BREAST CANCER

review articles

Receptor-Defined Breast Cancer in Five East African Countries and Its Implications for Treatment: Systematic Review and Meta-Analysis

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abstract

PURPOSE Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) are determinants of treatment and mortality for patients with breast cancer (BC). In East Africa, the estimated 5-year survival (37.7%) is far lower than the US average (90%). This meta-analysis investigates BC receptor subtypes within five East African countries to ascertain cross-country patterns and prioritize treatment needs.

METHODS From a PubMed search, January 1, 1998-June 30, 2019, for all English-only BC articles for Ethiopia, Kenya, Rwanda, Tanzania, and Uganda, eligible studies had receptor distributions for female BC samples ≥ 30 patients. Outcomes were proportions of ER+, PR+, and HER2-positive (HER2+), and/or molecular subtypes. Data included study characteristics and mean or median patient age. Using *metaprop*, Stata 16, we estimated pooled proportions (ES) with 95% CIs and assessed heterogeneity.

RESULTS Among 36 BC studies with receptor data, 21 met criteria. Weighted mean age was 47.5 years and median, 48. Overall ES were as follows: 55% for ER-positive (ER+) (95% CI, 47 to 62), 23% for HER2+ (95% CI, 20 to 26), and 27% for triple-negative BC (TNBC) (95% CI, 23 to 32).

CONCLUSION We found differences between countries, for example, lower distribution of TNBC in Ethiopia (21%) compared with Uganda (35%). ER+, the dominant BC subtype overall at 55%, emphasizes the need to prioritize endocrine therapy. Overall proportions of HER2+ BC (with or without ER+ or PR+), 23%, approached proportions of TNBC, 27%, yet HER2 testing and treatment were infrequent. Testing and reporting of receptor subtypes would promote delivery of more effective treatment reducing the mortality disparity.

JCO Global Oncol 7:289-301. © 2021 by American Society of Clinical Oncology

INTRODUCTION

Among women worldwide, breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer-associated deaths, accounting for almost one quarter of incident cancer cases and 15% of cancer deaths.[1] Although age-adjusted incidence in Eastern Africa is about one-third that of regions composed of high-income countries (HIC, ie, Northern America, Northern and Western Europe, Australia, and New Zealand),[1] this rate may underestimate the true incidence as registry data, even when available, are often restricted to a specific city or county. Also, multiyear assessments show increasing rates likely linked to population aging and lifestyle changes.[2,3] Despite substantially lower incidence, age-standardized BC mortality rates in Eastern Africa (15.4 per 100,000) are similar to rates in Western Europe and higher than other affluent regions.[1] The estimated 5-year BC survival in East Africa is 37.7%, compared with 35.2% and 48.1% in West Africa and South Africa, respectively.[4] For US women, the average 5-year BC survival is 90%.[5]

BC mortality in East African countries has been exacerbated by late diagnosis and treatment that fails to meet common international standards. Primary care physicians, nurses, and other healthcare professionals are in short supply, and credentialed specialists in oncology are rare.[6,7] There is limited or no access to radiation,[8] which constrains the possibility for breast-conserving surgery even among women with early-stage BC. Many cancer medications routinely used in HIC for treatment, palliative care, or to control adverse effects of treatment are unavailable, and supplies of available less expensive medications fall short of need.[9-11] Cancer treatment, such as chemotherapy, is confined to a few locations in an entire country in East Africa and care at these sites may not conform to current standards for diagnosis and treatment.[7,12] There is no system for routine preventive care or early detection of BC. Women seek care in response to

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Accepted on December 22, 2020 and published at ascopubs.org/journal/go on February 16, 2021: DOI https://doi.org/10.1200/GO.20.00398

CONTEXT

Key Objectives

To understand the overall distribution and differences in breast cancer (BC) subtypes among five East African countries. Estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor-2 (HER2) are determinants of BC treatment and mortality, yet there has been limited review and meta-analysis of receptor studies within this region.

Knowledge Generated

Overall, ER-positive (ER+) was the dominant subtype, whereas the proportion of HER2 positive approached that of triple-negative BC (TNBC). Country differences, for example, lower distribution of TNBC in Ethiopia (21%) compared with Uganda (35%), were only partly explained by publication year.

Relevance

Improved testing and reporting of receptor subtypes are essential for the delivery of effective treatment to reduce the mortality disparity. ER+, as the dominant BC receptor, emphasizes the need to prioritize accessible multiyear endocrine therapy. More robust interventions for TNBC should be incorporated as available. Anti-HER2 treatment will require global cost reduction and access strategies.

breast symptoms.[13,14] In addition, because clinical pathways for BC diagnosis are often poorly defined, women may have to pursue several levels of care before reaching a facility with the capacity to diagnose BC.[11,13]

BC is a heterogeneous disease with different morphologic and molecular subtypes.[15,16] Based on immunohistochemistry (IHC), it is characterized by the following receptor subtypes in the clinical setting: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2). These subtypes are prognostic markers for mortality and major determinants of evidence-based treatment guidelines.[12] ER-positive (ER+) tumors typically have a better prognosis since hormone-targeting therapy (such as tamoxifen and aromatase inhibitors) substantially decreases mortality.[17,18] HER2-positive (HER2+) patients acquire a significant survival advantage when treated with humanized monoclonal antibodies against HER2/neu. By contrast, triple-negative BC (TNBC), defined by the absence of ER, PR, and HER2 expression, is more aggressive and negatively associated with survival.[19]

Relative distribution of BC subtypes would provide prognostic and therapeutic information to guide treatment and health system planning. The first systematic review and meta-analysis of BC subtypes identified seven studies from countries in East Africa (two each from Kenya, Tanzania, and Uganda, and one from Madagascar) among 26 from sub-Saharan Africa.[20] Although results from this review suggested that ER+ BC was identified in 41% of patients in East Africa,[20] recent research has reported substantially higher proportions.[21-23] The clinical relevance of receptor subtypes for treatment and the variable findings for the relative proportions of ER+ BC and TNBC in East Africa highlight the need to update the prior review. Because individual countries frame policies and priorities for cancer care,[11,24] it is advantageous to examine receptor-defined patterns for BC nationally. We performed a systematic review and meta-analysis to characterize receptor-defined subtypes of BC in five East African countries, namely Ethiopia, Kenya, Rwanda, Tanzania, and Uganda. Although the region consists of 21 countries, we focused on the four most populous countries in the region with established cancer centers, plus Rwanda, a country undergoing recent expansion of its cancer services.[6] The countries we designated make up approximately 62% of the total population for East Africa.[25]

METHODS

We conducted the systematic review and meta-analysis following PRISMA guidelines.[26] Searches of PubMed for English-only articles used the term breast cancer combined with names of each of the five countries of interest for the period January 1, 1998 through June 30, 2019. For inclusion, studies had to report single receptor or combination subtypes (eg, ER+ or PR+/HER2–). Studies were required to have female BC samples of at least 30 patients. Study authors were not contacted.

Data abstraction was independently performed by two reviewers (E.M.G. or P.P.) using a prespecified Excel spreadsheet. Prior to coding, authors designated and defined variables in a data dictionary. Coding disagreements were resolved by consensus between the two reviewers or by a third coauthor (C.O.). Categories of information included (1) study characteristics (Table 1); (2) patient age, assessed by median or mean age; (3) BC pathology, consisting of reported cancer stage, grade, and histologic subtype (ductal proportion); (4) receptor testing, incorporating timing (prospectively collected *v* retrospectively archived tissue), and testing or scoring used for HER2+; and (5) outcomes, composed of three receptor statuses (ER+, PR+, and HER2+) and/or four receptor combinations (ER+ or PR+/HER2– [luminal A]; ER+ or PR+/HER2+ [luminal B]; ER–/PR–/HER2+ [HER2 enriched]; or ER–/PR–/HER2– [TNBC]). These receptor combinations, used by

TABLE 1. Overview of Included Studies

Study	Data Years	Design/Testing	N[a]/m = male[b]/Nr[c]	Location	Notes
Jiagge 2018[31]	2000-2014	Retro/Retro	90/m[b]	E: SPHMMC	OL[49]
Eber-Schultz 2018[32]	2010-2016	Pro/Pro	107	E: AH	
Hadgu 2018[21]	2012-2015	Retro/Retro	114	E: TASH or SPHMMC	
Kantelhardt 2014[22]	2005-2010	Retro/Pro	352	E: TASH	OL[48]
Brand 2018[39]	2008-2017	Retro/Pro	129	K: AKUHN	
Sayed 2018[33]	2012-2015	Pro/Pro	823	K: AKUHN+	OL[50]
Sawe 2016[34]	2011-2013	Pro/Pro	58/m = 4/Nr = 49	K: MTRH	OL and SD[51]
Sayed 2014[23]	2011-2012	Pro/Pro	304/m = 12	K: AKUHN	
Wata 2013[37]	2007-2008	Retro/Pro	219/Nr = 64	K: KNH	
Gakinya 2010[38]	2007-2008	Retro/Retro	101/m[b]	K: AKUHN	
Bird 2008[35]	2001-2007	Pro/Pro	129 (4)	K: AIC-KH	MA
Nyagol 2006[36]	2002-2004	Pro/Pro	158	K: AKUHN	MA
O'Neil 2018[9]	2012-2013	Retro/Pro	150	R: BCCOE	OL[60]
Mwakigonja 2017[40]	2013	Retro/Retro	70/Nr = 46	T: MNH	
Amadori 2014[41]	2003-2010	Retro/Retro	69	T: BMC	OL[52,53], SD[52]
Burson 2010[42]	2007-2009	Retro/Retro	488/m = 14/Nr = 65	T: MNH/ORCI	MA
Mbonde 2000[43]	1995-1997	Pro/Pro	60	T: MNH	OL[54]
Galukande 2015[44]	2004-2012	Mixed/Retro	262	U: MUL/UCI	MA, OL[56,57], SD[56]
Galukande 2014[45]	2008-2011	Retro/Retro	201/Nr = 172	U: MUL/UCI	
Roy 2011[46]	2000-2004	Retro/Retro	45	U: StFNH	
Nalwoga 2010[47]	1990-2002	Retro/Retro	192/m[b]	U: KCR	MA, OL[55,58,59]

NOTE. MA, included in prior meta-analysis[20]; OL indicates a study with an overlapping sample. SD indicates supplementary data abstracted from an overlapping study.

Abbreviations: Design and Timing: Retro, retrospective or Pro, prospective. Location: E, Ethiopia; K, Kenya; R, Rwanda; T, Tanzania; U, Uganda; Ethiopia: SPHMMC, St. Paul's Hospital Millennium Medical College, Addis Ababa; AH, Aira Hospital, Aira; TASH, Tikur Anbessa Specialized Hospital, Addis Ababa; Kenya: AKUHN, Aga Khan University Hospital, Nairobi; MTRH, Moi Teaching & Referral Hospital, Eldoret; KNH, Kenyatta National Hospital, Nairobi; AIC-KH, Africa Inland Church Kijabe Hospital, Kijabe; Rwanda: BCCOE, Butaro Cancer Center of Excellence, Butaro; Tanzania: MNH, Muhimbili National Hospital, Dar Es Salaam; BMC, Bugando Medical Center, Mwanza; ORCI, Ocean Road Cancer Institute, Dar Es Salaam; Uganda: MUL/UCI, Mulago Hospital & Cancer Uganda Institute, Kampala; StFNH, St. Francis Nysambya Hospital, Kampala; KCR, Kampala Cancer Registry.

[a]N, sample number for sex or age, m, no. of male specified or [b]unclear.

[c]Nr, receptor number if decreased > 10%.

the US SEER registries, are the most widely used.[27] When reported, we described treatment with oral endocrine therapy (tamoxifen or aromatase inhibitors), including treatment numbers and linkage of therapy to hormone receptor-positive (HR+, that is either ER+ and/or PR+) BC.

We examined three factors that may influence receptor status results: timing of receptor testing, study date, and proportion of grade 3 BC. In the prior meta-analysis composed of studies from both North and sub-Saharan Africa, ER+ was decreased by 10% among studies using archival tissue compared with prospectively collected tissue. In our study, we operationalized timing of receptor testing similarly.[20] We compared studies by year of publication (≥ 2014 [last 5 years] $v < 2014$) to reflect expansion of cancer care in the region, as well as potential for increased recognition of receptor status for BC treatment.[6,23,28] In addition, ER+ was 9% lower among studies reporting higher grade 3 disease compared to those with lower levels (≥ 40% grade 3 $v < 40\%$).[20] To ensure sufficient numbers in our comparison groups, we dichotomized studies based on the median value for proportion of grade 3.

We calculated the proportions with each relevant receptor outcome using the number with a positive status as the numerator and the total number with a known status as the denominator. Median or mean age in years was abstracted from each study as reported. Alternatively, we calculated a weighted estimate when means or medians were available only for subgroups.

Statistical Analysis

Using Stata 16 and the *metaprop* procedure, version 10.1 (2016), from Boston College Statistical Software Components, we pooled proportions from multiple studies applying a random-effects model that displayed results as forest plots.[29] We employed the exact or Clopper-Pearson

method to generate CIs for proportions from the selected individual studies and a Freeman-Tukey transformation to normalize outcomes before calculating pooled proportions (ES). *Metaprop* tests for intragroup heterogeneity of pooled proportions through the I^2 statistic and its *P* value, although only if the pooled proportion includes at least four studies. The null hypothesis reflects variation consistent with chance alone (presumed homogeneity), whereas rejection of the null hypothesis based on a significant *P* value reflects intragroup heterogeneity linked to clinical and methodologic diversity.[30] Given two or more groups, *metaprop* tests for subgroup or intergroup heterogeneity based on the heterogeneity statistic, degrees of freedom, and *P* value. If the *P* value for subgroup heterogeneity lacked significance, groups were considered homogeneous.[29]

We generated country-specific and overall pooled proportions, along with associated tests of heterogeneity, using available study data for all single and combination receptor statuses. In a second set of results, we explored the effect of potential bias and explanatory factors on receptor outcomes, by categorizing available studies separately on timing of receptor testing, publication year, and proportion of grade 3 disease, and then generating pooled proportions for receptor outcomes by these groupings. We applied a separate Bonferroni correction to our significance level of 0.05 for the nine and 12 tests of heterogeneity by explanatory factors for the single (0.05/9 = 0.005) and combination (0.05/12 = 0.004) receptor outcomes, respectively. Only levels below this threshold were considered significant.

RESULTS

Our PubMed search identified 319 publications after eliminating duplicates (Fig 1). After all exclusions, we had 21 eligible articles with the following distribution: Ethiopia = 4,[21,22,31,32] Kenya = 8,[23,33-39] Rwanda = 1,[9] Tanzania = 4,[40-43] and Uganda = 4.[44-47] Although 36 articles had receptor data, 13 articles were excluded because of identical or overlapping samples[48-60] and two did not meet study criteria.[61,62] When multiple publications addressed similar samples, we chose the earliest or most comprehensive profiling of receptors for inclusion and designated other publications as supplementary. For three eligible publications,[34,41,44] we amplified available data by using results from the supplementary publications (Table 1).

The overall weighted mean age was 47.5 years (SD 3.2) among 3,307 patients. By country, mean ages were 42.3 (SD 0.4) Ethiopia, 46.0 (0.4) Uganda, 49.3 (SD 2.5) Kenya, and 49.5 (SD 0.4) Tanzania (no mean age for Rwanda). The overall weighted median age was 48 years among 2,051 patients with country rankings similar to those for mean age. The weighted median age for Rwanda was 48 years, identical to Kenya.

Clinical characteristics included BC grade, stage, and histologic subtype, respectively addressed by 16, 14, and 15 publications with aggregated samples ranging from

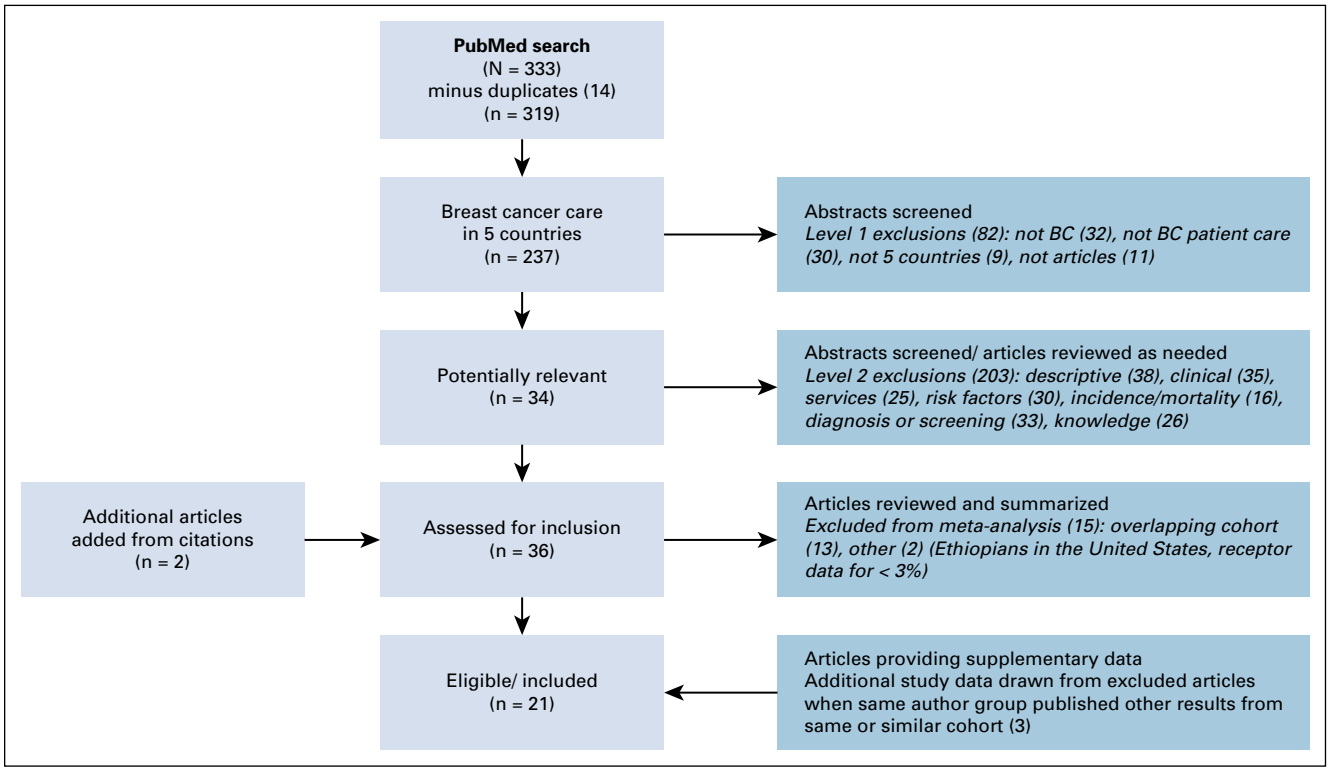

FIG 1. Flow diagram of search results.

2,167 (grade) to 1,951 patients (stage). The overall ES were 55% for grade 3 BC (95% CI, 50 to 60), I^2 of 82.7%, $P \leq .001$, range 75% in Rwanda (95% CI, 66 to 82) to 50% in Tanzania (95% CI, 33 to 67); 25% for stage 1 or 2 BC (95% CI, 18 to 33), I^2 of 93.5%, $P \leq .001$, range 37% in Kenya (95% CI, 33 to 42) to 17% in both Tanzania (95% CI, 7 to 29) and Uganda (95% CI, 13 to 20); and 88% for ductal subtype (95% CI, 84 to 91), I^2 of 76.8%, $P \leq .001$, range 89% in Kenya (95% CI, 84 to 93) to 86% in Ethiopia (95% CI, 70 to 97). Tests of heterogeneity by subgroup (country) showed significant differences by proportions of grade 3 ($P \leq .001$) and stage 1 or 2 ($P \leq .001$), although not ductal subtype ($P = .97$) (results not shown).

Eighteen publications (n = 2,875) addressed ER+ BC (Fig 2). The overall ES was 55% (95% CI, 47 to 62), range 62% in Ethiopia (95% CI, 52 to 71) to 42% in Uganda (95% CI, 36 to 49). Although the highest ES, 68% (95% CI, 59 to 75), was calculated for Rwanda, we substituted the combined number of ER+/PR+ as ER+ alone was not reported. Sixteen publications (n = 2,661) addressed PR+. The overall ES was 46% (95% CI, 38 to 54), I^2 of 93.2%, $P \leq .001$, range 52% in Kenya (95% CI, 40 to 63) to 28% in Uganda (95% CI, 22 to 36) (not shown). Eighteen publications (n = 2,689) addressed HER2+ BC (Fig 3). The overall ES was 23% (95% CI, 20 to 26), range 27% in Ethiopia (95% CI, 18 to 37) to 21% in both Tanzania (95% CI, 14 to 30) and Uganda (95% CI, 15 to 29). Tests for heterogeneity by country showed significant differences in proportions of ER+ ($P \leq .001$) and PR+ ($P \leq .001$), not HER2+ ($P = .85$).

For molecular subtypes, fourteen publications (n = 2,445) addressed luminal A and luminal B, whereas fifteen publications (n = 2,489) and sixteen publications (n = 2,575) addressed HER2-enriched and TNBC, respectively. No subtype data were available for Rwanda. For luminal A, 48% was the overall ES (95% CI, 43 to 54), I^2 of 84.9%, $P \leq .001$, range 53% in Kenya (95% CI, 45 to 60) to 41% in Uganda (95% CI, 37 to 45). For luminal B, 11% was the overall ES (95% CI, 8 to 14), I^2 of 82.0%, $P \leq .001$, range 19% in Ethiopia (95% CI, 14 to 25) to 7% in Uganda (95% CI, 4 to 11). For HER2-enriched, 11% was the overall ES (95% CI, 8 to 14), I^2 of 80.3%, $P \leq .001$, range 16% in Uganda (95% CI, 12 to 20) to 3% in Tanzania (95% CI, 0.3 to 7). For TNBC, 27% was the overall ES (95% CI, 23 to 32), range 35% in

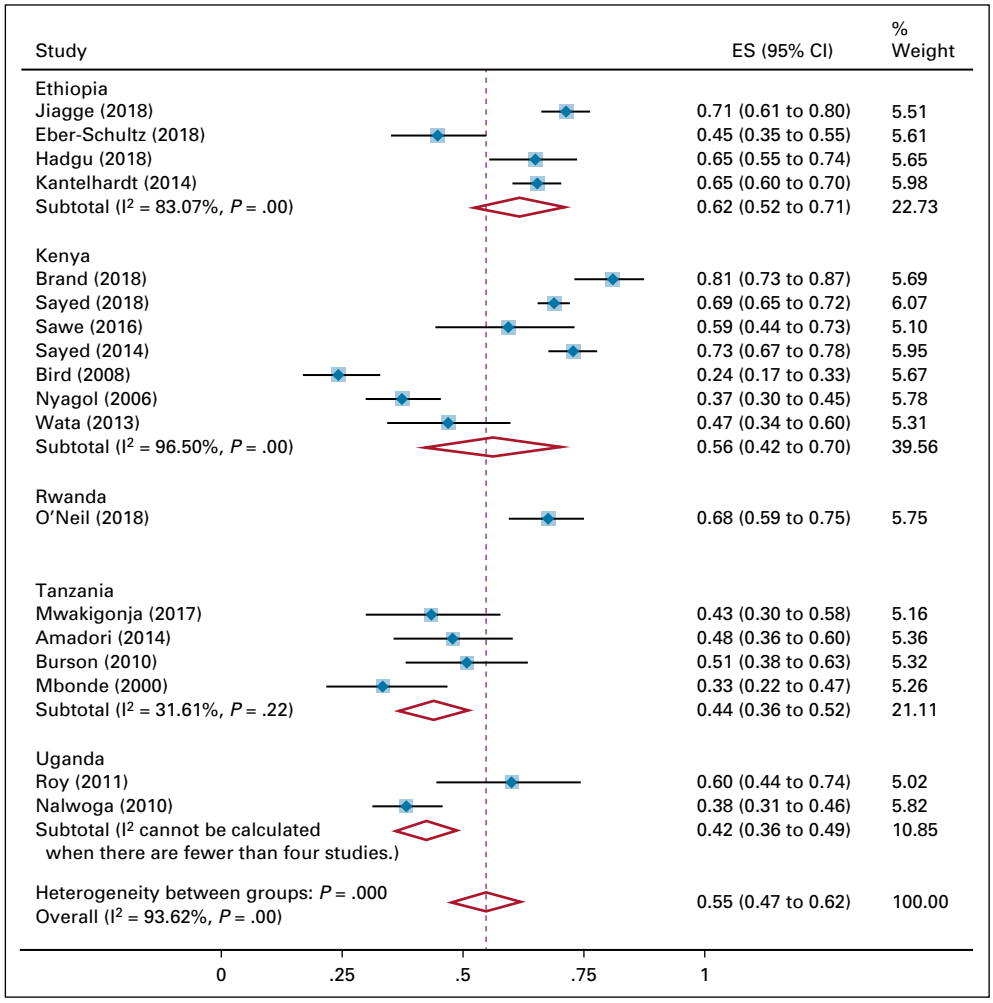

FIG 2. Proportion of ER+ breast cancer by study, designated country, and overall. ER+, ER-positive.

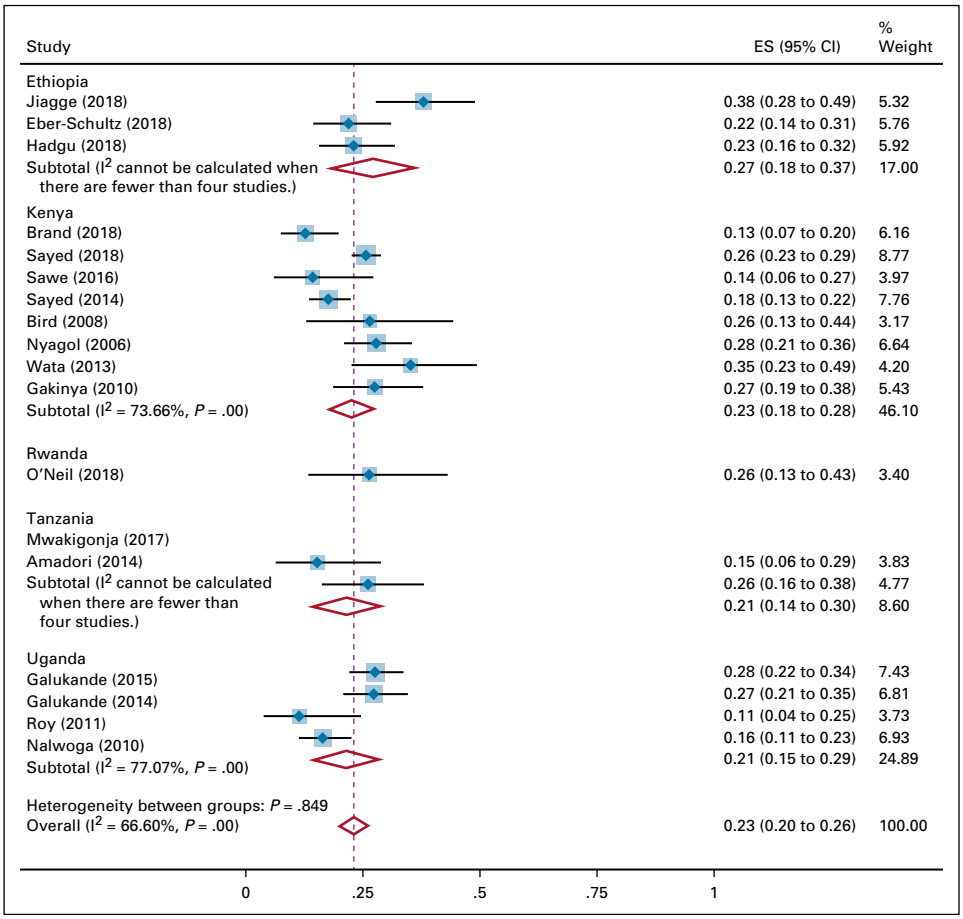

FIG 3. Proportion of HER2+ breast cancer* by study, designated country, and overall. *Among 18 studies, determinations of HER2+ were based on IHC + fluorescent in situ hybridization n = 6 (33.3%), IHC alone, score of 2 n = 2 (11.1%), IHC alone, score of 3 n = 6 (33.3%), not described n = 4 (22.2%). HER-2+, human epidermal growth factor receptor-2-positive; IHC, immunohistochemistry.

Uganda (95% CI, 29 to 41) to 21% in Ethiopia (95% CI, 16 to 27) (Fig 4). There was heterogeneity by country for proportions of luminal A ($P = .04$), luminal B ($P \leq .001$), HER2-enriched ($P \leq .001$), and TNBC ($P = .005$).

For factors potentially linked to receptor outcomes, we showed the following (Table 2): in comparisons by timing of testing (retrospective *v* prospective), we found no significant effects for timing in results for ER+, PR+, or HER2+ BC. By publication year (2014-2019 *v* 2000-2013), the heterogeneity test showed significant effects for publication year for ER+ ($P \leq .001$) and PR+ ($P = .003$), although not for HER2. For ER+ BC, the ES among recent versus earlier studies was 64% (95% CI, 58 to 69) compared with 40% (95% CI, 33 to 49). Similarly, the proportions of PR+ BC among recent versus earlier studies were 54% (95% CI, 46 to 61) and 34% (95% CI, 24 to 45%), respectively. By proportion of grade 3 BC ($\geq 54\%$ *v* $< 54\%$), we found a significant subgroup effect ($P \leq .001$) only for HER2+ proportions such that the ES among studies having higher versus lower distributions of grade 3 BC were 26% (95% CI, 24 to 29) and 17% (95% CI, 14 to 20), respectively.

We also examined the effect of explanatory factors on the four receptor combinations (table not shown). Tests between subgroups for timing of testing were only significant for proportions of luminal A ($P = .004$). Among studies conducted with prospective versus retrospective testing, luminal A was 54% (95% CI, 46 to 61) compared with 42% (95% CI, 39 to 45), respectively. For publication year, although tests for heterogeneity did not reach the corrected significance level for proportions of luminal A ($P = .06$), luminal B ($P = .21$), HER2-enriched ($P = .04$), and TNBC ($P = .04$), there was a consistent pattern of higher ES for luminal subtypes and lower ES for HER2-enriched and TNBC in more recent publications. For example, for TNBC, the ES in recent compared with prior years was 25% (95% CI, 20 to 29) versus 34% (95% CI, 26 to 43), respectively. We found no significant differences by proportions of grade 3 BC for any receptor combination.

Six of 21 studies addressed treatment with endocrine therapy. Three limited endocrine therapy to patients who were ER+ and/or PR+ with the following proportions treated: 42.0% (29/69),[32] 84.3% (86/102),[39] and 89.8% (88/98).[9] In two studies, endocrine therapy was not limited to patients with HR+ BC[37,42] and one early study reported no tamoxifen treatment.[43]

DISCUSSION

In our meta-analysis, ER+ was the predominant BC receptor, 55%, overall in the five East African countries,

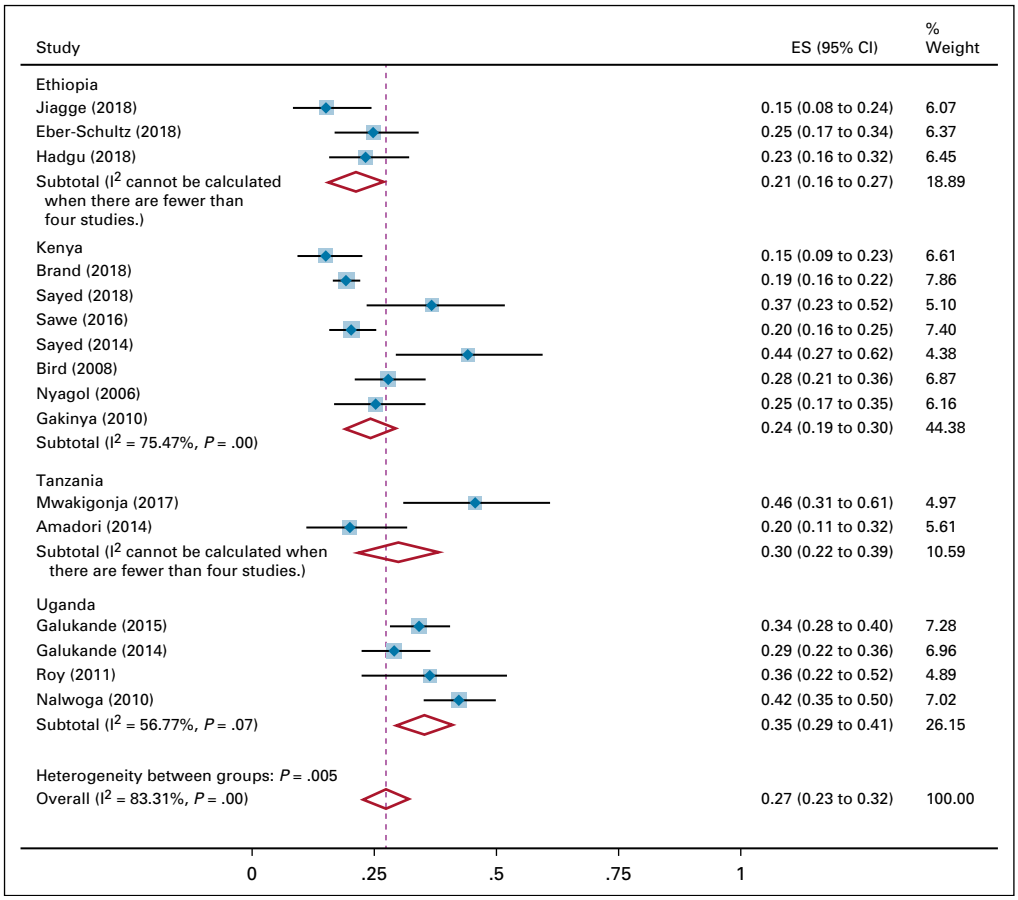

FIG 4. Proportion of triple-negative breast cancer (TNBC) by study, designated country, and overall.

compared with 72% in the United States.[27] The review revealed large between-country variability in the estimated pooled proportions of ER+ BC, ranging from 62% in Ethiopia to 42% in Uganda. In studies published from 2014 to 2018, the ER+ proportion was almost 25% higher compared with those from earlier years, 64% versus 40%. This difference in ER+ may explain why the prior meta-analysis had an overall proportion of 41% for East Africa, as six of seven studies were published prior to 2014.[20] Improved tissue handling with quality histopathology and IHC may have enhanced detection of ER+, sometimes through support and telepathology from international cancer facilities.[9,63] We found higher proportions of luminal A BC with prospective testing (54%) versus archival testing (42%). However, similar comparisons addressing other receptors and combinations subtypes were not significant.

Study recency and improved IHC evaluation may explain the higher overall proportions of ER+ BC in Ethiopia, Kenya, and Rwanda compared with Tanzania and Uganda. Biologic factors may also influence the lower ER+ proportions in Tanzania and Uganda. Prior BC studies have shown that younger women have lower rates of ER+ BC and higher rates of TNBC.[27] Yet, one study found a higher proportion of ER+ BC among Ethiopian women compared with African American and Ghanaian women despite their younger mean age (42.7 years compared with 60.2 and 49.3 for African Americans and Ghanaians, respectively).[31]

Endocrine therapy is an essential component of treatment for women with ER+ and/or PR+ BC, regardless of HER2 status,[12,18] although only six of the 21 studies included data on treatment with endocrine therapy. Furthermore, of the five that reported administration of endocrine therapy, only three limited such treatment to patients with HR+ BC, suggesting that other studies started patients on endocrine therapy when IHC for ER was unknown or the results were delayed. Despite its ease of use and the potential for clinic personnel to monitor administration outside specialized cancer centers, suboptimal use of endocrine therapy appears widespread. Because generic tamoxifen is relatively inexpensive, it could be readily available, although access is determined by multiple factors.[64]

The overall estimated proportion of HER2+ BC in our study was 23%, compared with under 15% in the United States.[27] Our review revealed minimal variability in pooled proportions of HER2+ across countries (21% to 27%), despite variability within each country. Because incongruency in defining HER2+ status may have contributed to

TABLE 2. Breast Cancer Receptor Outcomes by Timing of Testing, Publication Year, and Proportions of Grade 3 Breast Cancer: Estimated Proportions (ES) and 95% CI With Number of Published Studies (Pubs) and Weight Percentages (WT)[a]

	ER-Positive[b]			PR-Positive			HER2-Positive		
Explanatory Factors	No. of Pubs %WT	ES (95% CI)	I^2 *P*	No. of Pubs %WT	ES (95% CI)	I^2 *P*	No. of Pubs %WT	ES (95% CI)	I^2 *P*
Testing Retrospective	7 37.9%	0.54 (0.43 to 0.64)	84.4% $P \leq .001$	6 36.7%	0.42 (0.31 to 0.54)	87.3% $P \leq .001$	9 50.2%	0.24 (0.19 to 0.29)	67.0% $P = .002$
At diagnosis	11 62.1%	0.55 (0.45 to 0.65)	95.2% $P \leq .001$	10 63.3%	0.48 (0.39 to 0.58)	93.7% $P \leq .001$	9 49.8%	0.22 (0.18 to 0.27)	69.2% $P \leq .001$
Test between subgroups[c]			0.04 $P = .84$			0.63 $P = .43$			0.21 $P = .64$
Publication year 2014-2018	11 61.8%	0.64 (0.58 to 0.69)	84.7% $P \leq .001$	10 62.9%	0.54 (0.46 to 0.61)	89.3% $P \leq .001$	12 69.9%	0.23 (0.19 to 0.27)	68.4% $P \leq .001$
2000-2013	7 38.2%	0.40 (0.33 to 0.49)	77.1% $P \leq .001$	6 37.1%	0.34 (0.25 to 0.45)	85.8% $P \leq .001$	6 30.1%	0.24 (0.17 to 0.31)	68.8% $P = .007$
Test between subgroups[c]			20.96 $P \leq .001$			8.87 $P = .003$			0.04 $P = .84$
% Grade 3 ≥ 54%	6 40.6%	0.53 (0.40 to 0.65)	93.8% $P \leq .001$	5 38.8%	0.55 (0.47 to 0.62)	74.2% $P = .004$	7 49.9%	0.26 (0.24 to 0.29)	0.0% $P = .71$
< 54%	9 59.4%	0.53 (0.39 to 0.68)	95.3% $P \leq .001$	8 61.2%	0.40 (0.25 to 0.57)	96.1% $P \leq .001$	8 50.1%	0.17 (0.14 to 0.20)	7.5% $P = .37$
Test between subgroups[c]			0.00 $P = .95$			2.49 $P = .11$			25.65 $P \leq .001$

[a]All studies with relevant data.
[b]O'Neil 2018 (Rwanda) calculated with hormone receptor-positive in place of ER+.
[c]Test for heterogeneity between subgroups: statistic and *P* value.

within-country variability, standardization in scoring for future studies is recommended.

Although HER2+ BC is subdivided by ER and/or PR expression, both groups benefit from treatment with HER2-targeting therapy, for example, trastuzumab. Trastuzumab is now included in the WHO's model list of essential medicines (2015),[65] as its use in conjunction with chemotherapy has modified the formerly poor outcomes for this subtype.[66,67] Although the standard of care for HER2+ early BC has been one year of adjuvant trastuzumab with chemotherapy,[68] accumulating evidence indicates equivalence between 6 and 12 months of trastuzumab for selected patient profiles.[69]

In many countries of sub-Saharan Africa, there is currently minimal assessment of HER2, primarily because anti-HER2 agents are prohibitively expensive and often unavailable.[6,70] In a recent study, trastuzumab was not shown to be cost-effective in 11 African countries at current prices.[70] Shortened trastuzumab regimens for early BC, as well as availability of multiple biosimilars for all BC,[71] will reduce drug costs. Yet, affordability in sub-Saharan Africa may require global cost-reduction strategies similar to prior collaborations to bring effective antiretroviral medications to low-income countries.[72] The introduction of subcutaneous trastuzumab may increase treatment feasibility in East African countries,[73-75] where there are very few hospitals to administer infusion treatments.[65]

The overall estimated proportion of TNBC in our study was 27% with across-country variability from 21% to 35% in Ethiopia and Uganda, respectively. In the United States, the proportion of TNBC in SEER data was 12.2%,[27] although the proportions among White (10.7%) and African American women (22.5%) showed marked disparity.[27] Higher proportions of TNBC among people of African ancestry may be associated with inherited genetic susceptibility to TNBC.[76] In our meta-analysis, the proportion of TNBC was 9% lower among studies conducted in the last 5 years compared with studies conducted in prior years. The lower proportion of TNBC in Kenya and Ethiopia needs further study as it could be linked to testing and/or biologic factors.

Numerous studies have also identified multiparity and early age for the start of childbearing as strongly associated with the elevated incidence of TNBC.[77-79] Despite high average parity and early childbearing in Kenya and Ethiopia, these countries have lower estimated proportions of TNBC compared with Tanzania and Uganda. Median age at first birth ranged from 18.9 years (Uganda) to 23 years (Rwanda) and children per women from 3.4 (Kenya) to 5.5 (Uganda).[80]

Although TNBC currently has the worst prognosis, achievement of a pathologic complete response (pCR) after neoadjuvant chemotherapy confers a strong prognostic advantage.[81] Although studies do not include an African population, the proportion of patients achieving a pCR after optimal neoadjuvant chemotherapy is 33% to 45%.[82,83] Per NCCN guidelines, BRCA1/2 testing is part of treatment planning in HIC countries for patients that meet designated criteria. Women

with TNBC have a higher prevalence of germline BRCA mutations.[84] In two population-based studies in HIC, among patients with TNBC, 19.5%-22.7% had BRCA mutations.[85,86] Women with BRCA mutations have more than a 50% chance of developing TNBC, and founder *BRCA1* mutations have been identified in BC patients of African ancestry.[87] Most data regarding BRCA mutations in Africa are based upon northern and western African populations[88,89]; therefore, BRCA research needs to be conducted in East Africa.

In the present study, compared with BC among US women, the disease in East African women was characterized by presentation at a younger age, a more advanced stage, and a higher grade. Similar to other regions of the world, most BC among East African women had invasive ductal histology. Preventive health care and BC screening are limited or nonexistent in East Africa,[7,13,90] leading to BC diagnoses at advanced stages and higher grades. Although mammography screening has been linked to reduced BC mortality in US women,[91,92] timely access to BC diagnosis and treatment among symptomatic women in East Africa would likely improve BC mortality.[14,93-99] In our study, the overall proportion of grade 3 BC was 55%, and did not vary by proportion of receptor combination subtypes. In the United States, the proportions of grade 3 tumors were markedly different by subtype: 17% HR+/HER2−; 46% HR+/HER2+; 67% HER2-enriched; and 75% TNBC.[27] Our finding, which suggests ER+ tumors were often high grade, reinforces the need for extended endocrine therapy in East African countries.

The higher grade of BC on presentation could be because of the younger age of women diagnosed with BC in East Africa, about 15 years younger than their US counterparts, where it is 62 years.[5] The younger age in East Africa is likely related to the age profile rather than younger manifestations of BC.[34] In the United States, 30.8% of women are 55 years of age or older; in the countries we reviewed, 5%-7% are in this age category.[80] Relative to HIC, the disproportionate numbers of young and middle-aged women in East African countries has skewed the incidence of BC to younger ages. Yet, as average longevity increases, rates of BC are predicted to rise, a pattern already documented.[3]

Our study is the most comprehensive systematic review and meta-analysis for East Africa to date addressing five countries within this region and a total of 21 studies. Yet, the data available for the study had a number of limitations. Although the advantage of aggregating studies in a meta-analysis is to minimize biases in individual studies, it cannot compensate for insufficient study numbers or indefinite generalizability within a country. For ER+ BC, the range in number of studies per country was one to seven, whereas the median number of patients by country was 247 (range 148 in Rwanda to 1,594 in Kenya). We included the single Rwandan study[9] in our meta-analysis of ER+ by using their assessment of HR+ as a proxy for ER+. Rwanda was not included in the meta-analyses of receptor combinations because the single study[9] did not report this outcome. Future reviews should include available receptor studies from all countries designated as East Africa as those data become available.[25]

There was substantial within-country variability on receptor status and subtypes, which could be linked to sampling or methodologic issues. The significant variability among the seven studies of ER+ conducted in Kenya shows the secular pattern of higher and lower proportions of ER+ BC for recent and prior publication periods. The pooled estimate (56%) for Kenya may have been lowered by the inclusion of earlier studies. By contrast, the four studies of ER+ BC conducted in Tanzania appeared homogeneous despite variability in publication period.

Samples for included studies could be insufficiently representative or generalizable. Among the 18 studies, which drew samples from consecutive cases, more than a third (7 of 18) had receptor data for $< 70\%$ of the total.[21,22,37,41,42,44,47] The only population-based study sourced from the cancer registry in Kyadondo County, encompassing Kampala, Uganda, included only two-thirds of registry cases.[47]

The majority of studies were conducted at a single medical institution, typically in the country's capital or largest city, had patient samples < 100 (n = 9) or between 100 and 250 (n = 9), and may not reflect BC patterns in other regions of the country.

In summary, this study provides updated estimates for the proportion of BC receptor subtypes defined by ER, PR, and HER2 status in five countries within East Africa. The proportion of ER+ BC is higher than reported,[20] underscoring a substantial role for extended endocrine therapy. Since endocrine therapy is available orally, broader delivery to patients appropriate for this treatment should be feasible. The sizable proportion of HER2+ BC, higher compared with HIC, suggests a clear need for strategies to build capacity in assessment and affordable treatment of HER2+ BC. Finally, TNBC remains a considerable proportion of BC in these five East African countries, as compared with HIC, emphasizing the need to maximize robust treatment of this aggressive subtype. Testing and reporting of receptor subtypes is critical for delivery of more effective treatment to reduce the mortality disparity for BC in East Africa.

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PRIOR PRESENTATION

Presented in part elsewhere: Abstract titled "Breast cancer receptor subtypes in East Africa: A systematic review and meta-analysis" was electronically published at the 2020 ASCO Virtual Scientific Program (DOI: 10.1200/JCO.2020.38.15_suppl.e19074).

SUPPORT

Supported by grant funding from the Rutgers Global Health Institute.

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Conception and design: Elane M. Gutterman, Coral Omene, Richard Marlink
Financial support: Richard Marlink
Administrative support: Richard Marlink
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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Coral Omene
Consulting or Advisory Role: EISAI

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Stock and Other Ownership Interests: Ibris, Inspirata, Merck
Consulting or Advisory Role: Inspirata, Novartis, Roche, Foghorn Therapeutics, Foundation Medicine, Merck Sharp & Dohme
Research Funding: M2Gen
Patents, Royalties, Other Intellectual Property: I hold two patents for digital imaging that may be licensed to Ibris, Inc and Inspirata, Inc
Other Relationship: NCI/NIH

Richard Marlink
Research Funding: Bristol-Myers Squibb

No other potential conflicts of interest were reported.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
2. Forouzanfar MH, Foreman KJ, Delossantos AM, et al: Breast and cervical cancer in 187 countries between 1980 and 2010: A systematic analysis. Lancet 378:1461-1484, 2011
3. Wabinga HR, Nambooze S, Amulen PM, et al: Trends in the incidence of cancer in Kampala, Uganda 1991-2010. Int J Cancer 135:432-439, 2014
4. Ssentongo P, Lewcun JA, Candela X, et al: Regional, racial, gender, and tumor biology disparities in breast cancer survival rates in Africa: A systematic review and meta-analysis. PLoS One 14:e0225039, 2019
5. National Institute of Health NCIS, Epidemiology and End Results Program: Cancer Stat Facts: Female Breast Cancer, 2017. https://seer.cancer.gov/statfacts/html/breast.html
6. Stulac S, Binagwaho A, Tapela NM, et al: Capacity building for oncology programmes in sub-Saharan Africa: The Rwanda experience. Lancet Oncol 16:e405-e413, 2015
7. Scheel JR, Giglou MJ, Segel S, et al: Breast cancer early detection and diagnostic capacity in Uganda. Cancer 126(suppl 10):2469-2480, 2020
8. Abdel-Wahab M, Bourque JM, Pynda Y, et al: Status of radiotherapy resources in Africa: An International Atomic Energy Agency analysis. Lancet Oncol 14:e168-e175, 2013
9. O'Neil DS, Keating NL, Dusengimana JMV, et al: Quality of breast cancer treatment at a rural cancer center in Rwanda. J Glob Oncol 4:1-11, 2018
10. Mostert S, Njuguna F, Olbara G, et al: Corruption in health-care systems and its effect on cancer care in Africa. Lancet Oncol 16:e394-e404, 2015
11. Tanzania Breast Health Care Assessment 2017: An Assessment of Breast Cancer Early Detection, Diagnosis and Treatment in Tanzania. Seattle, WA, Breast Cancer Initiative 2.5, 2017
12. National Comprehensive Cancer Network: NCCN Harmonized Guidelines for Sub-Saharan Africa: Breast Cancer (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/breast_harmonized-africa.pdf.
13. Pace LE, Mpunga T, Hategekimana V, et al: Delays in breast cancer presentation and diagnosis at two rural cancer referral centers in Rwanda. Oncologist 20:780-788, 2015
14. Ginsburg O, Yip CH, Brooks A, et al: Breast cancer early detection: A phased approach to implementation. Cancer 126(suppl 10):2379-2393, 2020
15. Malhotra GK, Zhao X, Band H, et al: Histological, molecular and functional subtypes of breast cancers. Cancer Biol Ther 10:955-960, 2010
16. Sinn HP, Kreipe H: A brief overview of the Who Classification of Breast Tumors, 4th edition, focusing on issues and updates from the 3rd edition. Breast Care (Basel) 8:149-154, 2013
17. Early Breast Cancer Trialists' Collaborative Group (EBCTC): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005
18. Davies C, Godwin J, Gray R, et al: Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. Lancet 378:771-784, 2011
19. Amirikia KC, Mills P, Bush J, et al: Higher population-based incidence rates of triple-negative breast cancer among young African-American women: Implications for breast cancer screening recommendations. Cancer 117:2747-2753, 2011

20. Eng A, McCormack V, dos-Santos-Silva I: Receptor-defined subtypes of breast cancer in indigenous populations in Africa: A systematic review and meta-analysis. PLoS Med 11:e1001720, 2014
21. Hadgu E, Seifu D, Tigneh W, et al: Breast cancer in Ethiopia: Evidence for geographic difference in the distribution of molecular subtypes in Africa. BMC Womens Health 18:40, 2018
22. Kantelhardt EJ, Mathewos A, Aynalem A, et al: The prevalence of estrogen receptor-negative breast cancer in Ethiopia. BMC Cancer 14:895, 2014
23. Sayed S, Moloo Z, Wasike R, et al: Is breast cancer from sub Saharan Africa truly receptor poor? Prevalence of ER/PR/HER2 in breast cancer from Kenya. Breast 23:591-596, 2014
24. Tapela NM, Mpunga T, Hedt-Gauthier B, et al: Pursuing equity in cancer care: Implementation, challenges and preliminary findings of a public cancer referral center in rural Rwanda. BMC Cancer 16:237, 2016
25. Worldometer: Population of Eastern Africa 2019. https://www.worldometers.info/world-population/eastern-africa-population/
26. Moher D, Liberati A, Tetzlaff J, et al: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. J Clin Epidemiol 62:1006-1012, 2009
27. Howlader N, Altekruse SF, Li CI, et al: US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 106:dju055, 2014
28. Vanderpuye V, Grover S, Hammad N, et al: An update on the management of breast cancer in Africa. Infect Agent Cancer 12:13, 2017
29. Nyaga VN, Arbyn M, Aerts M: Metaprop: A Stata command to perform meta-analysis of binomial data. Arch Public Health 72:39, 2014
30. Higgins JP, Thompson SG, Deeks JJ, et al: Measuring inconsistency in meta-analyses. BMJ 327:557-560, 2003
31. Jiagge E, Jibril AS, Davis M, et al: Androgen receptor and ALDH1 expression among internationally diverse patient populations. J Glob Oncol 4:1-8, 2018
32. Eber-Schulz P, Tariku W, Reibold C, et al: Survival of breast cancer patients in rural Ethiopia. Breast Cancer Res Treat 170:111-118, 2018
33. Sayed S, Moloo Z, Wasike R, et al: Ethnicity and breast cancer characteristics in Kenya. Breast Cancer Res Treat 167:425-437, 2018
34. Sawe RT, Kerper M, Badve S, et al: Aggressive breast cancer in western Kenya has early onset, high proliferation, and immune cell infiltration. BMC Cancer 16:204, 2016
35. Bird PA, Hill AG, Houssami N: Poor hormone receptor expression in East African breast cancer: Evidence of a biologically different disease? Ann Surg Oncol 15:1983-1988, 2008
36. Nyagol J, Nyong'o A, Byakika B, et al: Routine assessment of hormonal receptor and HER-2/Neu status underscores the need for more therapeutic targets in Kenyan women with breast cancer. Anal Quant Cytol Histol 28:97-103, 2006
37. Wata DE, OsanjoGO, Oluka M, et al: Predictors of breast cancer treatment outcomes in Kenyan women. Afr J Pharmacol Ther 2:109-115, 2013
38. Gakinya SM, Sayed S, Chauhan R, et al: Breast cancer molecular subtypes and their clinicopathological characteristics amongst patients at the Aga Khan University Hospital (Nairobi). Ann Afr Surg 5:19-24, 2010
39. Brand NR, Wasike R, Makhdomi K, et al: Sentinel lymph node biopsy pathology and 2-year postsurgical recurrence of breast cancer in Kenyan women. J Glob Oncol 4:1-7, 2018
40. Mwakigonja AR, Lushina NE, Mwanga A: Characterization of hormonal receptors and human epidermal growth factor receptor-2 in tissues of women with breast cancer at Muhimbili National Hospital, Dar es salaam, Tanzania. Infect Agent Cancer 12:60, 2017
41. Amadori D, Serra P, Bravaccini S, et al: Differences in biological features of breast cancer between Caucasian (Italian) and African (Tanzanian) populations. Breast Cancer Res Treat 145:177-183, 2014
42. Burson AM, Soliman AS, Ngoma TA, et al: Clinical and epidemiologic profile of breast cancer in Tanzania. Breast Dis 31:33-41, 2010
43. Mbonde MP, Amir H, Schwartz-Albiez R, et al: Expression of estrogen and progesterone receptors in carcinomas of the female breast in Tanzania. Oncol Rep 7:277-283, 2000
44. Galukande M, Wabinga H, Mirembe F: Breast cancer survival experiences at a tertiary hospital in sub-Saharan Africa: A cohort study. World J Surg Oncol 13:220, 2015
45. Galukande M, Mirembe F, Wabinga H: Patient delay in accessing breast cancer care in a sub Saharan African Country: Uganda. Br J Med Med Res 4:2599-2610, 2014
46. Roy I, Othieno E: Breast carcinoma in Uganda: Microscopic study and receptor profile of 45 cases. Arch Pathol Lab Med 135:194-199, 2011
47. Nalwoga H, Arnes JB, Wabinga H, et al: Expression of aldehyde dehydrogenase 1 (ALDH1) is associated with basal-like markers and features of aggressive tumours in African breast cancer. Br J Cancer 102:369-375, 2010
48. Weiner CM, Mathewos A, Addissie A, et al: Characteristics and follow-up of metastatic breast cancer in Ethiopia: A cohort study of 573 women. Breast 42:23-30, 2018
49. Jiagge E, Jibril AS, Chitale D, et al: Comparative analysis of breast cancer phenotypes in African American, White American, and West versus East African patients: Correlation between African ancestry and triple-negative breast cancer. Ann Surg Oncol 23:3843-3849, 2016
50. ShaikhAJ, MulloolyM, SayedS, et al: Mammographic breast density and breast cancer molecular subtypes: The Kenyan-African Aspect. Biomed Res Int 2018:6026315, 2018
51. Sawe RT, Mining SK, Ofulla AV, et al: Tumor infiltrating leukocyte density is independent of tumor grade and molecular subtype in aggressive breast cancer of Western Kenya. Trop Med Health 45:19, 2017
52. Bravaccini S, Ravaioli S, Amadori D, et al: Are there differences in androgen receptor expression in invasive breast cancer in African (Tanzanian) population in comparison with the Caucasian (Italian) population? Front Endocrinol (Lausanne) 9:137, 2018
53. Rambau P, Masalu N, Jackson K, et al: Triple negative breast cancer in a poor resource setting in North-Western Tanzania: A preliminary study of 52 patients. BMC Res Notes 7:399, 2014
54. Mbonde MP, Amir H, Akslen LA, et al: Expression of oestrogen and progesterone receptors, Ki-67, p53 and BCL-2 proteins, cathepsin D, urokinase plasminogen activator and urokinase plasminogen activator-receptors in carcinomas of the female breast in an African population. East Afr Med J 78:360-365, 2001
55. Ahmed L, Nalwoga H, Arnes JB, et al: Increased tumor cell expression of Axl is a marker of aggressive features in breast cancer among African women. APMIS 123:688-696, 2015
56. Galukande M, Wabinga H, Mirembe F, et al: Molecular breast cancer subtypes prevalence in an indigenous sub Saharan African population. Pan Afr Med J 17:249, 2014
57. GalukandeM, WabingaH, MirembeF, et al: Difference in risk factors for breast cancer by ER status in an indigenous African population. ISRN Oncol 2013:463594, 2013
58. Nalwoga H, Arnes JB, Wabinga H, et al: Frequency of the basal-like phenotype in African breast cancer. APMIS 115:1391-1399, 2007

59. Nalwoga H, Arnes JB, Wabinga H, et al: Expression of EGFR and c-kit is associated with the basal-like phenotype in breast carcinomas of African women. APMIS 116:515-525, 2008
60. Pace LE, Dusengimana JM, Hategekimana V, et al: Benign and malignant breast disease at Rwanda's first public cancer referral center. Oncologist 21:571-575, 2016
61. Yesufe AA, Assefa M, Bekele A, et al: Adequacy of pathologic reports of invasive breast cancer from mastectomy specimens at Tikur Anbessa Specialized Hospital Oncology Center in Ethiopia. J Glob Oncol 4:1-12, 2018
62. Jemal A, Fedewa SA: Is the prevalence of ER-negative breast cancer in the US higher among Africa-born than US-born black women? Breast Cancer Res Treat 135:867-873, 2012
63. Anglade F, Milner DA Jr, Brock JE: Can pathology diagnostic services for cancer be stratified and serve global health? Cancer 126(suppl 10):2431-2438, 2020
64. Kerr DJ, Midgley R: Can we treat cancer for a dollar a day? Guidelines for low-income countries. N Engl J Med 363:801-803, 2010
65. Shulman LN, Wagner CM, Barr R, et al: Proposing essential medicines to treat cancer: Methodologies, processes, and outcomes. J Clin Oncol 34:69-75, 2016
66. Baselga J, Perez EA, Pienkowski T, et al: Adjuvant trastuzumab: A milestone in the treatment of HER-2-positive early breast cancer. Oncologist 11(suppl 1): 4-12, 2006
67. Leone JP, Leone J, Zwenger AO, et al: Prognostic significance of tumor subtypes in women with breast cancer according to stage: A population-based study. Am J Clin Oncol 42:588-595, 2019
68. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al: 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): An open-label, randomised controlled trial. Lancet 382:1021-1028, 2013
69. Deng H, Du X, Wang L, et al: Six months vs. 12 months of adjuvant trastuzumab among women with HER2-positive early-stage breast cancer: A meta-analysis of randomized controlled trials. Front Oncol 10:288, 2020
70. Gershon N, Berchenko Y, Hall PS, et al: Cost effectiveness and affordability of trastuzumab in sub-Saharan Africa for early stage HER2-positive breast cancer. Cost Eff Resour Alloc 17:5, 2019
71. Miller EM, Schwartzberg LS: Biosimilars for breast cancer: A review of HER2-targeted antibodies in the United States. Ther Adv Med Oncol 11:1758835919887044, 2019
72. Forsythe SS, McGreevey W, Whiteside A, et al: Twenty years of antiretroviral therapy for people living with HIV: Global costs, health achievements, economic benefits. Health Aff (Millwood) 38:1163-1172, 2019
73. Denys H, Martinez-Mena CL, Martens MT, et al: Safety and tolerability of subcutaneous trastuzumab at home administration, results of the phase IIIb open-label BELIS study in HER2-positive early breast cancer. Breast Cancer Res Treat 181:97-105, 2020
74. Pivot X, Spano JP, Espie M, et al: Patients' preference of trastuzumab administration (subcutaneous versus intravenous) in HER2-positive metastatic breast cancer: Results of the randomised MetaspHer study. Eur J Cancer 82:230-236, 2017
75. Ismael G, Hegg R, Muehlbauer S, et al: Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): A phase 3, open-label, multicentre, randomised trial. Lancet Oncol 13:869-878, 2012
76. Brewster AM, Chavez-MacGregor M, Brown P: Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. Lancet Oncol 15:e625-e634, 2014
77. Shinde SS, Forman MR, Kuerer HM, et al: Higher parity and shorter breastfeeding duration: Association with triple-negative phenotype of breast cancer. Cancer 116:4933-4943, 2010
78. Millikan RC, Newman B, Tse CK, et al: Epidemiology of basal-like breast cancer. Breast Cancer Res Treat 109:123-139, 2008
79. Yang XR, Chang-Claude J, Goode EL, et al: Associations of breast cancer risk factors with tumor subtypes: A pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst 103:250-263, 2011
80. Central Intelligence Agency: The World Factbook 2020. https://www.cia.gov/library/publications/resources/the-world-factbook/index.html
81. Cortazar P, Zhang L, Untch M, et al: Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet 384:164-172, 2014
82. Pandy JGP, Balolong-Garcia JC, Cruz-Ordinario MVB, et al: Triple negative breast cancer and platinum-based systemic treatment: A meta-analysis and systematic review. BMC Cancer 19:1065, 2019
83. Biswas T, Efird JT, Prasad S, et al: The survival benefit of neoadjuvant chemotherapy and pCR among patients with advanced stage triple negative breast cancer. Oncotarget 8:112712-112719, 2017
84. Sharma P, Klemp JR, Kimler BF, et al: Germline BRCA mutation evaluation in a prospective triple-negative breast cancer registry: Implications for hereditary breast and/or ovarian cancer syndrome testing. Breast Cancer Res Treat 145:707-714, 2014
85. Gonzalez-Angulo AM, Timms KM, Liu S, et al: Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 17:1082-1089, 2011
86. Musolino A, Bella MA, Bortesi B, et al: BRCA mutations, molecular markers, and clinical variables in early-onset breast cancer: A population-based study. Breast 16:280-292, 2007
87. Zhang J, Fackenthal JD, Zheng Y, et al: Recurrent BRCA1 and BRCA2 mutations in breast cancer patients of African ancestry. Breast Cancer Res Treat 134:889-894, 2012
88. KaramiF, MehdipourP: A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int 2013:928562, 2013
89. Newman LA: Disparities in breast cancer and African ancestry: A global perspective. Breast J 21:133-139, 2015
90. DyeTD, BogaleS, HobdenC, et al: Experience of initial symptoms of breast cancer and triggers for action in Ethiopia. Int J Breast Cancer 2012:908547, 2012
91. Plevritis SK, Munoz D, Kurian AW, et al: Association of screening and treatment with breast cancer mortality by molecular subtype in US women, 2000-2012. JAMA 319:154-164, 2018
92. Berry DA, Cronin KA, Plevritis SK, et al: Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 353:1784-1792, 2005
93. Yip CH: Downstaging is more important than screening for asymptomatic breast cancer. Lancet Glob Health 7:e690-e691, 2019
94. Atuhairwe C, Amongin D, Agaba E, et al: The effect of knowledge on uptake of breast cancer prevention modalities among women in Kyadondo County, Uganda. BMC Public Health 18:279, 2018
95. Pace LE, Dusengimana JMV, Shulman LN, et al: Cluster randomized trial to facilitate breast cancer early diagnosis in a rural district of Rwanda. J Glob Oncol 5:1-13, 2019
96. Sayed S, Moloo Z, Ngugi A, et al: Breast camps for awareness and early diagnosis of breast cancer in countries with limited resources: A multidisciplinary model from Kenya. Oncologist 21:1138-1148, 2016

97. Sayed S, Ngugi AK, Mahoney MR, et al: Breast Cancer knowledge, perceptions and practices in a rural Community in Coastal Kenya. BMC Public Health 19:180, 2019

98. McKenzie F, Zietsman A, Galukande M, et al: Drivers of advanced stage at breast cancer diagnosis in the multicountry African breast cancer - disparities in outcomes (ABC-DO) study. Int J Cancer 142:1568-1579, 2018

99. Songiso M, Pinder LF, Munalula J, et al: Minimizing delays in the breast cancer pathway by integrating breast specialty care services at the primary health care level in Zambia. JCO Glob Oncol 6:859-865, 2020