Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): A prospective cohort study

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Summary

Background Breast cancer is the second leading cause of death from cancer in women in sub-Saharan Africa, yet there are few well characterised large-scale survival studies with complete follow-up data. We aimed to provide robust survival estimates in women in this setting and apportion the survival gaps.

Methods The African Breast Cancer-Disparities in Outcomes (ABC-DO) prospective cohort study was done at eight hospitals across five sub-Saharan African countries (Namibia, Nigeria, South Africa, Uganda, and Zambia). We prospectively recruited women (aged ≥18 years) who attended these hospitals with suspected breast cancer. Women were actively followed up by use of a telephone call once every 3 months, and a mobile health application was used to keep a dynamic record of follow-up calls due. We collected detailed sociodemographic, clinical, and treatment data. The primary outcome was 3-year overall survival, analysed by use of flexible proportional mortality models, and we predicted survival under scenarios of modified distributions of risk factors.

Findings Between Sept 8, 2014, and Dec 31, 2017, 2313 women were recruited from these eight hospitals, of whom 85 did not have breast cancer. Of the remaining 2228 women with breast cancer, 58 women with previous treatment or recurrence, and 14 women from small racial groups (white and Asian women in South Africa), were excluded. Of the 2156 women analysed, 1840 (85%) were histologically confirmed, 129 (6%) were cytologically confirmed, and 187 (9%) were clinically confirmed to have breast cancer. 2156 (97%) women were followed up for up to 3 years or up to Jan 1, 2019, whichever was earlier. Up to this date, 879 (41%) of these women had died, 1118 (52%) were alive, and 159 (7%) were censored early. 3-year overall survival was 50% (95% CI 48–53), but we observed variations in 3-year survival between different races in Namibia (from 90% in white women to 56% in Black women) and in South Africa (from 76% in mixed-race women to 59% in Black women), and between different countries (44–47% in Uganda and Zambia *vs* 36% in Nigeria). 215 (10%) of all women had died within 6 months of diagnosis, but 3-year overall survival remained low in women who survived to this timepoint (58%). Among survival determinants, improvements in early diagnosis and treatment were predicted to contribute to the largest increases in survival, with a combined absolute increase in survival of up to 22% in Nigeria, Zambia, and Uganda, when compared with the contributions of other factors (such as HIV or aggressive subtypes).

Interpretation Large variations in breast cancer survival in sub-Saharan African countries indicate that improvements are possible. At least a third of the projected 416 000 breast cancer deaths that will occur in this region in the next decade could be prevented through achievable downstaging and improvements in treatment. Improving survival in socially disadvantaged women warrants special attention.

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Introduction

Breast cancer and cervical cancer constituted half of all new cases of cancer in women in sub-Saharan Africa in 2018.[1] There are fewer preventive approaches for breast cancer than for cervical cancer, thus improving breast cancer survival is an urgent priority to reduce the increasing mortality burden, projected to reach 112 000 deaths in 2040.[1] Breast cancer has the potential for a good prognosis, through multimodal treatments for early-stage disease. The 5-year survival of women with breast cancer (of all cancer stages) is 85–90% in high-income countries,[2] although 5-year survival is lower

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Research in context

Evidence before this study

We searched PubMed using the search terms "breast cancer", "survival" and "sub-Saharan Africa" to identify studies published between database inception up to June 1, 2019, with no language restrictions. We identified 20 studies that included breast cancer survival estimates in sub-Saharan Africa. Our review revealed large variations in breast cancer survival in this region, ranging from less than 20% to more than 90% at 5 years. However, many of the studies identified have limited value when informing strategies to improve survival because they are outdated, have excessive losses to follow-up, and because of sparse epidemiologic, clinical, or therapeutic data.

Added value of this study

The African Breast Cancer-Disparities in Outcomes study is a hospital-based breast cancer cohort of 2228 women prospectively recruited in 2014–17 in five sub-Saharan Africa countries. Detailed epidemiological and clinical data on this cohort is being collected with a successfully implemented mobile health application-based follow-up protocol, in which participants are followed up once every 3 months. In public sector settings, crude overall survival in women at 3 years after diagnosis varied substantially, with an overall survival of 90% in white Namibian women, 69–76% in mixed-race Namibian and South African women, 55–59% in black Namibian and South African women, 44–47% in Ugandan and Zambian women, and 36% in Nigerian women. These differences were largely accounted for by prognostic factors. The largest survival gains can be achieved through near equal contributions of earlier diagnosis and improved treatment, and if these factors were combined, they would lead to a 28–37% reduction in the number of deaths in black women in a given setting. A young age at diagnosis and a high prevalence of HIV represented a small contribution (<2% each) to low survival in these sub-Saharan African countries.

Implications of all the available evidence

A projected 416 000 women will die from breast cancer in sub-Saharan Africa in 2020–29, which is an excessive mortality toll for a cancer that is potentially curable if diagnosed and treated early. The results of our study suggest that, through downstaging of symptomatic disease and treatment improvements, a substantial proportion (ie, at least a third) of deaths from breast cancer could be averted.

in Black women (80%) than in white women in the USA,[3] and it is lower in women with hormone receptor-negative tumours than in those with hormone receptor-positive tumours.[4] These survival estimates contrast with those of women with breast cancer in sub-Saharan Africa (appendix pp 2–3). The compiled population-based survival estimates from the International Agency for Research on Cancer (now two decades old),[5] the CONCORD-3 study,[2] and the African Cancer Registry Network (AFCRN)[6] cover 13 of 48 sub-Saharan African countries. The 5-year survival estimates in these reports[2,5,6] range from less than 20% survival in Mali and The Gambia, to 35–50% in Uganda, and to 85% in Mauritius. Many of these survival estimates had unknown selection biases and substantial losses to follow-up of 20–40% at 2–3 years.[6–8] Another important limitation of these reports is the scarce clinical, histological, epidemiological, and treatment data. Poor survival in sub-Saharan Africa has been associated with late diagnosis, aggressive tumour subtypes, a young age (ie, <30 years) at diagnosis, being HIV-positive, and suboptimal treatment,[6,9–11] but a comprehensive estimation of the combined quantitative impact of these factors on survival is missing.

See Online for appendix

Herein, we report on survival in the African Breast Cancer-Disparities in Outcomes (ABC-DO) breast cancer cohort during 3 years of follow-up, and we provide estimates of the survival gains associated with modifying the drivers of poor prognosis, with the aim of informing effective actions to reduce future deaths due to breast cancer. We intended that our estimates of survival gains associated with modifying risk factor distributions would be based on the survival effects observed in the ABC-DO cohort only. Thus, unlike previous models,[12] our predictions would not rely on assumptions derived from high-income settings.

Methods

Study design and participants

This prospective cohort study was done at eight hospitals across five sub-Saharan African countries (Namibia, Nigeria, South Africa, Uganda, and Zambia). We prospectively recruited women (aged ≥18 years) who attended these hospitals with suspected breast cancer, typically based on symptoms such as a breast mass, nipple retraction, or discharge and skin changes (appendix p 4). Per protocol,[13] women were recruited irrespective of any treatment subsequently received, race, residence, or insurance status. Recruitment centres (ie, hospitals) and their catchment populations are provided in the appendix (pp 4–5). All hospitals included in the study could offer surgery and chemotherapy, and most were tertiary public hospitals. Hospitals located in the Namibian, Ugandan, and Zambian capitals were the only hospitals in the country with radiation oncology units. In Nigeria, recruitment was done at two tertiary public hospitals in the states of Imo and Abia (each with a population of >4 million people) and at an 18-bed private hospital in Aba. These three hospitals provide surgery and chemotherapy and can refer patients for radiotherapy. The South African hospital located in Soweto, which has a population of approximately 2 million people, is part of

another ongoing cohort study.[14] The ABC-DO study was approved by all institutional ethics committees (appendix p 1), and all women provided written or thumbprint informed consent, witnessed by the study interviewer.

Procedures

Participants completed an interviewer-administered questionnaire at recruitment, consented to allow the study team access to their clinical data, and took part in regular follow-up. The questionnaire collected detailed data on sociodemographic factors, including education level, the nine amenities used to generate site-specific tertiles of socioeconomic position, breast cancer awareness, cohabitation (yes or no), and residential area (urban or rural). Participants were tested for HIV infection in South Africa, but HIV infection status was self-reported (yes, no, or not known) in all other countries.

Clinical data included breast cancer stage, and if documented, grade and receptor subtype. The presence of oestrogen receptors and progesterone receptors (ie, hormone receptors) was defined as greater than 1% immunohistochemical staining for these receptors, and the presence of human epidermal growth factor Receptor 2 (HER2) was defined as a score of 3 by immunohistochemistry or a positive fluorescence in-situ hybridisation result (defined as a HER2:CEP17 fluorescence ratio of >2) Information on treatment was sourced from medical records and women's self-reports.[15] We obtained data on life-prolonging treatments, considered as surgical removal of the tumour, systemic therapy (defined has having had chemotherapy, or endocrine therapy, or both), or both received within 12 months of diagnosis.

Outcomes

The primary outcome was 3-year overall survival, which was measured by ascertaining vital status by use of a telephone call to the participant or their next of kin once every 3 months. The dynamic list of participants who were due follow-up calls and their contact details were managed by use of a mobile health application (appendix p 13). If a woman was attending the hospital for routine clinical management (that was not organised by the study), this information was used to update her vital status.

Statistical analysis

We analysed 3-year overall survival on a time-since-diagnosis scale. Follow-up time commenced on the date of diagnosis, which was defined as the date of biopsy according to the European Network of Cancer Registry guidelines.[16] If this date was unavailable, the date of the histology report or the recruitment date was used. Follow-up continued to the earliest of the date of death, the date on which the participant was last known to be alive, 3 years after diagnosis, or Jan 1, 2019, whichever came first. Crude Kaplan-Meier survival curves were used to visually represent the results. We calculated net survival, accounting for background age-specific national mortality,[17,18] and estimated age-standardised net survival to the International Cancer Survival Standard[19] (see appendix [p 1] for further details). Age-adjusted and cancer stage-adjusted determinants of survival were examined by use of Cox proportional hazards models, stratified by group and by flexible parametric survival models (group-adjusted), which were used to predict group-specific 3-year survival under seven cumulative scenarios. The first scenario was downstaging to a stage-at-diagnosis distribution of 35% of patients at stage I or IIA, 25% at stage IIB, 15% at stage IIIA, 10% at stage IIIB, 7% at stage IIIC, and 8% at stage IV. This distribution was considered achievable, since it represented a marginal improvement in the stage distribution from that observed in Black South African women (who are not screened for breast cancer) and is similar to previous models.[12] For racial groups in whom this distribution had already been achieved, downstaging to 60% stage I or IIA, 20% stage IIB, 5% stage IIIA, 5% stage IIIB, 5% stage IIIC, and 5% stage IV was applied. Survival predictions for the improved cancer stage distribution assumed that treatment was provided at the observed site and stage-specific treated proportions. The second scenario was of all women receiving systemic therapy and surgery, with treatment effects restricted to those observed for non-metastatic disease. Increased mortality associated with no treatment in metastatic patients was interpreted as capturing a decision not to treat patients with stage IV disease or terminally ill patients, as opposed to an effect of the absence of treatment when recommended. The third scenario was reducing social inequalities (ie, education level) that lead to survival deficits, such that the survival of women grouped by education level (none, primary, or secondary) was shifted to that of women in the level above. The final three scenarios were removing survival deficits associated with HIV infection; a young age at diagnosis (<30 years); and non-hormone receptor-positive, HER2-negative tumours (when tumour subtypes were known). Hormone receptor-positive tumours were those in which either the oestrogen receptor or the progesterone receptor was positive.

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. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 8, 2014, and Dec 31, 2017, 2313 women were recruited from eight hospitals, of whom 85 did not have breast cancer. Of the remaining 2228 women with breast

cancer, 58 women with previous treatment or recurrence, and 14 women from small racial groups (white and Asian women in South Africa), were excluded. Of the 2156 women analysed, 1840 (85%) were histologically confirmed, 129 (6%) were cytologically confirmed, and 187 (9%) were clinically confirmed to have breast cancer. TNM stage[16] was primarily assessed clinically, with the aid of ultrasound (654 [43%] of 1466 women), x-ray (478 [33%]), or surgical information (220 [15%]), and rarely by bone scan (four [<1%]), CT scan (28 [<1%]), or MRI (five [<1%]). We excluded minority racial groups of women in South Africa (six Asian women and eight white women), seven women with no follow-up data, and 51 women with potentially recurrent cancer or who had received previous treatment. The remaining 2156 (97%) women were categorised into nine country-specific and race-specific groups: three in Namibia (white, mixed-race, or Black women), two in South Africa (Black or mixed-race women), one in Uganda, and one in Zambia, in addition to two groups in Nigeria that were stratified by public or private hospitals, but not race. Mean age at breast cancer diagnosis ranged from 45 years in women recruited from the Nigerian private hospital to 59 years in white Namibian women (appendix pp 4–5). 73 (76%) of

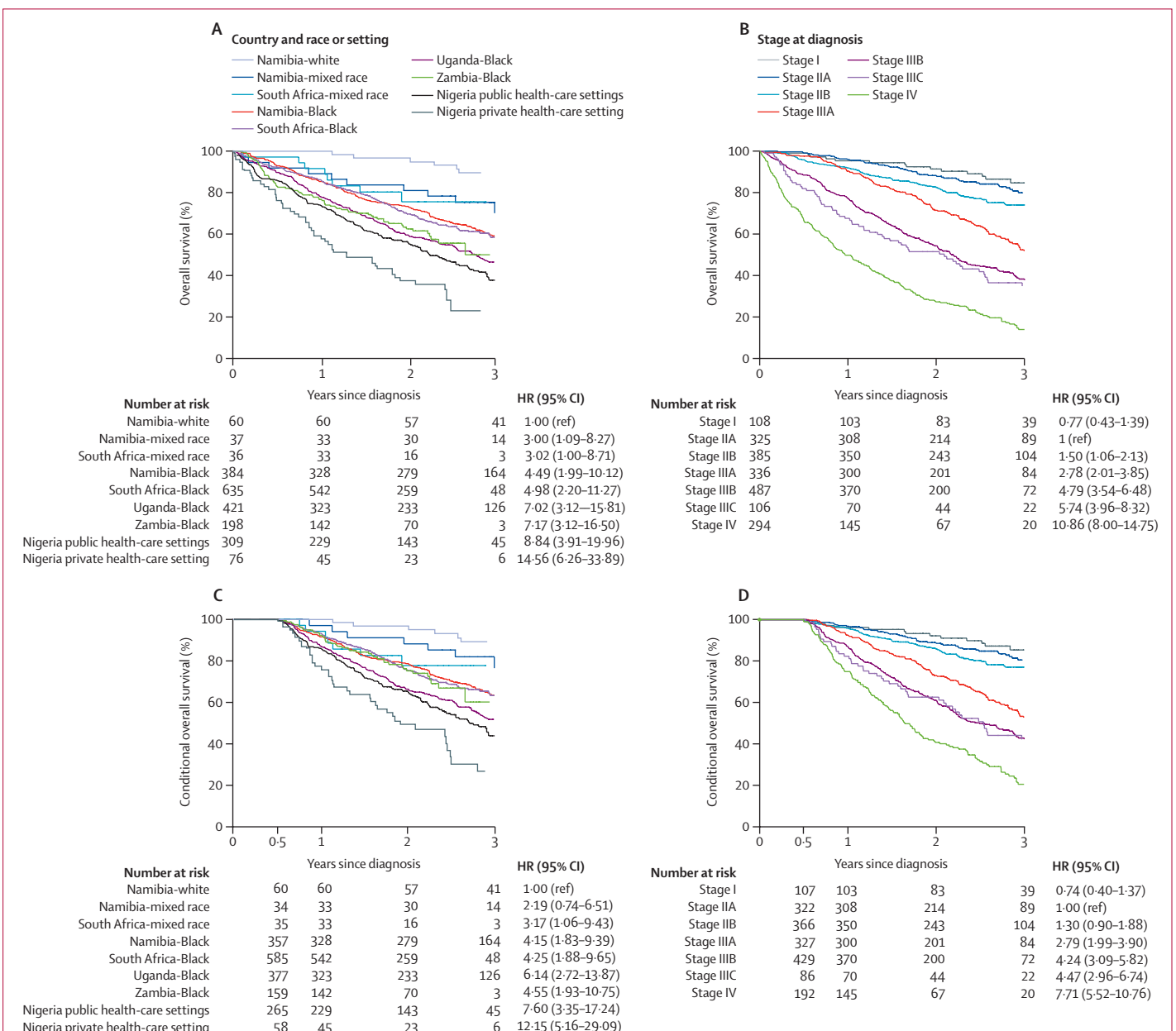
	Total (all)	Namibia			South Africa		Uganda (all)	Zambia (all)	Nigeria	
		White	Mixed race	Black	Black	Mixed race			Public sector	Private clinic
Number of women followed up	2156	60	37	384	635	36	421	198	309	76
Median time since diagnosis (range), years*	2·8 (1·0–3·0)	3·0 (2·1–3·0)	3·0 (2·0–3·0)	3·0 (1·9–3·0)	2·2 (1·0–3·0)	2·2 (1·0–3·0)	3·0 (1·8–3·0)	2·2 (1·4–3·0)	2·8 (1·7–3·0)	2·9 (1·8–3·0)
Status at end of follow-up†										
Died	879 (41%)	6 (10%)	10 (27%)	152 (40%)	196 (31%)	8 (2%)	211 (50%)	73 (37%)	169 (55%)	54 (71%)
Administrative censoring at 3 years	450 (21%)	41 (68%)	14 (38%)	164 (43%)	48 (8%)	3 (8%)	126 (30%)	3 (2%)	45 (15%)	6 (8%)
Administrative censoring before 3 years	668 (31%)	11 (18%)	13 (35%)	60 (16%)	309 (49%)	23 (64%)	66 (16%)	79 (40%)	91 (29%)	16 (21%)
Early censoring (lost to follow-up)	159 (7%)	2 (3%)	0	8 (2%)	82 (13%)	2 (6%)	18 (4%)	43 (22%)	4 (1%)	0
Number of deaths during the time period since diagnosis, years										
0 to <0·5	215	0	3	26	48	1	43	33	43	18
0·5 to <1	183	0	1	30	39	2	49	12	37	13
1 to <2	306	2	3	46	82	5	75	22	55	16
2 to <3	175	4	3	50	27	0	44	6	34	7
Median age at death (IQR), years	51 (42–62)	53 (41–65)	57 (49–64)	53 (43–66)	57 (45–66)	55 (39–63)	47 (39–57)	51 (40–69)	51 (40–60)	45 (40–51)
Number aged <40 years‡	181 (21%)	1 (17%)	0	26 (17%)	24 (12%)	2 (25%)	55 (26%)	16 (23%)	42 (25%)	14 (26%)
1-year survival										
Crude survival	79% (77–81)	100%	87% (69–95)	82% (77–86)	86% (83–89)	92% (76–97)	74% (69–79)	74% (66–80)	70% (64–75)	56% (43–66)
Net survival§	..	..	89% (77–100)	84% (79–88)	89% (86–91)	..	76% (71–80)	75% (68–81)	72% (66–77)	57% (45–68)
Age-standardised net survival	..	..	89%	83%	89%	..	79%	70%	71%	53%
3-year survival										
Crude survival	50% (48–53)	90% (78–95)	69% (49–82)	56% (51–62)	59% (53–64)	76% (56–87)	44% (39–49)	47% (33–59)	36% (30–42)	18% (9–29)
Net survival§	..	..	73% (56–90)	60% (54–66)	64% (57–70)	..	46% (41–52)	49% (36–63)	39% (32–45)	19% (9–29)
Age-standardised net survival	..	..	72%	62%	68%	..	52%	51%	38%	16%
3-year survival conditional on surviving to 6 months										
Crude survival	58% (55–60)	90% (78–95)	76% (56–88)	63% (57–68)	63% (57–69)	78% (58–89)	51% (46–57)	59% (41–73)	43% (36–50)	25% (13–40)
Net survival§	..	..	81% (65–97)	66% (61–72)	68% (61–75)	..	54% (48–59)	62% (46–78)	46% (38–54)	26% (13–40)
Age-standardised net survival	..	..	75%	69%	72%	..	60%	64%	45%	20%

Data are n (%) or percentage surviving (95% CI) unless otherwise indicated. NA=not applicable. *Regardless of vital status. †End of follow-up to earliest of 3 years after diagnosis or Jan 1, 2019, whichever came first. ‡Expressed as a proportion of those who had died at the end of follow-up. §Net survival accounts for background age-specific national mortality in women, but was not estimated in mixed-race groups in South Africa because of the absence of race-specific mortality data for this minority race.

Table: **Information on deaths and patients who died and survival estimates in the ABC-DO cohort, by country and subgroup**

97 non-Black Namibian women, 321 (48%) of 669 South African women, 138 (36%) of 384 Black Namibian women, 146 (38%) of 389 Ugandan women, 68 (42%) of 161 Zambian women, and only 77 (27%) of 283 women from public hospitals had stage I or II disease. 63 (85%) of 74 women in the Nigerian private hospital had stage III or stage IV disease.

The study protocol[20] proved feasible, with a median of 3·1 months (IQR 3·0–3·8) between each follow-up telephone call, minimal losses to follow-up, and timely study notification of deaths at a median of 10 weeks (IQR 5–16) after the date of death. Of the 2156 women followed for up to 3 years, 879 (41%) died, 1118 (52%) were alive at administrative censoring, and 159 (7%) were censored early (table and appendix p 14). 809 (92%) deaths were reported by the participant's next of kin, and records of 53 (6%) deaths were obtained from hospital records and 17 (2%) deaths were obtained from staff at



Number at risk					HR (95% CI)
Namibia-white	60	60	57	41	1·00 (ref)
Namibia-mixed race	37	33	30	14	3·00 (1·09–8·27)
South Africa-mixed race	36	33	16	3	3·02 (1·00–8·71)
Namibia-Black	384	328	279	164	4·49 (1·99–10·12)
South Africa-Black	635	542	259	48	4·98 (2·20–11·27)
Uganda-Black	421	323	233	126	7·02 (3·12—15·81)
Zambia-Black	198	142	70	3	7·17 (3·12–16·50)
Nigeria public health-care settings	309	229	143	45	8·84 (3·91–19·96)
Nigeria private health-care setting	76	45	23	6	14·56 (6·26–33·89)

Number at risk					HR (95% CI)
Stage I	108	103	83	39	0·77 (0·43–1·39)
Stage IIA	325	308	214	89	1 (ref)
Stage IIB	385	350	243	104	1·50 (1·06–2·13)
Stage IIIA	336	300	201	84	2·78 (2·01–3·85)
Stage IIIB	487	370	200	72	4·79 (3·54–6·48)
Stage IIIC	106	70	44	22	5·74 (3·96–8·32)
Stage IV	294	145	67	20	10·86 (8·00–14·75)

Number at risk					HR (95% CI)
Namibia-white	60	60	57	41	1·00 (ref)
Namibia-mixed race	34	33	30	14	2·19 (0·74–6·51)
South Africa-mixed race	35	33	16	3	3·17 (1·06–9·43)
Namibia-Black	357	328	279	164	4·15 (1·83–9·39)
South Africa-Black	585	542	259	48	4·25 (1·88–9·65)
Uganda-Black	377	323	233	126	6·14 (2·72–13·87)
Zambia-Black	159	142	70	3	4·55 (1·93–10·75)
Nigeria public health-care settings	265	229	143	45	7·60 (3·35–17·24)
Nigeria private health-care setting	58	45	23	6	12·15 (5·16–29·09)

Number at risk					HR (95% CI)
Stage I	107	103	83	39	0·74 (0·40–1·37)
Stage IIA	322	308	214	89	1·00 (ref)
Stage IIB	366	350	243	104	1·30 (0·90–1·88)
Stage IIIA	327	300	201	84	2·79 (1·99–3·90)
Stage IIIB	429	370	200	72	4·24 (3·09–5·82)
Stage IIIC	86	70	44	22	4·47 (2·96–6·74)
Stage IV	192	145	67	20	7·71 (5·52–10·76)

Figure 1: **Crude overall survival to 3 years after breast cancer diagnosis**

Kaplan-Meier survival curves showing crude 3-year overall survival in 2156 women by country and race or setting (A), and by stage at diagnosis (B). Kaplan-Meier survival curves showing crude 3-year overall survival in 1934 women who survived for 6 months or longer, by country and race or setting (C) and stage at diagnosis (D). HRs (95% CIs) in (A) and (C) show the comparison with Namibian white women, and HRs (95% CIs) show the comparison with stage IIA cancer at diagnosis. HR=hazard ratio.

hospices and health centres. Less than 4% of participants in all groups, apart from the group of Black women in South Africa (13%) and of women in Zambia (22%), were lost to follow-up (table). Losses to follow-up in Zambia were due to staffing issues that led to temporary interruption of the follow-up process. Median age at death was 51 years (IQR 42–62), with 181 (21%) of 879 deaths occurring in women under the age of 40 years (table).

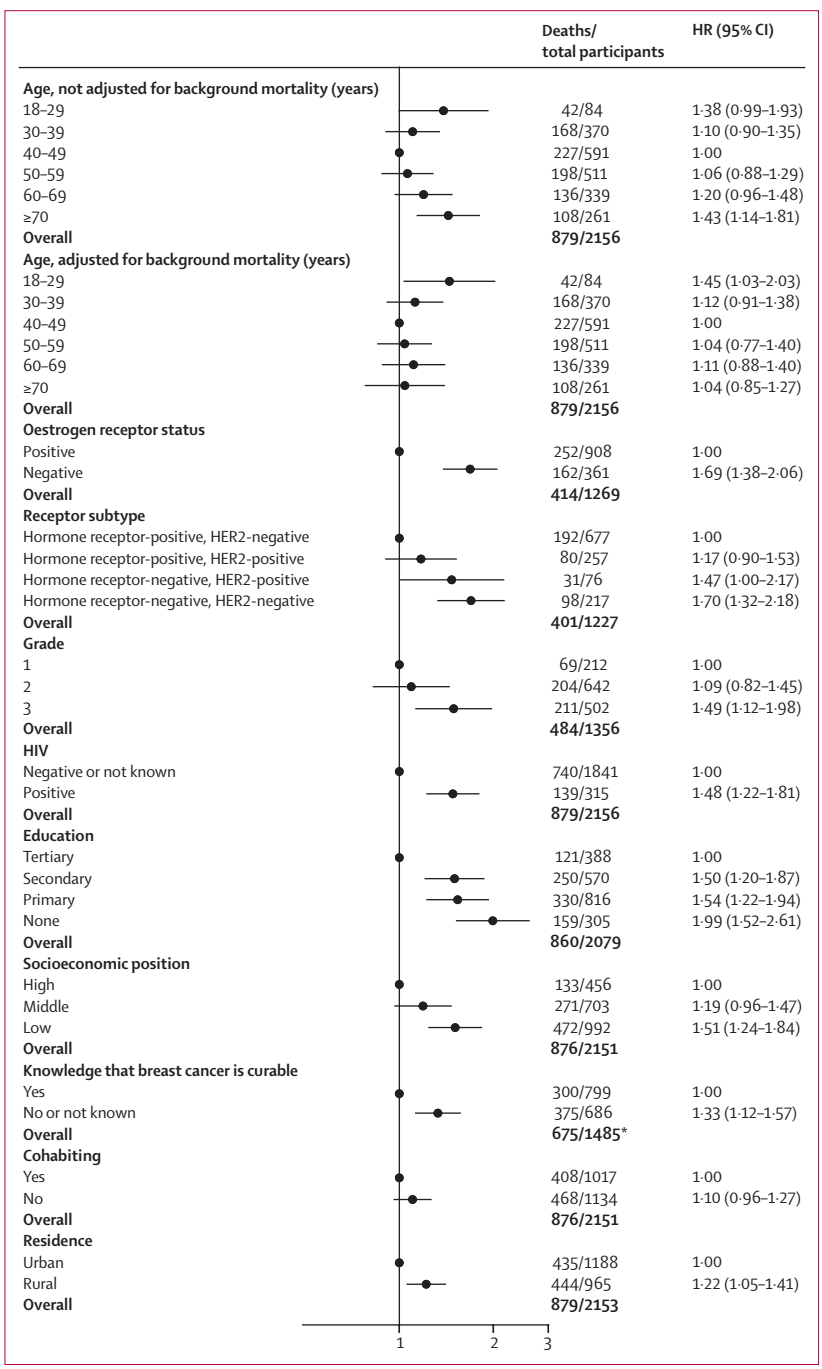


Figure 2: **Age-stage adjusted HRs for 3-year all-cause mortality in all 2156 women, by age, tumour characteristics, HIV status, and sociodemographic characteristics**
HR=hazard ratio. Hormone receptor-positive=oestrogen receptor-positive or progesterone receptor-positive. Hormone receptor-negative=oestrogen receptor-negative and progesterone receptor-negative. HER2=human epidermal growth factor Receptor 2. *In all countries except South Africa.

16 (0·7%) of all 2156 women were recorded as having stage 0 cancer and were not included in the Kaplan-Meier survival estimates because of the small number, but these patients were included in the same group as those with stage I or IIA cancer or with stage I, IIA, or IIB cancer in later analyses.

Crude 3-year survival was 50% (95% CI 48–53) in the entire cohort, but variations in 3-year survival were observed between those of different races in Namibia (90% [78–95] in white women, 69% [49–82] in mixed-race women, and 56% [51–62] in Black women) and South Africa (76% [56–87] in mixed-race women and 59% [53–64] in Black women), between different countries (44% [39–49] in Uganda, 47% [33–59] in Zambia, and 36% [30–42] in Nigeria), and between the two public sector hospitals (36% [30–42]) and the private clinic (18% [9–29]) in Nigeria, (table, figure 1, and appendix p 15). Net 3-year survival estimates were higher than crude estimates by 1–5% (absolute differences), and age-standardised net survival estimates were a further 2–6% higher and led to a small widening of between-group survival differences (table). Overall, 215 (10%) of patients in the cohort died within 6 months of diagnosis, reflecting the extent of advanced disease at diagnosis. However, crude 3-year survival conditional on surviving to 6 months (58%) was only marginally higher than the crude 3-year overall survival of the entire cohort, by 7% in most groups, or larger (12% higher) in Zambia (figure 1 and table).

Cancer stage was the strongest prognostic factor, with 3-year survival ranging from 80% in patients with stage IIA disease, 73% in those with stage IIB disease, 51% in those with stage IIIA disease, 32–36% in those with stage IIIB or IIIC disease, and 11% in those with stage IV disease (figure 1 and appendix p 6 and pp 16–17). However, the effect of cancer stage on mortality was stronger between the start of follow-up to 6 months after diagnosis than between 6 months after diagnosis to the end of follow-up, with 99 (37%) deaths reported in 271 women with stage IV disease between the start of follow-up and 6 months after diagnosis compared with five (1%) deaths in 430 women with stage I or IIA disease (hazard ratio [HR] 36 [95% CI 15–89]), and 134 (69%) deaths in 194 women with stage IV disease recorded between 6 months after diagnosis and the end of follow-up compared with 66 (15%) deaths in 444 women with stage I or IIA disease (HR 7 [5–10]; appendix p 17). These results again reflect that a high proportion of women had advanced (ie, stage III or stage IV disease) at diagnosis. Deaths that occurred within 6 months of diagnosis were not only observed in women who were diagnosed with metastatic disease, but also in those recorded as having stage IIC and IIIB disease (appendix p 6). The effect of

advanced cancer stage on prognosis was consistent across groups. However, for a given stage there remained absolute differences in 3-year survival of over 30% between groups, with the lowest 3-year survival estimates observed in Nigeria, Zambia, and in women with stage IIIB, IIIC, or IV disease in Uganda (appendix p 6). The effects of all other survival determinants were smaller in magnitude than the effect of cancer stage (figure 2).

Age had a U-shaped association with survival, characterised by lower survival in younger women (those aged <30 years) than in older women (those aged 40–49 years; HR 1·45 [95% CI 1·03–2·03]). The increased mortality in older women was entirely due to background mortality. After adjusting for age and cancer stage, mortality was higher for poorly differentiated tumours versus well-differentiated tumours (1·49 [1·12–1·98]), for oestrogen receptor-negative tumours versus oestrogen receptor-positive tumours (1·69 [1·38–2·06]), for hormone receptor-positive, HER2-positive tumours versus hormone receptor-positive, HER2-negative tumours (1·17 [0·90–1·53]), for hormone receptor-negative, HER2-positive tumours versus hormone receptor-positive, HER2-negative tumours (1·47 [1·00–2·17]), and for triple-negative tumours versus hormone receptor-positive, HER2-negative tumours (1·70 [1·32–2·18]; figure 2).

Survival differentials by social indicators (education and socioeconomic position) and breast cancer awareness were also evident, approaching two times higher mortality in the least educated women compared with the most educated women (figure 2). Absolute differences in race-adjusted 3-year survival between women grouped by education level (none, primary, secondary, and tertiary) were 15% in Namibia and 30% in Uganda, with smaller differences between groups observed in South Africa and Nigeria. Higher mortality was observed in women who did not know that breast cancer is curable compared with those who did (HR 1·33 [1·12–1·57]), and in those who lived in a rural residence compared with those who lived in an urban residence (1·22 [1·05–1·41]; figure 2). The ABC-DO study included HIV-endemic hospitals in South Africa, thus 315 (15%) of 2156 women in the cohort were HIV-positive, of whom 263 (83%) were already taking antiretrovirals at the time of cancer diagnosis. HIV-positive women tended to be younger at cancer diagnosis (211 [67%] of 315 HIV-positive women were aged <50 years *vs* 834 [45%] of 1841 HIV-negative women) and, independently of age, had 1·48 times (95% CI 1·22–1·81) higher mortality than HIV-negative women.

Treatment varied among the five countries (appendix p 7). In countries where women were given chemotherapy, approximately three-quarters was neoadjuvant chemotherapy, except in Uganda, where 39% was neoadjuvant chemotherapy (appendix p 7). Predominant first-line regimens consisted of cyclophosphamide, anthracycline, and taxanes, fluorouracil, or both. Mastectomies outnumbered breast conserving surgery in all countries. Endocrine therapy (largely tamoxifen) and radiotherapy were provided in Namibia and South Africa. The country-specific effects of treatment on survival were similar for cancer stages 0, I, or II and stage III across all countries (appendix p 8); compared with those who received both surgery and systemic therapy, mortality was higher in women who did not receive treatment (stage II or below HR 2·1 [95% CI 1·3–3·3]; stage III 2·4 [1·8–3·2]), and among those who received systemic therapy only (stage II or below 2·2 [1·4–3·5]; stage III 2·1 [1·6–2·6]). HRs were of larger magnitude for stage IV cancer, as most (60 [97%]) of the 62 women who did not receive treatment died (indicating terminal frailty at diagnosis) compared with 166 (74%) of 225 women who received treatment. In addition, survival differences by treatment group were greater for all cancer stages in the first 6 months than beyond 6 months (appendix p 9).

Scenario-based 3-year overall survival predictions in public hospitals are noted (figure 3; predictions and HRs

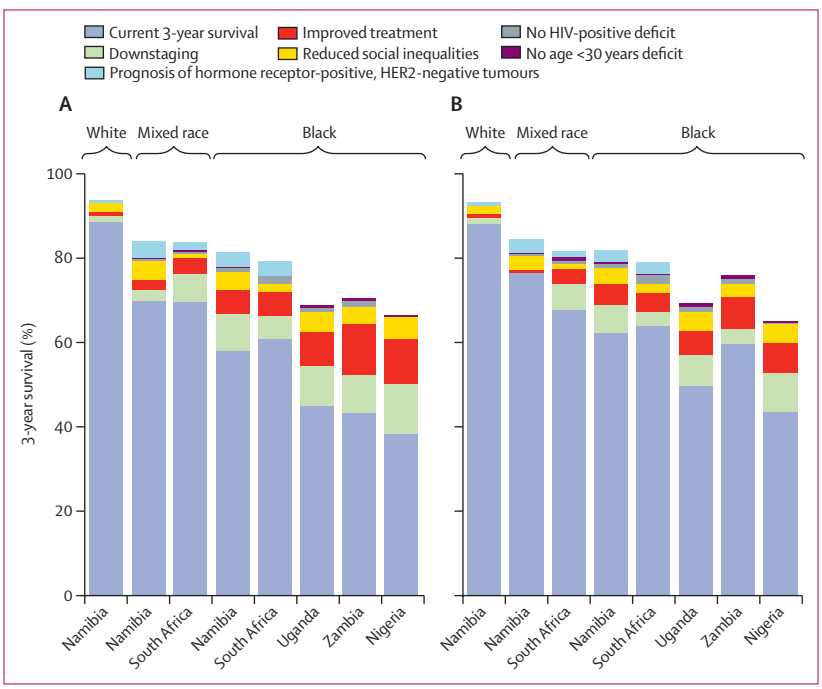


Figure 3: **Observed and predicted 3-year survival from diagnosis (A) and conditional on surviving to 6 months (B) at the observed distribution of prognostic factors, and under specified improved scenarios, by site and race, and in public hospitals only**

Above the bar showing observed 3-year survival is the predicted survival of women if the following specified added improvements had been made: (1) downstaging to a stage at diagnosis distribution of 35% at stage I or IIA, 25% at stage IIB, 15% at stage IIIA, 10% at stage IIIB, 7% at stage IIIC, and 8% at stage IV, or in Namibian white and mixed-race women, in whom this distribution is already achieved, downstaging to a stage at diagnosis distribution of 60% at stage I or IIA, 20% at stage IIB, 5% at stage IIIA, 5% at stage IIIB, 5% at stage IIIC, and 5% at stage IV; (2) improving treatment, whereby all women receive surgery and systemic therapy; (3) reducing survival deficits associated with social inequalities (measured by level of education), whereby, for a given site-race group, women in each of the three education categories (none, primary, and secondary) have the same survival as that of women in the category above; (4) eliminating survival deficits associated with a HIV-positive status (5) eliminating survival deficits associated with being aged younger than 30 years; and (6) eliminating survival deficits associated with not having hormone receptor-positive, HER2-negative tumours. Survival model fits are provided in the appendix (p 10). HR=hazard ratio. HER2=human epidermal growth factor Receptor 2. Hormone receptor-positive=oestrogen receptor positive or progesterone receptor-positive.

provided in the appendix pp 10–12). Predictions include shifting actionable factors together with the theoretical elimination of other factors (being aged <30 years, a HIV-positive status, and an aggressive tumour subtype) that are not modifiable in themselves, however, quantifying their influence on survival helps prioritise research efforts and defines the limits of survival improvements that are currently possible. The largest survival gains would be achieved through downstaging and improvements in treatment, with these factors contributing near equally to a combined 18–22% absolute survival gain in Nigeria, Zambia, and Uganda, and contributing to approximately a third reduction in breast cancer deaths in every race or country (appendix pp 11–12). Less than 2% of survival deficits were because of a HIV-positive status or a young age. In countries where tumour subtypes were known (ie, in Namibia and South Africa), up to 4% of survival deficits were attributed to tumours that were not hormone receptor-positive plus HER2-negative. Independent of the aforementioned factors, survival disadvantages associated with social inequalities, as measured by education level, remained substantial contributors to survival deficits. These findings were broadly similar between the entire cohort and in women who survived to 6 months (figure 3). Finally, after taking all of these factors into account, the observed 3-year survival range of 39–89% reduced by a half, with 3-year predictions above 65% in every group, thus between-group survival differences were attenuated. The only remaining unexplained group-level differences in survival was an estimated lower mortality in white Namibian women (HR 0·5 [95% CI 0·2–1·2]) and higher mortality in Nigerian women (1·5 [1·0–2·2]) both compared with Black Namibian women (appendix p 10).

Discussion

Using a large prospective cohort of women with breast cancer in sub-Saharan Africa, we have provided robust survival estimates for women who attended tertiary hospitals in five countries, and we have apportioned survival gaps into immediately actionable factors (late stage, treatment, and social inequalities) and other factors (HIV status, a young age, and tumour subtype). Among Black women, crude 3-year survival was alarmingly low, with near 40% in Nigeria, 45–50% in Uganda and Zambia, and 56–59% in South Africa and Namibia. By comparison, white Namibian women had a 3-year survival of 90%. Survival gap apportionment analyses revealed that, by contrast with the strong focus on implementing tailored therapies in high-income settings (eg, expensive anti-HER2 therapies), in the sub-Saharan African setting of late-stage presentation and inadequate therapy, a population shift to earlier stage at diagnosis and access to improved therapy would considerably improve survival, thus averting a third of deaths. This improvement in survival was predicted despite the presence of young patients, HIV-positive patients, and triple-negative or HER2-positive tumours.

Three previous estimates indicated that breast cancer survival in Ugandan women was higher than that observed in our cohort (5-year survival estimates of 44%, 53%, and 56% *vs* 3-year survival of 44% in our cohort) and one survival estimate was lower (3-year survival of 32%), but was subject to a 34% loss to follow-up.[6,21,22] To our knowledge, ABC-DO estimates are the first for Zambia. Nevertheless, our survival estimates for this country are similar to those of neighbouring Zimbabwe.[6] For Nigeria, ABC-DO estimates are similar to those of two previous studies,[23,24] although, the Ibadan 5-year survival estimate of 98% appears implausible.[2] For Namibia, the AFCRN population-based study[6] found that 3-year survival in 64 women with unknown race was 79%, which is higher than the 3-year survival of 56% in Black women in the ABC-DO cohort. Racial differences in survival appear to be large in both Namibia and South Africa, albeit based on small samples, reflecting persisting inequalities after their histories of racial segregation. Prognostic factors in our study are consistent with those in international literature,[25] including for HIV.[11] Although, HIV status in our study was self-reported in all countries apart from South Africa, which could have led to an underestimation of the effect of HIV on survival. In addition, similar to findings in high-income settings, we found that social inequalities in survival remained large, even when stage and crude treatment pathways were adjusted for. Such inequalities could represent residual confounding by cancer stage, quality, and completeness of therapy, implying that cancer stage and treatment effects are underestimated, while other pathways, such as the presence of comorbidities could play a role.[15,26–28] Thus, even though it is prudent to be mindful of differences in breast cancer survival between different settings, races, and socioeconomic groups across sub-Saharan Africa, and to apply caution in extrapolating the survival estimates to the region or nationally, the overall picture of low survival needing improvement remains. Furthermore, our survival estimates refer to women who reach treatment centres, thus, for the many women who do not, survival could unfortunately be worse still.

Cancer survival estimates ideally need to be population-based, have few losses to follow-up, and quantify heterogeneity by clinical and epidemiological factors. There are no studies for sub-Saharan Africa that meet these criteria. As such, although the ABC-DO study is hospital-based rather than population-based, our cohort is characterised by detailed socio-demographic and clinical data, with a low number of women lost to follow-up, enabling survival gap apportionment analyses that use minimal assumptions or external data, which often originate from high-income countries. The next of kin of women were the main source of information on deaths in our study, and the short time between death and death

notification to the study by the next of kin was likely to have increased the accuracy of the date of death. Compared with crude survival, higher net survival and age-standardised net survival, of a few percent in each, show that the background mortality and younger age distributions of populations in sub-Saharan Africa contribute to the low crude survival of women with breast cancer. Nevertheless, ranking of countries and races in terms of survival did not change with use of crude, net, or age-standardised net survival. However, age-standardised net survival should be interpreted with caution, as the age distribution of the standard patient population applies a much higher proportion to older age groups than in the ABC-DO cohort (proportion of individuals aged <65 years in the standard population is 82% compared with 42% in the ABC-DO cohort).

The survival estimates among Black women in the ABC-DO cohort were as low, or lower, than those in women diagnosed in 1935–54 in Connecticut, USA (with a crude 3-year survival of approximately 57%),[29] but they are considerably higher than if this disease was left untreated (28% at 4 years from symptom onset in women diagnosed in the UK from 1805 to 1933).[30] The survival estimates of women with breast cancer in Connecticut in 1935–54[29] were before the introduction of screening or modern therapies, indicating that large improvements in survival can be made through early diagnosis of palpable tumours. Consistently, survival gap apportionment analyses done in our study identified two important areas that need to be strengthened, namely downstaging and improved treatment. These findings emphasise the importance of a parallel health systems approach to simultaneously strengthen early detection, diagnosis, and disease management, as recommended in the phased implementation guidelines[31] by the Breast Health Global Initiative.

The shift in stage at diagnosis modelled in our study predicts an absolute reduction in deaths of up to 12%. In the context of sub-Saharan Africa, where organised population-based screening is not currently feasible, and considering that only a small proportion of breast cancers are detected through screening, even in settings with operational programmes (37% of breast cancers are detected through screening in the UK[32]), downstaging needs to be achieved by educating women, the community, and health-care providers about breast cancer, thus accelerating time-to-presentation and referral for diagnosis and treatment. For women of a given cancer stage, there will be a large range in the duration of the presymptomatic period, because of variability in tumour size at symptom recognition, and in tumour growth rates. Nevertheless, self-reported time to diagnosis remains one of the strongest drivers of late stage at diagnosis in all ABC-DO settings, apart from Nigeria.[27] Between-country differences in cancer stage distributions show that accelerating the path to diagnosis is not only possible, but it can also be achieved within a short (5-year) timeframe, as seen in the ABC-DO-participating South African hospital, where the percentage of women diagnosed with stage III or stage IV breast cancer was reduced from 70% to 50%.[33] While advanced stage led to a high proportion of women dying within 6 months of diagnosis in the ABC-DO cohort, these deaths included those not recorded as metastatic at diagnosis, indicating that underestimating cancer stage at diagnosis is prevalent in our data, and implying that the real need for and the impact of downstaging on survival could be larger still. Under-staging is not surprising, given that imaging technologies in this setting are overstretched or unavailable. More critically, under-staging might also lead to ill-informed and inappropriate treatment decisions, with limited benefits, large costs, and side-effects for patients.

Improved treatment will lead to an absolute reduction in deaths of up to 12%, independent of cancer stage at diagnosis. That therapeutic gaps contributed as much to low survival as advanced stage warrants immediate action to maximise survival gains through early detection schemes. This action is needed to ensure that an earlier diagnosis is also actively supported to achieve timely access to appropriate therapies. Treatment gaps include not only women who do not receive either systemic therapy or surgery, and the quality and completeness of these treatments, but also women who receive no treatment whatsoever (14% of women with stage I–III disease).[15] These women tended to be from lower socioeconomic groups and believed in traditional medicine.[15] Diagnosis and therapeutic facilities need to be expanded in terms of infrastructure and capacity for immunohistochemistry to inform decisions on the use of endocrine therapy, which is a more affordable therapy for hospitals in sub-Saharan Africa when compared with other therapies (eg, herceptin and aromatase inhibitors), and to provide greater access to high quality surgery and chemotherapy.

The emerging social inequalities in breast cancer survival in sub-Saharan Africa are large, and can potentially be tackled through navigational, financial, educational, and emotional support. When designing interventions to shorten the prediagnostic journey and improve treatment access and quality, all women need to be reached, including those in rural communities, illiterate women, and those who are socioeconomically disadvantaged. Provision of universal health coverage, as has now been adopted in some sub-Saharan Africa countries, will contribute to the alleviation of such inequities.

In conclusion, in the decade from 2020 to 2029, a projected 416 000 women will die from breast cancer in sub-Saharan Africa,[1] yet, with downstaging and improved treatment, at least a third of these deaths could be averted.

Contributors

VM statistically analysed the data and drafted the paper. VM, Id-S-S, JS, FM, MF, BOA, BA-A, CA, AA, AZ, GP, LFP, HC, MG, and MJ designed

the study and contributed to interpretation of the results and writing of the report. BA-A provided histology support. TB, MQ, and KT contributed to the statistical analyses, the interpretation of the results, and writing of the report.

Declaration of interests

We declare no competing interests.

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