Few Losses to Follow-up in a Sub-Saharan African Cancer Cohort via Active Mobile Health Follow-up

The African Breast Cancer—Disparities in Outcomes Study

Milena Foerster*, Angelica Anele, Charles Adisa, Moses Galukande, Groesbeck Parham, Annelle Zietsman, Christopher Sule Oyamienlen, Kingsley Chukwunyere Iwuoha, Esther Ezeigbo, Evelyn Bakengesa, Agnes Kaggwa, Allen Naamala, Anne Nteziryayo, Teopista Nakazibwe, Leeya F. Pinder, Emily Walubita, Johanna Pontac, Benjamin O. Anderson, Fiona McKenzie, Joachim Schüz, Isabel dos Santos Silva, and Valerie McCormack

* Correspondence to Dr. Milena Foerster, Section of Environment and Radiation, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France (e-mail: foersterm@fellows.iarc.fr).

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Accurate survival estimates are needed for guiding cancer control efforts in sub-Saharan Africa, but previous studies have been hampered by unknown biases due to excessive loss to follow-up (LTFU). In the African Breast Cancer—Disparities in Outcomes Study, a prospective breast cancer cohort study, we implemented active mobile health follow-up, telephoning each woman or her next-of-kin (NOK) trimonthly on her mobile phone to update information on her vital status. Dates of every contact with women/NOK were analyzed from diagnosis in 2014–2017 to the earliest of September 1, 2018, death, or 3 years postdiagnosis. The cumulative incidence of being LTFU was calculated considering deaths as competing events. In all, 1,490 women were followed for a median of 24.2 (interquartile range (IQR), 14.2–34.5) months, corresponding to 8,529 successful contacts (77% of total contacts) with the women/NOK. Median time between successful contacts was 3.0 (IQR, 3.0–3.7) months. In all, 71 women (5.3%) were LTFU at 3 years: 0.8% in Nigeria, 2.2% in Namibia, and 5.6% in Uganda. Because of temporary discontinuity of active follow-up, 20.3% of women were LTFU after 2 years in Zambia. The median time to study notification of a death was 9.1 (IQR, 3.9–14.0) weeks. Although the present study was not a randomized controlled trial, in this cancer cohort with active mobile health follow-up, LTFU was much lower than in previous studies and enabled estimation of up-to-date and reliable cancer survival.

breast cancer; cancer survival; loss to follow-up; mobile health; prospective studies; sub-Saharan Africa

Abbreviations: ABC-DO, African Breast Cancer—Disparities in Outcomes; CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; LTFU, loss/lost to follow-up; mHealth, mobile health; NOK, next-of-kin; SHR, subhazard ratio; SIM, subscriber identity module; SSA, sub-Saharan Africa.

Accurate cancer survival estimates are needed for sub-Saharan Africa (SSA) in order to gauge the magnitude of survival improvements needed, especially for potentially curable and common cancers like breast cancer (1). The International Agency for Research on Cancer and the African Cancer Registry Network lead the collection of population-based cancer data across the region (2), but there remains a paucity of reliable survival estimates unhampered by excessive loss to follow-up (LTFU) (3–13). In particular, in studies with retrospective follow-up approaches applied within health information systems with incomplete or no death registration, high LTFUs may represent large clinical losses and lack of treatment completion; thus, LTFU does not occur at random and survival may be overestimated. In the African Cancer Registry Network's recent retrospective estimates of breast cancer survival from 14 cancer registries,

follow-up was conducted primarily through clinical records supplemented with active tracing (i.e., telephone contacts, home visits): 1-year LTFU ranged from 0% in 3 registries (1 with record linkage to a national death register) to 8%–19% in 4 registries and 20%–45% in the remaining 7 (12). Further, in a retrospective South African breast cancer study in which the cohort was followed through medical records alone, the 42% of women who were LTFU at 3 years were more likely to have had advanced disease at diagnosis than women who were not LTFU, which is suggestive of biased survival estimates (11). In another study, among 1,328 Kaposi sarcoma patients diagnosed in 2009–2012 in 33 clinics across 5 countries and followed using medical records, the "nominal" proportion of 22% deaths at 2 years was clouded by 40% LTFU (9). However, a subsequent report by Semeere et al. (10) showed that the majority of those losses could be successfully traced through a combination of telephone calls and physical tracking via the local clinics involved.

Cognizant of the need to minimize LTFU, investigators designed the African Breast Cancer—Disparities in Outcomes (ABC-DO) Study, a multicountry breast cancer cohort study, to employ a highly active follow-up approach using mobile telephones, by means of mobile-Health (mHealth) technology (14). Management of the follow-up schedule for over 1,500 women was implemented via a tailor-made mHealth application. Herein, we evaluate the real-life implementation of this follow-up approach in terms of the proportion LTFU, the profile of women who were LTFU, and the timeliness of death notifications to the study. The practicalities and challenges of implementing mHealth follow-up in SSA settings are also discussed.

METHODS

Ethics

The ABC-DO Study protocol was approved by the ethics committees of all involved institutions: the International Agency for Research on Cancer (Lyon, France); the London School of Hygiene and Tropical Medicine (London, United Kingdom); the Federal Medical Centre Owerri (Owerri, Nigeria); the Abia State University Teaching Hospital (Aba, Nigeria); the University of Zambia (Lusaka, Zambia); the University of the Witwatersrand (Johannesburg, South Africa); the Uganda National Council for Science and Technology (Kampala, Uganda); and the Ministry of Health and Social Services of Namibia (Windhoek, Namibia). All participants provided written or fingerprint informed consent.

Study design and setting

The ABC-DO Study is a prospective, hospital-based breast cancer cohort study spanning 5 SSA countries. The ABC-DO protocol has been published elsewhere (14). Briefly, all women aged ≥18 years who were newly diagnosed with breast cancer (with histological/cytological (90%) or clinical confirmation) at participating hospitals from September 2014 to early 2017 were invited to participate (99% participation rate). Women were included irrespective of ethnicity, language spoken, and area/country of residence. The present analysis includes the ABC-DO sites in Namibia, Zambia, Nigeria, and Uganda, which implemented the same follow-up protocol, but does not include the South African site, which used a different protocol.

Participation involved completion of a face-to-face baseline questionnaire, consent to use clinical records and tumor blocks, and agreement to be regularly contacted by mobile phone. For this anticipated contact, up to 6 cell phone numbers for each woman (4 per woman plus 2 for her next-of-kin (NOK)) were obtained. Women who did not have a cell phone were provided with a basic handset (an Internet connection or smartphone was required on the participant's handset). Each woman was also provided with 2 cards with the study research assistant's phone number on them, enabling her and/or her NOK to contact the local study team at any time.

ABC-DO follow-up protocol and its implementation via mHealth

A highly active follow-up protocol of trimonthly phone calls to each woman was planned following a standardized study protocol. Calls were made by one of the local research assistants, from their smartphone to the woman's basic (or otherwise) cell phone. If the assistant did not succeed in reaching the woman after several attempts over 2–3 weeks, they contacted the NOK (see Web Figure 1, available at https://academic.oup.com/aje). At each of these contacts, vital status or contact details were updated and quality-of-life information was obtained. Vital status was also updated during the woman's in-person visits to the hospital, whenever the woman or her NOK phoned the research assistant, and via treatment data. Where possible, each woman was followed by the same research assistant for every trimonthly contact. Translators assisted in various languages during follow-up calls as appropriate—for example, in various indigenous languages in Namibia, in English, in Afrikaans, and, for Angolan patients, in Portuguese.

mHealth technologies were also used for data collection and study management. The follow-up call questionnaire was administered from, and responses were instantaneously entered into, a tailored ABC-DO mobile application (app). This app was implemented for Android by Mobenzi Technologies Pty. (Cape Town, South Africa) and installed on research assistants' smartphones/tablets. All questionnaires (including baseline, treatment, follow-up calls, and hospital visits) were programmed into the app, allowing for real-time data capture (Web Figure 1). Upon interview completion, data were automatically uploaded to a secure server, leaving no data on the phone. Each full-time research assistant had up to 400 women to follow on a trimonthly basis (approximately 133 contacts/month; 35 contacts/week). Management of this dynamic schedule of follow-ups was complex; thus, the mHealth app included an auto-updated list of women who were due to receive a follow-up call. A woman was removed from the list only when her vital status was updated (via her or her NOK), and she was permanently removed only upon receipt of death information or upon her wish to discontinue participation.

Table 1. Sociodemographic Characteristics of Participants in the African Breast Cancer—Disparities in Outcomes Study, Overall and by Study Site, 2014–2018[a]

Characteristic	Total (*n* = 1,490)		Study Site							
			Namibia (*n* = 481)		Nigeria (*n* = 387)		Uganda (*n* = 421)		Zambia (*n* = 201)	
	No.	%[b]	No.	%	No.	%	No.	%	No.	%
Age at diagnosis, years[c]	50.3 (13.7)		53.4 (14.7)		48.7 (12.3)		48.3 (12.7)		49.9 (14.8)	
Age group, years										
<35.0	183	12	46	10	51	13	56	13	30	15
35.0–44.9	390	26	99	21	117	30	123	29	51	25
45.0–54.9	420	28	130	27	106	27	129	31	55	27
55.0–64.9	269	18	102	21	72	19	65	15	30	15
≥65.0	228	15	104	22	41	11	48	11	35	17
Age, years[c]	50.3 (13.7)		53.4 (14.7)		48.7 (12.3)		48.3 (12.7)		49.9 (14.8)	
Tumor stage										
I or II	512	34	211	44	89	23	144	34	68	34
III	672	45	202	42	209	54	178	42	83	41
IV	207	14	68	14	61	16	65	15	13	6
Missing data	99	7	0	0	28	7	34	8	37	18
Socioeconomic position[d]										
Low	655	44	170	35	167	43	248	59	70	35
Medium	501	34	173	36	166	43	89	21	73	36
High	334	22	138	29	54	14	84	20	58	29
Distance to hospital, km[e]	67 (6–289)		375 (83–572)		7 (2–30)		90 (15–193)		210 (8–417)	
HIV-positive	146	10	56	12	9	2	48	11	33	16
Any non-HIV comorbidity[f]	754	51	256	53	294	76	131	31	73	36
Urban residency	797	53	307	64	250	65	110	26	130	65
Knowing someone with breast cancer	672	45	246	51	179	46	205	50	42	21
Not married	736	49	301	63	126	33	223	53	86	43
Lower educational level[g]	1,171	79	392	82	250	65	370	88	159	79
Unskilled employment[h,i]	1,036	70	309	66	254	66	320	76	153	76
Belief that breast cancer is treatable	801	54	380	79	124	32	164	39	133	66
Belief in spiritual medicine[i]	1,023	70	349	78	298	77	202	48	174	87
Belief in traditional medicine[i]	362	25	60	13	88	23	162	38	52	26

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

[a] Participating hospitals in each country were as follows: Namibia—AB May Cancer Care Centre and Windhoek Central Hospital; Nigeria—Federal Medical Center Owerri, Abia State University Teaching Hospital, and Marantha Clinic, Aba; Uganda—Mulago Hospital and Uganda Cancer Institute, Kampala; Zambia—University Teaching Hospital and Cancer Diseases Hospital, Lusaka.

[b] Column percentages.

[c] Values are expressed as mean (standard deviation).

[d] Low, medium, and high socioeconomic position were calculated, by country, as tertiles of a socioeconomic position score (range, 1–10) based on the following self-reported possessions and facilities: home ownership; indoor water; flush toilet; electricity; vehicle; refrigerator; landline telephone; gas or electric stove; and bed.

[e] Values are expressed as median (interquartile range).

[f] Assessed comorbid conditions included hypertension, diabetes, chronic obstructive pulmonary disease, hepatitis, heart disease, anemia, asthma, and tuberculosis.

[g] Lower than tertiary level.

[h] Including 277 housewives.

[i] Values were missing in Namibia due to a data collection error. There were 12 missing values for employment and 33 missing values each for belief in spiritual medicine and belief in traditional medicine.

Table 2. Indicators of Mobile Health Follow-up, Overall and by Study Site, in the African Breast Cancer—Disparities in Outcomes Study, 2014–2018

mHealth Follow-up Indicator	Total (*n* = 1,490)		Study Site							
			Namibia (*n* = 481)		Nigeria (*n* = 387)		Uganda (*n* = 421)		Zambia (*n* = 201)	
	No.	%[a]	No.	%	No.	%	No.	%	No.	%
Access to a mobile phone[b]	1,340	90	450	94	384	99	312	74	193	96
NOK contact number provided	1,431	96	444	92	383	99	406	96	198	99
mHealth database entries										
All entries	11,136	100	5,369	100	1,853	100	3,032	100	882	100
Woman reached—FU interview conducted	7,358	66	3,016	56	1,284	69	2,629	87	429	49
Woman reached—interview rescheduled	374	3	330	6	15	1	19	1	10	1
NOK confirmed that woman was alive	160	1	53	1	20	1	15	0.5	72	8
NOK notified study of woman's death	637	6	158	3	211	11	201	7	67	8
Patient/NOK not reached	2,607	23	1,812	34	323	17	168	6	304	34
Time between consecutive follow-up interviews, months[c]	3.0 (3.0–3.7)		3.2 (3.0–3.9)		3.7 (3.2–4.9)		3.0 (3.0–3.0)		3.3 (3.0–4.6)	
Call duration, minutes[c]										
When FU interview was conducted	12.4 (8.4–21.2)		8.8 (7.1–11.8)		17.0 (11.9–27.0)		19.9 (12.6–33.1)		18.1 (12.1–26.7)	
When FU interview was not conducted	2.5 (1.5–5.0)		1.8 (1.4–2.8)		3.9 (2.6–6.9)		8.6 (1.7–16.0)		5.3 (3.0–10.4)	

Abbreviations: FU, follow-up; NOK, next-of-kin.
[a] Column percentages.
[b] Either the participant's own phone or someone else's (e.g., family member).
[c] Values are expressed as median (interquartile range).

Statistical analysis

We analyzed risk of being LTFU in a time-to-event analysis, starting from the woman's diagnosis date (earliest of the date of histology/cytology sample collection or the baseline interview) to the earliest of 3 years postdiagnosis, the date of death, or the closing date for the present analysis, namely September 1, 2018 (i.e., 6 months before data extraction to allow for follow-up contacts in the 3-monthly protocol). A woman was considered LTFU if her vital status was not known on the closing date. The cumulative incidence percentage of LTFU and its 95% confidence interval were calculated considering deaths as competing risks (referred to hereafter as $LTFU_{CR}$), using the "stcompet" command in Stata (StataCorp LLC, College Station, Texas). Competing-risks regression analyses, adjusted for tumor stage, age at diagnosis, and socioeconomic position, were performed to identify correlates of being LTFU, and subhazard ratios were estimated using the Stata command "stcrreg." Predictor variables are described in the Web Appendix. For some women, reasons for LTFU were noted by the research assistant in an optional open text field in the follow-up questionnaire. These data were reviewed, and reasons are presented descriptively.

Median values and their interquartile ranges or mean values and their 95% confidence intervals, time between consecutive follow-up contacts, and time between the date of a woman's death (from any cause) and the date of its notification to the study were estimated. For the latter, only deaths that occurred earlier than September 1, 2018, were considered in the analysis.

RESULTS

In all, 1,541 women were enrolled in the 4 countries included in the present analysis. Of these, 51 (3.3%) were not included because of an indication that they may not have been incident cases, since they were told they had breast cancer or had a biopsy conducted more than 24 months prior to their baseline interview. Of the remaining 1,490 women with breast cancer, 481 were from Namibia, 421 were from Uganda, 387 were from Nigeria, and 201 were from Zambia (Table 1). All women were Black African, except in Namibia (80% Black, 20% White/mixed-race). Mean age at diagnosis was 50 (standard deviation, 13.7) years, and most women were diagnosed with stage III cancer. More than 50% of the women lived in urban areas, apart from those in Uganda (26%). Most women (70%) did not hold a skilled job.

Follow-up using mHealth technologies

All 1,490 women provided at least 1 personal contact number, and 1,431 (96%) provided one for their NOK (Table 2). The median follow-up time was 24.2 (interquartile

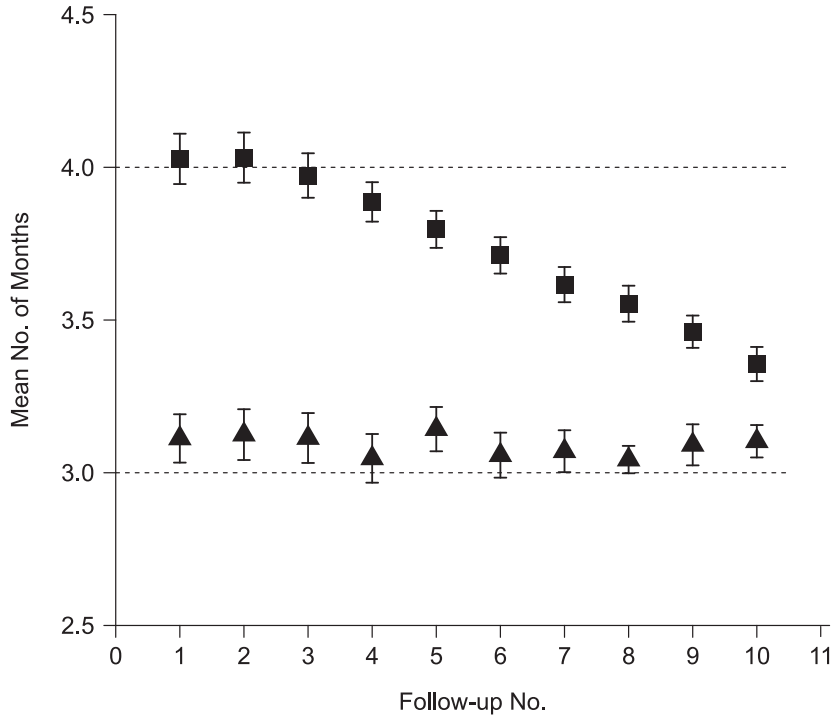

Figure 1. Mean duration (months) between consecutive successful follow-up calls among ABC-DO cohort members known to still be alive, by follow-up number and total number of follow-up contacts (squares, participants with <10 follow-up interviews; triangles, participants with ≥10 follow-up interviews), African Breast Cancer—Disparities in Outcomes Study, 2014–2018. Mean values, 95% confidence intervals (CIs), and numbers of women are provided in Web Table 1. Follow-up call number 1 was the first call scheduled 3 months after the baseline interview. Bars, 95% CIs.

range (IQR), 14.2–34.5) months (31.1 months excluding deaths). Up to this time point, 11,136 mHealth follow-up entries (attempted calls plus those where the woman/NOK was successfully reached) were logged into the mHealth platform. Of these, 7,358 (66%) were completed interviews with the woman herself, 374 (3%) were instances where the assistant reached the participant but she asked to reschedule the interview, 160 (1%) were contacts with the NOK indicating that the woman was alive, and 637 (6%) were death notifications. The remaining 2,607 entries (23%) were unsuccessful contact attempts, many of which were subsequently followed by a successful contact. The median duration of a (successful) call with the woman was 12.4 (IQR, 8.4–21.2) minutes. At the study closing date, half of the cohort had completed at least 5 follow-up interviews (IQR, 2–8), and 195 women (13%) had completed 10 or more, whereas 132 women (9%) had none due to early death (n = 127, at a median of 2.8 (IQR, 1.4–5.0) months). Only 5 (0.3%) were early LTFUs with no follow-up contacts after the baseline interview. Updated follow-up status was almost always obtained through the mHealth phone contacts, but for 15 women their last known date alive was sourced from medical records.

The median and mean number of months between consecutive contacts that resulted in successful follow-up interviews with the woman were 3.0 (IQR, 3.0–3.7) and 3.6 (95% confidence interval (CI): 3.6, 3.7), respectively—that is, in line with the trimonthly protocol. However, the length of this interval decreased over time, with a stronger gradient in the mean (from 3.8 (95% CI: 3.7, 3.9) months between the first and second contacts to 3.1 (95% CI: 3.0, 3.1) months between the ninth and 10th contacts) than in the median (from 3.2 (IQR, 3.0–3.9) months to 3.0 (IQR, 3.0–3.0) months, respectively). This time trend reflected a "self-selection" process whereby terminal and difficult-to-trace women were lost or died over time. Consequently, although the mean length between consecutive follow-up interviews decreased gradually for the whole cohort, it remained constant for the subset of women who completed at least 10 interviews (Figure 1).

A cumulative total of 19 women had become LTFU by the end of year 1 and 58 by the end of year 2, yielding $LTFU_{CR}$ percentages of 1.3% (95% CI: 0.8, 1.9) and 4.0% (95% CI: 3.1, 5.1), respectively (Table 3, Figure 2). At 3 years, $LTFU_{CR}$ percentages were low in Nigeria (n = 3; $LTFU_{CR}$ = 0.8%, 95% CI: 0.2, 2.2) and Namibia (n = 10; $LTFU_{CR}$ = 2.2%, 95% CI: 1.1, 3.9) and slightly higher in Uganda (n = 21; $LTFU_{CR}$ = 5.6%, 95% CI: 3.6, 8.3). Because of a later commencement of recruitment, $LTFU_{CR}$ in Zambia could only be analyzed up to 2 years, by which time losses were already much higher than in other countries (n = 37; $LTFU_{CR}$ = 20.3%, 95% CI: 14.8, 26.5).

Reasons for LTFU were known for 46 women (65%). The most commonly reported reason was an unavailable

Table 3. Numbers and Proportions[a] of Women Lost to Follow-up According to Time Since Diagnosis, Overall and by Study Site, African Breast Cancer—Disparities in Outcomes Study, 2014–2018

Study Site	No. of Women Followed	LTFU by End of First Year			LTFU by End of Second Year			LTFU by End of Third Year		
		No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
All	1,490	19	1.3	0.8, 1.9	58	4.0	3.1, 5.1	71	5.3	4.2, 6.6
Namibia	481	0	0	0, 0.8	5	1.0	0.4, 2.3	10	2.2	1.1, 3.9
Nigeria	387	0	0	0, 0.9	3	0.8	0.2, 2.2	3	0.8	0.2, 2.2
Uganda	421	6	1.4	0.6, 2.9	13	3.1	1.7, 5.1	21	5.6	3.6, 8.3
Zambia	201	13	6.5	3.6, 10.4	37	20.3	14.8, 26.5	—[b]	—	—

Abbreviations: CI, confidence interval; LTFU, lost to follow-up.

[a] Cumulative incidence of being LTFU considering death as a competing risk ($LTFU_{CR}$).

[b] Because of later recruitment, Zambian patients had not yet completed the third year of follow-up (n = 37 LTFU) at the closing date of the study.

telephone number (83%), followed by a discontinued, incorrect, or changed number (n = 5 (11%)). Two patients (4%) left the country, while withdrawal from the study was reported for 1 woman (2%). In Namibia, of the 10 LTFU participants, 6 were women from neighboring Angola and Zimbabwe. Although it was not noted by the research assistant, it seems likely that they returned to their home countries after cancer treatment.

Determinants of being LTFU were examined in the countries where there were sufficient numbers of women lost—that is, in Zambia (n = 37 lost) and in Namibia (n = 10) and Uganda (n = 21) combined—but such analyses were not relevant for Nigeria due to only 3 losses. The risk of being LTFU decreased with increasing age at breast cancer diagnosis in Zambia (per 10-year increment in age, subhazard ratio (SHR) = 0.74, 95% CI: 0.59, 0.92) (Table 4) and in Uganda and Namibia (SHR = 0.76, 95% CI: 0.57, 1.01). In Zambia only, LTFU was also lower with increasing socioeconomic position (per tertile, SHR = 0.64, 95% CI: 0.42, 0.98) (Table 4) and for human immunodeficiency virus (HIV)-positive women compared with HIV-negative women (SHR = 0.30, 95% CI: 0.12, 0.86) (Table 5). In Uganda and Namibia, urban residency was associated with a higher risk of being LTFU (SHR = 2.15, 95% CI: 1.07, 4.34) (Table 5). Risk of being LTFU was not associated with tumor stage at diagnosis; however, there was weak evidence that it may have been higher among those with missing stage information. No other associations with risk of being LTFU were found, but the 95% confidence intervals for most estimates were wide because of the small number of LTFUs in most settings.

Notification of deaths

Until September 1, 2018, the study had gained information on 676 deaths. These deaths were reported to the study a median of 9.1 (IQR, 3.9–14.0) weeks after their occurrence. Country-specific intervals were shorter in Namibia and Uganda (median lag times of 7.9 (IQR, 3.4–11.6) weeks and 7.7 (IQR, 2.7–11.4) weeks, respectively) than in Nigeria

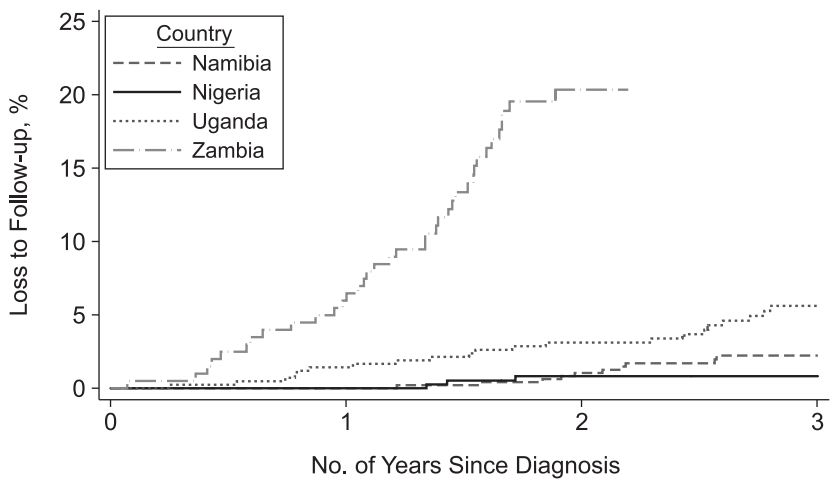

Figure 2. Cumulative incidence of being lost to follow-up in the African Breast Cancer—Disparities in Outcomes Study, by country, 2014–2018.

Table 4. Associations of Tumor Stage, Age, Socioeconomic Position, and Residential Distance From a Hospital With Being Lost to Follow-up[a], African Breast Cancer—Disparities in Outcomes Study, 2014–2018

Variable	Uganda and Namibia				Zambia			
	No.	%	SHR[b]	95% CI	No.	%	SHR[b]	95% CI
Tumor stage								
I or II	13	4	1.00	Referent	10	14	1.00	Referent
III	13	3	0.85	0.39, 1.84	16	19	1.12	0.51, 2.47
IV	2	2	0.35	0.78, 1.58	0	0		
Missing data	3	9	1.86	0.51, 6.76	11	30	1.72	0.74, 4.01
Age group at diagnosis, years								
<35.0	8	8	2.57	0.97, 6.84	9	30	1.06	0.45, 2.46
35.0–44.9	7	3	1.02	0.37, 2.84	10	20	0.83	0.36, 1.91
45.0–54.9	8	3	1.00	Referent	15	27	1.00	Referent
55.0–64.9	7	4	1.50	0.56, 4.07	1	3	0.13	0.02, 0.99
≥65.0	1	1	0.24	0.03, 2.00	2	6	0.15	0.03, 0.68
Age, per 10-year increment			0.76	0.57, 1.01			0.74	0.59, 0.92
Distance to hospital, per 100-km increment			1.15	1.03, 1.28			0.92	0.76, 1.11
Socioeconomic position[c]								
Low	13	3	1.00	Referent	14	20	1.00	Referent
Middle	10	4	1.50	0.69, 3.28	16	22	0.84	0.39, 1.84
High	8	4	1.23	0.50, 3.00	7	12	0.38	0.15, 0.97
Socioeconomic position, per tertile increment			1.13	0.75, 1.69			0.64	0.42, 0.98

Abbreviations: CI, confidence interval; SHR, subhazard ratio.

[a] Assessed using SHRs in a competing-risks survival model. Because of the small numbers of women lost to follow-up in Nigeria (n = 3 at 3 years), Nigeria was not included in this analysis.

[b] SHR estimated from a competing-risk regression model with death as a competing event, adjusted for population group (Uganda and Namibia), tumor stage at diagnosis, socioeconomic position, and age (linear increase per year).

[c] Low, medium, and high socioeconomic position were calculated, by country, as tertiles of a socioeconomic position score (range, 1–10) based on the following self-reported possessions and facilities: home ownership; indoor water; flush toilet; electricity; vehicle; refrigerator; landline telephone; gas or electric stove; and bed.

(median, 10.9 (IQR, 5.9–17.3) weeks) and Zambia (median, 11.9 (IQR, 5.3–24.3) weeks) (Figure 3). The length of this time interval did not vary by factors investigated, including age, calendar period, urban/rural residence, or woman's educational level (not shown), but it was longer for foreign patients receiving treatment in Namibia (a median of 20.1 (IQR, 7.2–33.2) weeks among 24 deaths).

DISCUSSION

With rapidly growing mobile phone coverage, mHealth has the potential to transform health and health research in Africa. Its uses are widespread, including in pathology, multidisciplinary oncology meetings, and the setup of cohort studies for noncommunicable diseases (15). mHealth has been incorporated as a research tool in the study of infectious diseases and noncommunicable diseases, usually embedded in disease surveillance programs, but less often for active follow-up (16, 17). In the present study, we utilized mHealth for almost every aspect of the first multicountry prospective breast cancer cohort study in SSA. Active follow-up was conducted on a trimonthly basis via calls to a participant's or her NOK's mobile phone, from the study research assistant's smartphone/tablet, and during the call, assistants entered real-time updated information on vital status and quality of life. Using this mHealth follow-up protocol, by the end of the first 3 years, LTFUs were below 10% overall and less than 3% in 2 countries. Regularity of contact was crucial to achievement of low LTFU, as evidenced by the much higher LTFU in Zambia. In this setting, a change in fieldwork personnel led to a disruption in active follow-up; that is, there was a period of approximately 5 months during which women were not contacted. Although active follow-up was gradually resumed upon employment of new study personnel, the disruption in regular calls led to irreversible losses of some women. mHealth contacts also achieved impressive timeliness of death notification, with a median of 9 weeks. Research assistants did not feel that this contact with the NOK soon after a woman's death was insensitive or an inconvenience to the NOK or the family.

Table 5. Associations of Baseline Sociocultural Factors and Comorbidity With Being Subsequently Lost to Follow-up[a], African Breast Cancer—Disparities in Outcomes Study, 2014–2018

Variable	Uganda and Namibia				Zambia			
	No.	%	SHR[b]	95% CI	No.	%	SHR[b]	95% CI
HIV-positive								
No	3	3	1.00	Referent	34	20	1.00	Referent
Yes	28	4	0.80	0.22, 2.93	3	9	0.30	0.12, 0.86
Any comorbidity[c]								
No	23	4	1.00	Referent	25	20	1.00	Referent
Yes	8	2	0.60	0.26, 1.41	12	16	1.43	0.67, 3.04
Urban residency								
No	13	3	1.00	Referent	13	18	1.00	Referent
Yes	18	4	2.15	1.07, 4.34	24	18	1.17	0.47, 2.90
Knowing someone with breast cancer								
No	14	3	1.00	Referent	29	18	1.00	Referent
Yes	17	4	1.16	0.53, 2.54	8	19	1.08	0.46, 2.53
Not married								
No	15	4	1.00	Referent	23	20	1.00	Referent
Yes	16	3	0.93	0.45, 1.92	14	16	1.07	0.55, 2.08
Low educational level[d]								
No	25	3	0.88	0.34, 2.27	31	20	1.20	0.44, 3.30
Yes	6	4	1.00	Referent	6	14	1.00	Referent
Unskilled employment[e,f]								
No	17	3	0.54	0.27, 1.09	31	20	1.35	0.53, 3.41
Yes	14	5	1.00	Referent	6	13	1.00	Referent
Belief that breast cancer is treatable								
No	17	3	1.00	0.47, 2.08	26	20	1.02	0.48, 2.16
Yes	14	4	1.00	Referent	11	16	1.00	Referent
Belief in spiritual medicine[f]								
No	14	3	0.57	0.26, 1.26	31	18	1.10	0.49, 2.50
Yes	17	5	1.00	Referent	6	22	1.00	Referent
Belief in traditional medicine[f]								
No	7	3	0.70	0.29, 1.71	6	12	0.54	0.22, 1.36
Yes	24	4	1.00	Referent	31	21	1.00	Referent

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; SHR, subhazard ratio.

[a] Assessed using SHRs in a competing-risks survival model. Because of the small numbers of women lost to follow-up in Nigeria (n = 3 at 3 years), Nigeria was not included in this analysis.

[b] SHR estimated from a competing-risk regression model with death as a competing event, adjusted for population group (Uganda and Namibia), tumor stage at diagnosis, socioeconomic position, and age (linear increase per year).

[c] Assessed comorbid conditions included hypertension, diabetes, chronic obstructive pulmonary disease, hepatitis, heart disease, anemia, asthma, and tuberculosis.

[d] Lower than tertiary level.

[e] Including 277 housewives.

[f] Values were missing in Namibia due to a data collection error. There were 12 missing values for employment and 33 missing values each for belief in spiritual medicine and belief in traditional medicine.

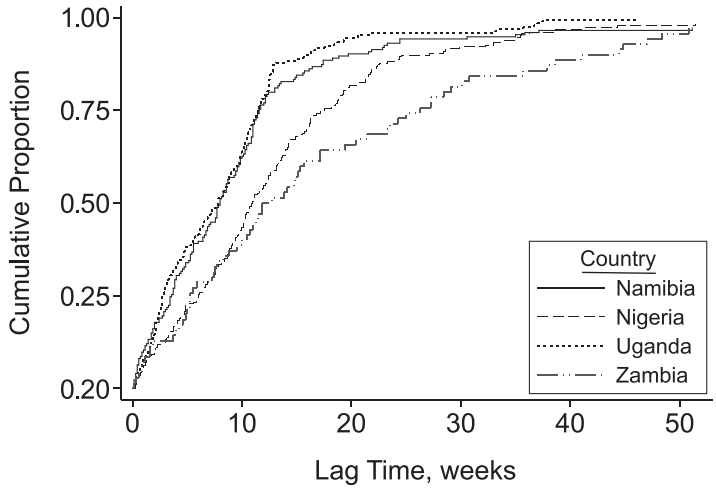

Figure 3. Cumulative proportion of time between the occurrence of a death and the study investigators' being informed of the death (median lag time), by country, African Breast Cancer—Disparities in Outcomes Study, 2014–2018.

Comparison with previous findings

Compared with other recent studies of breast cancer survival in SSA, LTFUs in ABC-DO were low (Web Figure 2). Only a few previous cohorts were prospectively followed. In one study by Kantelhardt et al. (6), follow-up was passive, relying on data captured during routine hospital visits. The percentage LTFU was 22% after 2 years, despite the study's free provision of endocrine treatment to breast cancer patients. Generally, most previous studies had retrospective designs (7, 11–13, 18). Particularly high losses, of up to 45%, were reported in studies that relied on follow-up through hospital records alone (7, 11, 13). In recently published breast cancer survival estimates from 14 registries in the African Cancer Registry Network, combining retrospective data collection with active tracing of lost cases, most LTFU estimates were over 20% (12). Only 3 settings achieved few LTFU at 3 years (Mauritius, Seychelles, and Zimbabwe-Harare), and 2 of these (Mauritius, Seychelles) were higher-income settings with high-quality population-based cancer and, in Mauritius, mortality registers and thus do not depict typical situations across SSA. Sensitivity analyses of worst- and best-case scenarios can be conducted to assess the likely impact of LTFU on survival estimates; however, with large LTFU, they increase uncertainty and produce considerably different survival estimates (e.g., an estimate of an absolute difference of 15 percentage points at 2 years (6)). Across previous studies, definitions of LTFU differed. Most publications lacked this information, and where available, the predominant definition was "unknown vital status at the censoring date." With the exception of 1 other study (11), LTFU percentages were presented in raw numbers instead of accounting for deaths as competing events as we did. Nevertheless, despite these differences in methodology, the differences in LTFU between the present study's prospective mHealth follow-up approach and other approaches was sufficiently large in magnitude and sufficiently consistent across the 4 countries to reasonably attribute the few LTFU to the mHealth approach. It must be acknowledged, however, that the follow-up approach was not evaluated in a randomized controlled trial; thus, the low LTFU may not have been entirely due to the follow-up methodology but may additionally have partially reflected other features of the study, such as the particular settings, motivation of women, and study personnel.

Generally, LTFU in retrospective studies that rely entirely on medical records are clinical losses, and thus there is a risk of overestimating survival if women LTFU are actually deaths occurring due to no treatment or incomplete treatment. In ABC-DO, study LTFUs are necessarily also clinical losses; however, use of the mHealth methodology ensured that the reverse was not true—that is, not all clinical losses were study losses. A recent publication documented a high percentage (20%, particularly affecting low-socioeconomic-status groups) of untreated women, especially in Nigeria, despite its very few statistical LTFU (19).

Implementing mHealth follow-up

The low percentage of LTFU achieved in ABC-DO makes the active mHealth follow-up approach an attractive method. The availability of multiple phone numbers for patients and their NOK helped the study investigators to maintain contact with participants. Initial concerns that the high regularity of contact might become a nuisance to women were not realized; on the contrary, the study research assistants reported that for many women, being part of the ABC-DO Study was accompanied by a sense of belonging and experiencing psychosocial support. Although the study was intended to be observational, it would have been unethical to withhold advice from women during the prospective follow-up contact, though no specific intervention or training of research nurses was part of the protocol. Occasionally nurses informed women about the importance of completing their

treatment or the possibilities of finding financial support if asked, and therefore they increased compliance and presumably reduced clinical and study losses.

mHealth in ABC-DO incorporated a programmed study management protocol, which prompted research assistants about when to call each woman. This system ensured smooth and time-efficient adherence to the study protocol and provided real-time data for a dynamic cohort. As an asset of the mHealth application used in ABC-DO, only the research assistant's phones/tablets needed to be smartphones; participants' phones could be basic handsets.

Although mHealth produced low LTFU overall, 1 ABC-DO site experienced significant losses. In Zambia, a change in study personnel led to irreversible losses, emphasizing the need for regularity of contact. Other challenges concerned changing phone numbers. SSA has the world's fastest emerging telecommunications market, with competing providers attracting customers with new offers; thus, multiple subscriber identity module (SIM) cards and regular changes of phone numbers are common. During the study period, authorities were also tightening the regulation of SIM card registration. For example, in Uganda, unregistered SIM cards are periodically deactivated (e.g., in March 2017). Despite this, in ABC-DO we did not detect a specific increase in LTFU subsequent to these dates, and a discontinued mobile phone number was the reported reason for LTFU in only a few instances. Even when a mobile phone number was valid, contact was occasionally challenging for women residing in very remote areas where network coverage, even third-generation (3G) mobile telecommunications technology, was poor (19). In a vast country like Namibia, there are areas with poor network coverage. However, local study teams report that the basic Global System for Mobile Communications (GSM) network (second-generation (2G)) was available for almost all women within a reasonable distance. Another consideration for use of mHealth contact is a supply of electricity with which to recharge phones. Power banks were provided to study personnel, but participants' phones were occasionally affected, since power outages in the study area can last more than a week. With the combination of these obstacles, repeated contact attempts were made, and discretion was used prior to and when contacting a participant's NOK. In contrast, we did not experience other concerns, such as phone theft, and because we did not use text messaging to contact women, breaches of confidentiality were not encountered (20). In addition, the design ensured no follow-up costs to patients. Once the mHealth app was programmed, the running costs included data-hosting charges and an annual contract to a phone provider with a maximal call and data time. One full-time research assistant was able to follow up to 300 women.

Profile of women LTFU

Characteristics of women LTFU in cancer cohorts in SSA are rarely described. In the ABC-DO Study, younger age (<35 years) was a risk factor for being LTFU, a finding consistent across countries. Previous findings from ABC-DO have shown that stage at diagnosis was slightly more advanced in younger women (21), and very young women also have lower survival; thus, some of the women LTFU may have died. Study nurses felt that other reasons for these losses might have been sociocultural—for example, the family may have been ashamed of the death or may have still been in mourning and did not want to answer the phone. Such losses may also have occurred simply due to more frequent changes of the mobile phone number. In ABC-DO, more losses occurred among women with missing tumor stage data (15 of 99), but where stage was known, losses were not higher in women with more advanced disease, as has been seen in previous studies (11). Considering that missing stage information might indicate very advanced disease or a woman's being too fragile for diagnostic workup, such a finding should be kept in mind for studies where this subgroup is large. In Zambia, women of lower socioeconomic position were more likely to be LTFU, which may also arise from lower survival, because in ABC-DO, an accumulation of social disadvantages has been identified as a major barrier to early diagnosis through a long prediagnostic journey, and is a barrier to receiving breast cancer treatment (22). Finally, HIV-positive women in Zambia were less likely to be LTFU. This finding is probably due to the more frequent health-care contacts among these women.

Research implications

Few losses and timely death ascertainment achieved via mHealth research methodology are desirable features for all cancer cohorts. Follow-up methods may need to be adjusted for the cancer and setting in question. For cancers with a poorer prognosis, contact intervals and total follow-up time may need to be reduced to capture deaths in a timely fashion. A prospective study design was essential in the mHealth approach adopted in ABC-DO; thus, applications of mHealth to population-based studies would require access to a patient's phone number and rapid case identification to initiate follow-up. A further consideration in applying mHealth follow-up is the outcome of interest. For the outcome of death from all causes, vital status information provided by a family member or NOK can be considered reliable, but if cause-specific information on mortality is needed, validation of an NOK's reported cause of death or other sources of this information would be needed. Data on other cancer endpoints, such as progression-free or metastasis-free survival, would be difficult to capture in a phone call to a layperson. Examination of such outcomes may be better pursued through the conduct of smaller-scale in-depth clinical studies with physical patient recall to incorporate physical, imaging, and biomarker evaluations. Nevertheless, because survival rates for most cancers in SSA currently lag considerably behind those of higher-income countries, the hard outcome of death from all causes remains a valuable one at present, for which an mHealth follow-up approach is effective in large-scale studies.

Of greater importance than mHealth for research follow-up is the potential for mHealth to improve patient survival and clinical follow-up. Thus, the success of prospective mHealth follow-up may be an avenue through which improvements in treatment completion and survival can be achieved. Mobile technologies could be used not only for

giving advice and appointment reminders to women but also, in the African setting, for money transfers if transportation costs and other costs are prohibiting continuation of treatment. Randomized trials are needed to evaluate whether use of mHealth can improve survival in such a fashion.

In summary, mHealth technologies have the potential to transform cancer survival studies in low-resource settings through real-time, high-quality follow-up data with minimal LTFUs and timely ascertainment of deaths.

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Author affiliations: Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France (Milena Foerster, Fiona McKenzie, Joachim Schüz, Valerie McCormack); Federal Medical Centre Owerri, Owerri, Nigeria (Angelica Anele, Christopher Sule Oyamienlen, Kingsley Chukwunyere Iwuoha); Abia State University Teaching Hospital, Aba, Nigeria (Charles Adisa, Christopher Sule Oyamienlen, Esther Ezeigbo); Makerere University, Kampala, Uganda (Moses Galukande, Evelyn Bakengesa, Agnes Kaggwa, Allen Naamala, Anne Nteziryayo, Teopista Nakazibwe); Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina (Groesbeck Parham, Leeya F. Pinder, Emily Walubita); Department of Surgery, School of Medicine, University of Washington, Seattle, Washington (Benjamin O. Anderson); Windhoek Central Hospital, Windhoek, Namibia (Annelle Zietsman, Johanna Pontac); Maranatha Specialist Mission Hospital, Aba, Nigeria (Christopher Sule Oyamienlen, Esther Ezeigbo); Fred Hutchinson Cancer Research Center, Seattle, Washington (Benjamin O. Anderson); and Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom (Isabel dos Santos Silva).

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