⁵ as do the indirect costs of transport, accommodation, and supportive therapy.

A recent hospital-based study that prospectively included 2,228 patients with BC presented the survival effects of different risk factors, including the impact of late stage, lack of treatment, tumor biology, positive HIV status, and age. Notably, little education, poor awareness, rural residence, and lower socioeconomic status were associated with poorer survival outcomes. The authors showed that survival improvement (up to 22%) was achievable through downstaging and the availability of basic treatment. Patients from Namibia showed much better outcomes compared with patients from South Africa,

Uganda, Zambia, and Nigeria.²⁶ This better 3-year survival for patients from Namibia is similar to findings from the population-based registries included in the current study.⁵

Thus, although therapy guidelines are useful tools to help ensure good-quality cancer care in low- and middle-income countries, patients in resource-poor settings still face challenges such as differences in access to quality cancer diagnostics and care, especially in settings where treatment costs are not subsidized.

Limitations

A limitation of our study is its retrospective nature, which is prone to biases, and the difficulties of obtaining complete treatment data retrospectively in these settings. In addition, we could not measure and control for all potential confounders. We did not adjust for the time until onset of therapy (delay) in the final model because it was not consistently recorded for many patients. We could not measure and adjust for other factors that could influence survival, such as adherence to endocrine therapy and RT, comorbidities, molecular tumor type, and nutritional status, along with psychosocial factors influencing patient acceptance of diagnosis and therapy. In addition, relatively large proportions of patients were lost to follow-up in the first year after diagnosis, despite the active methods used to ascertain their vital status, which could result in an overestimation of survival. These high proportions of LTFU were linked to a lack of plans for patient navigation and retention and equally poor recordkeeping in some of these health systems. There could equally be the risk of immortal time bias in some of the associations seen²⁷; for instance, only women who survived long enough postsurgery could be prescribed systemic therapy. We tried to minimize this bias by excluding patients who died or were lost to follow-up within the first 30 days. A correlation between the severity of disease and choice of therapy or “confounding by indication” is a challenge in observational studies.²⁸ The relative contribution of these different therapy modalities to survival outcomes would ideally be disentangled with the use of randomized controlled trials. However, randomized controlled trials to measure outcomes in relation to the basic therapy options we investigated are not ethically feasible—thus observation and sensible deduction are the only courses available, with very careful interpretation of any observed associations between prognostic factors and outcome.

The records of 36.1% of patients registered in the PBCRs could not be traced to a treatment facility. We assumed that many of these patients never actually initiated therapy, and therefore never had a clinical treatment file opened after the pathology report. However, inadequate paper-based record systems and the absence of technological frameworks to facilitate record linkage could be a reason for the lack of tracing.

Despite these limitations, this study provides a clearer picture of the actual therapy received by a random sample of women with BC in SSA at the population level, not simply among patients attending reference treatment centers. We included women from both public and private institutions from 10 countries and patients with no record of therapy, reflecting different pathways to care, thus providing a deeper insight into the therapy routinely received by women in SSA and how this influences their survival.

Conclusions

In SSA, most women are diagnosed with BC before 50 years of age, and have a <50% chance of surviving 5 years after diagnosis. Many patients do not have access to adequate therapy or—even worse—receive inappropriate cancer care with limited survival benefits and potential adverse effects. The resulting impact of lost health and productivity cannot be overemphasized. Improving access to adequate cancer therapy to prolong life, prevent recurrence, reduce stigma, and alleviate pain is necessary. Adequate therapy requires awareness of therapy options, willingness to receive conventional medical therapy, availability of these resources locally, and the means to finance healthcare. Our study sites are almost all large urban centers; access to care would even be poorer in rural settings, with more limited awareness, fewer health facilities, longer travel time to access care, and even lower ability to pay for healthcare. Despite these conditions, there are approaches available to improve access to adequate care in SSA.

Governments and nongovernmental organizations should keep working toward improving the infrastructure, such as availability of HRS testing and cancer care facilities locally based on the strategies outlined in the NCCN Harmonized Guidelines for SSA⁹ so that guideline-concordant treatments can effectively be administered. It is imperative to improve recordkeeping and data management facilities to support patient monitoring and retention and to facilitate cancer surveillance and implementation research. The inherent challenge remains financing healthcare in low-resource settings. In the meantime, we must keep emphasizing improving awareness and facilitating access to quality care to help downstage BC and improve survival outcomes. A greater focus on systemic and systematic building of infrastructure is needed to overcome the huge discrepancy between well-known effective cancer care and what is actually received on the ground.

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Supplemental online content for:

Breast Cancer Diagnostics, Therapy, and Outcomes in Sub-Saharan Africa: A Population-Based Registry Study

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eFigure 1: Data Management and Patient Flow-Chart for Study Inclusion

eFigure 2: Breast Cancer Stage Distribution at Diagnosis by Population-Based Cancer Registry

eFigure 3: Therapy Receipt by Age at Diagnosis Among Women With Breast Cancer

eFigure 4: Patient Cohorts Showing Use of at Least One Type of CDT, and OS by Therapy

eFigure 5: 3-Year Relative Survival and Excess Risk of Death From Breast Cancer

eTable 1: Median Age at Diagnosis, Proportion of Deaths, and Loss to Follow-Up in First 3 Years After Diagnosis by Registry Index

eFigure 1. Data management and patient flow-chart for study inclusion.

Note: The original sample included patients diagnosed from January to March 2012 and 2014 from Ethiopia (which was the first pilot site); however, to prevent an overweighting of any outcomes by patients from Ethiopia, we included only patients diagnosed in 2012.

Abbreviation: PBCR, population-based cancer registry.

eFigure 2. Breast cancer stage distribution at diagnosis by population-based cancer registry.

eFigure 3. Therapy receipt by age at diagnosis among women with breast cancer in the population-based cohort.

eFigure 4. (A) Patient cohorts showing use of at least one type of CDT. **(B)** OS by therapy among patients with minimum criteria for NCCN therapy evaluation. Abbreviations: CDT, cancer-directed therapy; HRS, hormone receptor status; OS, overall survival.

eFigure 5. 3-year RS and excess risk of death from breast cancer among women in the population-based cohort without known metastases and with at least 30 days of follow-up (n=525) adjusted for age, stage, registry area, and country-level HDI.

Abbreviations: ER, estrogen receptor; HDI, Human Development Index; HR, hazard ratio; HRS, hormone receptor status; RR, risk ratio; RS, relative survival.

eTable 1. Median Age at Diagnosis, Proportion of Deaths, and Loss to Follow-Up in First 3 Years After Diagnosis by Registry Index

Registry	Cases Included for Survival Analyses n	Median Age at Diagnosis y	Year 1		Year 2		Year 3		Median Follow-Up y
			Deaths n (%)	LTFU n (%)	Deaths n (%)	LTFU n (%)	Deaths n (%)	LTFU n (%)	
Abidjan	53	48	3 (5.7)	24 (45.2)	2 (3.8)	5 (9.4)	1 (1.9)	0 (0)	1.0
Addis Ababa	93	44	3 (3.2)	29 (31.2)	7 (7.5)	4 (4.3)	7 (7.5)	4 (4.3)	2.7
Bamako	47	45	13 (27.7)	7 (14.9)	5 (10.6)	3 (6.4)	4 (8.5)	1 (2.1)	1.2
Brazzaville	75	52	8 (10.7)	51 (68.0)	2 (2.7)	2 (2.7)	2 (2.7)	1 (1.3)	0.5
Bulawayo	53	57	19 (35.8)	15 (28.3)	9 (17.0)	2 (3.8)	2 (3.8)	3 (5.7)	0.7
Cotonou	92	47	12 (13.0)	42 (45.7)	8 (8.7)	3 (3.3)	5 (5.4)	2 (2.2)	0.7
Eldoret	69	47	10 (14.5)	13 (18.8)	11 (15.9)	5 (7.2)	2 (2.9)	3 (4.3)	1.5
Kampala	42	46	9 (21.4)	11 (26.2)	6 (14.3)	2 (4.8)	5 (11.9)	0 (0.0)	1.0
Maputo	41	49	5 (12.2)	11 (26.8)					1.3
Nairobi	55	51	1 (1.8)	19 (34.5)	4 (7.3)	6 (10.9)	4 (7.3)	1 (1.8)	1.8
Namibia	64	52	3 (4.7)	5 (7.8)	2 (3.1)	2 (3.1)	6 (9.4)	1 (1.6)	4.7
Total	684	48	86 (12.6)	227 (33.2)	56 (8.7)	34 (5.3)	38 (5.9)	16 (2.5)	1.2

Abbreviation: LTFU, lost to follow-up.