Breast Cancer Phenotypes in Africa: A Scoping Review and Meta-Analysis

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ABSTRACT

PURPOSE Africans have been associated with more aggressive forms of breast cancer (BC). However, there is a lack of data regarding the incidence and distribution of different subtypes on the basis of phenotypic classification. This scoping review and meta-analysis was undertaken to determine the distribution pattern of BC phenotypes (luminal, human epidermal growth factor receptor 2 [HER2]+, and triple-negative breast cancer [TNBC]) across the African region.

METHODS Four online databases (PubMed, Scopus, ProQuest, and EBSCOhost) were accessed to identify studies published between 2000 and 2022 reporting the representation of receptor status (estrogen receptor, progesterone receptor, and HER2) in African patients with BC. Furthermore, the meta-analysis was carried out using a random-effects model and pooled using the inverse variance method and logit transformation. 95% CI and I^2 statistics were calculated using the Clopper-Pearson method to estimate between-study heterogeneity.

RESULTS A total of 2,734 records were retrieved, of which 2,133 were retained for further screening. After the screening, 63 studies were finally selected for the scoping review and meta-analysis. The pooled frequency of luminal, HER2-positive (HER2+), and TNBC was estimated at 56.30%, 12.61%, and 28.10%, respectively. Northern Africa had the highest frequency of the luminal subtype, while West Africa showed higher frequencies of HER2+ and TNBC subtypes. The review also had a representation of only 24 countries in Africa.

CONCLUSION Our results highlight the disparity in the representation of molecular subtypes among the people in different regions of Africa. There is a need to incorporate routine molecular subtyping into the management of African patients with BC.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Breast cancer (BC) is the most diagnosed cancer afflicting women globally and accounts for about 11% of all female cancers.[1] In Africa, BC incidence and mortality rates are estimated at 186,598 and 85,787, respectively.[1] This burden, however, varies widely among different African regions.[2] This disease ranks highest among female cancer-causing deaths in Northern and Western Africa, accounting for 24.7% and 27.1%, respectively. In Middle Africa and Eastern Africa, BC is the second leading cause of cancer death after cervical cancer, estimated at 23.9% and 17.9%, respectively. The lowest mortality of BC occurs in Southern African countries, where it accounts for about 15% of cancer death, ranking as the second leading cause of cancer death in that region.[1] The high mortality of BC in lower-income continents such as Africa is attributed to the lack of education and awareness, late diagnosis and treatment, poverty, and aggressive tumor subtypes, resulting in worse disease progression in the region.[3]

BC is a heterogeneous disease showing varied characteristics, progression, and response to therapy.[4] The subtypes of BC are derived based on the ASCO/College of American Pathologists recommendation that posits that immunohistochemical testing of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) be incorporated into routine BC treatment protocols.[5,6] Understanding the subtype of BC helps identify patients who could benefit from personalized treatments. Perou et al[7] further delineated BC on the basis of the variation of gene expression patterns into four molecular subtypes: luminal A (Lum A), luminal B (Lum B), HER2-positive, and triple-negative breast cancer (TNBC). The molecular

subtyping of BC is therefore based on the expression pattern of these receptors.[8] The preferred method of choice for molecular subtyping is the use of molecular techniques such as in situ hybridization, fluorescence in situ hybridization (FISH), polymerase chain reaction, or surrogate immunohistochemical methods.[8] However, classical subtyping with immunohistochemistry (IHC) is commonly used because of the high cost of other molecular techniques.[7] The molecular subtypes that individuals present with have prognostic implications and influence clinical outcomes and overall survival.[9] The Lum A and Lum B molecular subtypes are associated with a better prognosis and long-term survival estimated at 80%-85% for 5 years.[10] The HER2 subtype overly expressed in 20%-25% of BC cases has adverse survival outcomes.[4,11] The TNBC, which is predicted to be the dominant subtype in the African population and associated with African ancestry,[12] has the highest mortality rate compared with other molecular subtypes. It accounts for about 15%-20% of all cancers and a mortality rate of 40% within a 5-year diagnostic period.[13] The TNBC subtype tumor, which lacks the expression of the three receptors, is characterized by aggressiveness and higher resistance to therapies, and it is generally difficult to manage.[14] The role of racial and ethnic disparities in the incidences and distribution of BC subtypes has been documented.[15] However, the exact distribution of BC subtypes in Africa remains largely unknown.[16]

This scoping review and meta-analysis was carried out to identify the distribution of molecular subtypes of BC in the African region. The following research questions were formulated for the review: (1) To what extent has research on BC molecular subtypes been undertaken in Africa? (2) Are all African countries/populations represented in these studies? (3) What is the distribution pattern of BC molecular subtypes in Africa? (4) Are there regional patterns of BC molecular subtypes?

METHODS

Protocol

This scoping review was carried out using the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.[17]

Eligibility Criteria

Four online databases (PubMed, Scopus, ProQuest, and EBSCOhost) were accessed to identify studies published between January 2000 and December 2022. The search strategy used for PubMed was modified for the other databases (Data Supplement, Table S1). The search keywords used were terms such as "Molecular subtypes," "luminal," and "TNBC" (Data Supplement, Table S1) and names of African countries ("Africa" and names of the 54 African countries). All articles found during the searches were saved into a reference manager software (EndNote, X9) and duplicates across the four databases were removed. Three reviewers participated in the review process. Two of the three reviewers independently read the titles and abstracts of the articles, and irrelevant articles were removed, leaving 89 articles for the full review. Before this, a calibration exercise was performed to ensure a standardized review of the papers by the reviewers. For standardization, two of the three reviewers screened each paper independently from the searches and compared it until a consensus was reached. All conflicts generated during the screening stages between the reviewers were discussed and 88% agreement was reached on the articles included in the review. Three studies in the French language[18-20] were translated using Google Translate before inclusion in the review. The inclusion criteria for selected studies were studies done in Africa, or of African origin where the sample location could be identified, studies where the location of the sample in Africa can be identified, studies limited to BC molecular subtypes in women, otherwise, the majority of the sample population (98%) must be women, and studies with qualitative or quantitative reports indicating receptor status ER, PR, and HER2.

The following exclusion criteria were used: nondisclosure of sample country/city of origin, studies on populations outside Africa, studies that were written in other languages where a translation could not be obtained, studies where the full text cannot be accessed, studies on other cancers apart from BC, as well as studies on animals and cell lines. Review articles, book chapters, and conference proceedings were also excluded from the list.

The electronic database search retrieved 2,734 citation records. After removing duplicates, 2,136 articles were retained. Further screening of titles and abstracts resulted in the removal of 2,133 articles and a total of 113 articles were selected for full-text screening. Finally, 63 articles were included in the scoping review, while 50 articles were excluded from the screening process as they did not meet the inclusion criteria (Fig 1). The included studies were reviewed by three different reviewers and a consensus was reached on 63 eligible studies that met the criteria for the scoping review.

Quality Assessment

The systematic quality assessment of studies was not performed as it is not required in a scoping review.

Patient and public involvement: None.

Synthesis of Results

To organize data from the selected articles, we used a Microsoft Excel spreadsheet to extract relevant data on the basis of the research questions. Two reviewers extracted and charted the data independently, while the third reviewer validated them for accuracy. The following data were recorded in the spreadsheet: author(s), the title of publication, publication year, the country where the study was conducted, study design, analytical method, and outcomes measured (Data Supplement, Table S2).

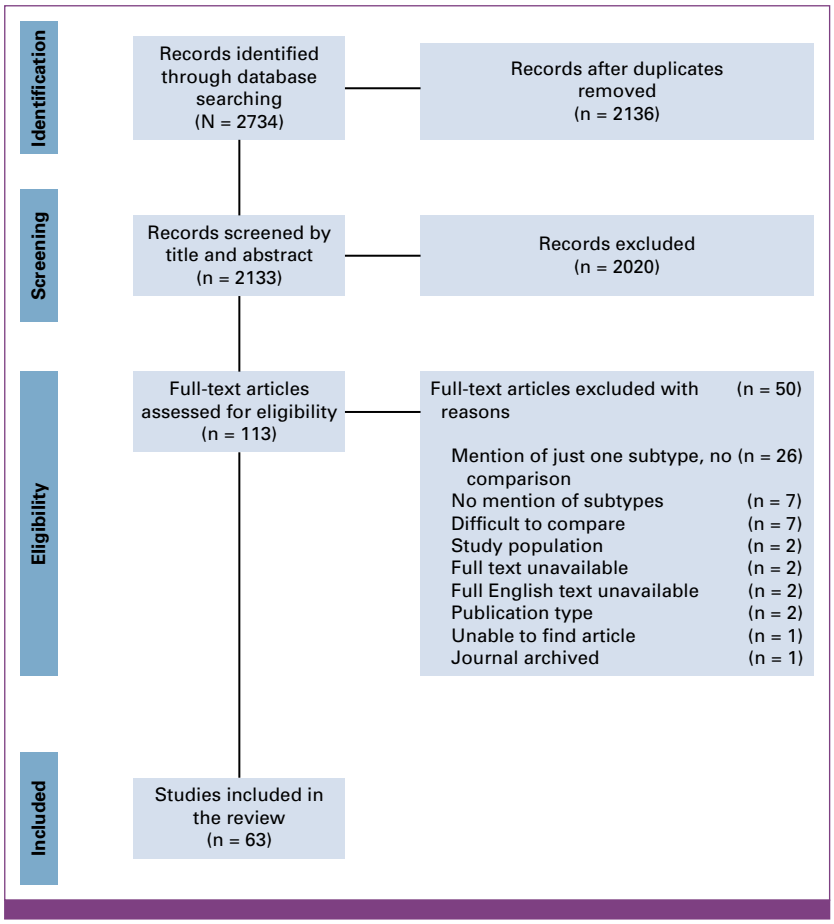

FIG 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart for studies included in the scoping review and meta-analysis.

Data Analysis

From the list of eligible studies, a heatmap of Africa was designed to show the represented countries and the proportion of BC molecular subtypes in each country using Tableau (2021-2-1). The meta-analysis was completed using R (V4.2.1).[21] The analysis of Luminal, HER2-positive (HER2+), and TNBC frequencies was carried out for African women, stratified by region and individual country, using the meta and metafor packages in R. A random-effects model pooled using the inverse variance method and logit transformation was used. 95% CI and I^2 statistics were calculated using the Clopper-Pearson method to estimate between-study heterogeneity. Between-study heterogeneity was assessed with Cochrane's Q, I^2, and H statistics as described previously by Hercules et al.[2]

RESULTS

The review had representations from 24 countries in Africa (Fig 2). The highest number of articles were from Nigeria (n = 10), followed by Egypt and Morocco (n = 7), Tunisia and South Africa (n = 4), Algeria, Ghana, Kenya, Uganda (n = 3), Ethiopia, Mali, Ivory Coast, Tanzania (n = 2), Angola, Cameroon, Democratic Republic of Congo, Eritrea, Guinea, Malawi, Mozambique, Republic of Congo, Rwanda, and Togo (n = 1). A particular study also combined participants from two countries: Sudan and Eritrea (n = 1; Data Supplement, Table S2).

After analysis of the results, the pooled luminal frequency was 56.30% (95% CI, 51.88 to 60.67; I^2 = 98%). When pooled by region, North Africa (n = 21) had the highest frequency of 63.42 (95% CI, 58.57 to 68.13; I^2 = 97). Central Africa also showed a high frequency of 81.89% but had representation from just two studies. The frequency of the luminal subtype was lowest in West Africa (n = 15) with 41.04% (95% CI, 31.27 to 51.17; I^2 = 97; Fig 3). Pooling by individual countries showed Kenya (n = 3) had the highest frequency (68.44%; 95% CI, 62.65 to 73.96; I^2 = 63%). Luminal frequency was lowest in Ghana (n = 2) with 27.46% (95% CI, 10.88 to 48.09; I^2 = 94%; Data Supplement, Table S3). The level of between-study heterogeneity (I^2) was found to be high at 94% (Data Supplement, Fig S1).

The pooled HER2+ frequency was 12.61% (95% CI, 11.37 to 13.91; I^2 = 86%). When pooled by region, West Africa (n = 19) had the highest frequency of 14.87 (95% CI, 11.52 to 18.56;

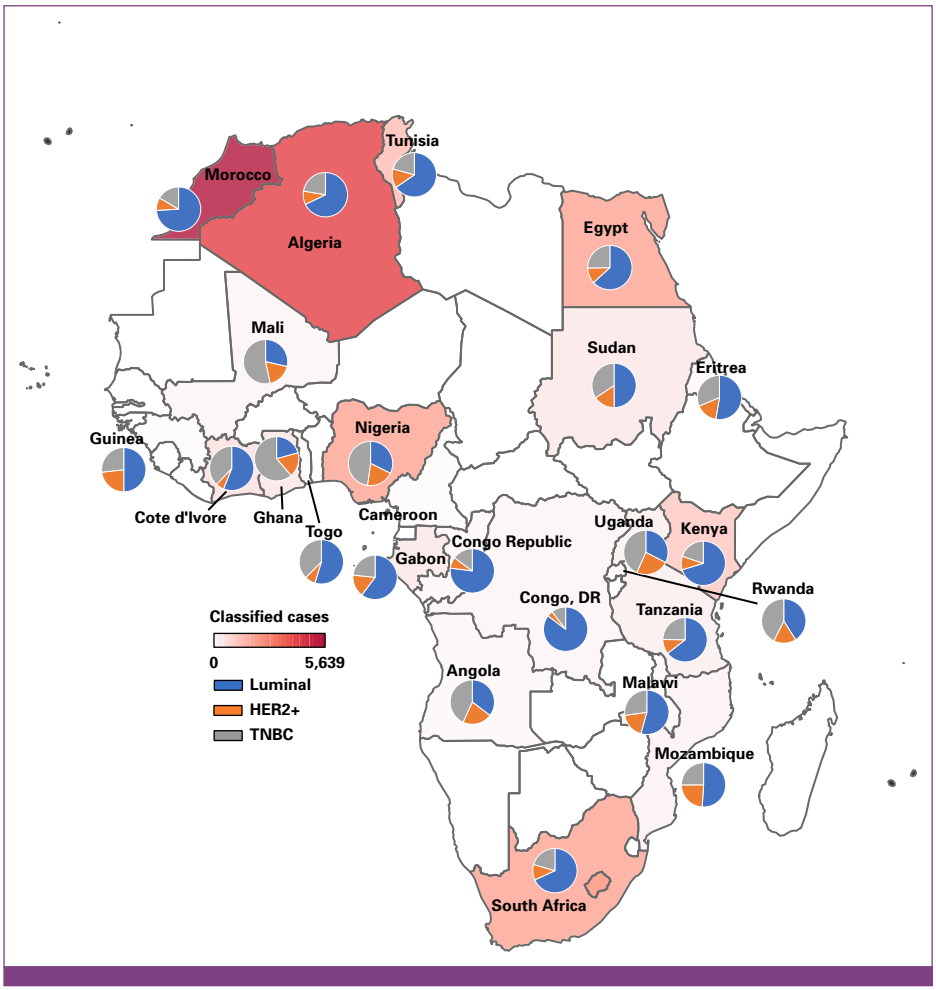

FIG 2. Heat map of Africa showing the total number of BC reported and the pie charts of the proportion of BC subtypes reported for each country. BC, breast cancer; HER2+, human epidermal growth factor receptor 2–positive; TNBC, triple-negative breast cancer.

I^2 = 88%). It was lowest in Central Africa (n = 3) with 8.05% (95% CI, 2.33 to 116.31; I^2 = 72; Fig 4). Pooling by individual countries showed that Uganda (n = 3) had the highest HER2+ frequency (18.72%; 95% CI, 13.67 to 24.33; I^2 = 34%). It was lowest in Kenya (n = 3) with 9.45% (95% CI, 7.81 to 11.23; I^2 = 0%; Data Supplement, Table S4). The level of between-study heterogeneity (I^2) was found to be high at 86% (Data Supplement, Fig S1).

The pooled TNBC frequency was 28.10% (95% CI, 24.77 to 31.55; I^2 = 97%). When pooled by region, West Africa (n = 19) had the highest frequency of 42.36 (95% CI, 35.88 to 48.97; I^2 = 94%). It was lowest in Central Africa (n = 3) with 18.25% (95% CI, 7.53 to 32.08; I^2 = 83; Fig 5). Pooling by individual countries showed that Ghana (n = 3) had the highest TNBC frequency of 56.17% (95% CI, 49.77 to 62.47; I^2 = 54%). It was lowest in Morocco (n = 7) with 15.52% (95% CI, 12.32 to 19.01; I^2 = 91%; Data Supplement, Table S5). The level of between-study heterogeneity (I^2) was found to be high at 97% (Data Supplement, Fig S1).

DISCUSSION

BC remains the leading cause of cancer deaths among women in Africa.[1,22,23] Despite a lower incidence than the Western population, its mortality has continued to surge in the Black population.[1] The lack of consideration for an individualized approach according to molecular BC subtypes or IHC phenotypes, rather than a holistic approach, worsens BC prognosis in the region.[24] Studies have shown that even within the African population, BC inter-regional variability exists.[25] To our knowledge, this study provides evidence as the first scoping review and meta-analysis assessing the distribution of BC phenotypes in Africa.

This study examined 63 publications that reported the subtypes of BC across African countries. Our results confirm that variability exists in the distribution of phenotypes of BC in African regions and countries (Fig 2). The method of choice used in most of the studies analyzed for molecular subtyping was classical IHC. Only four studies[26-29] incorporated FISH

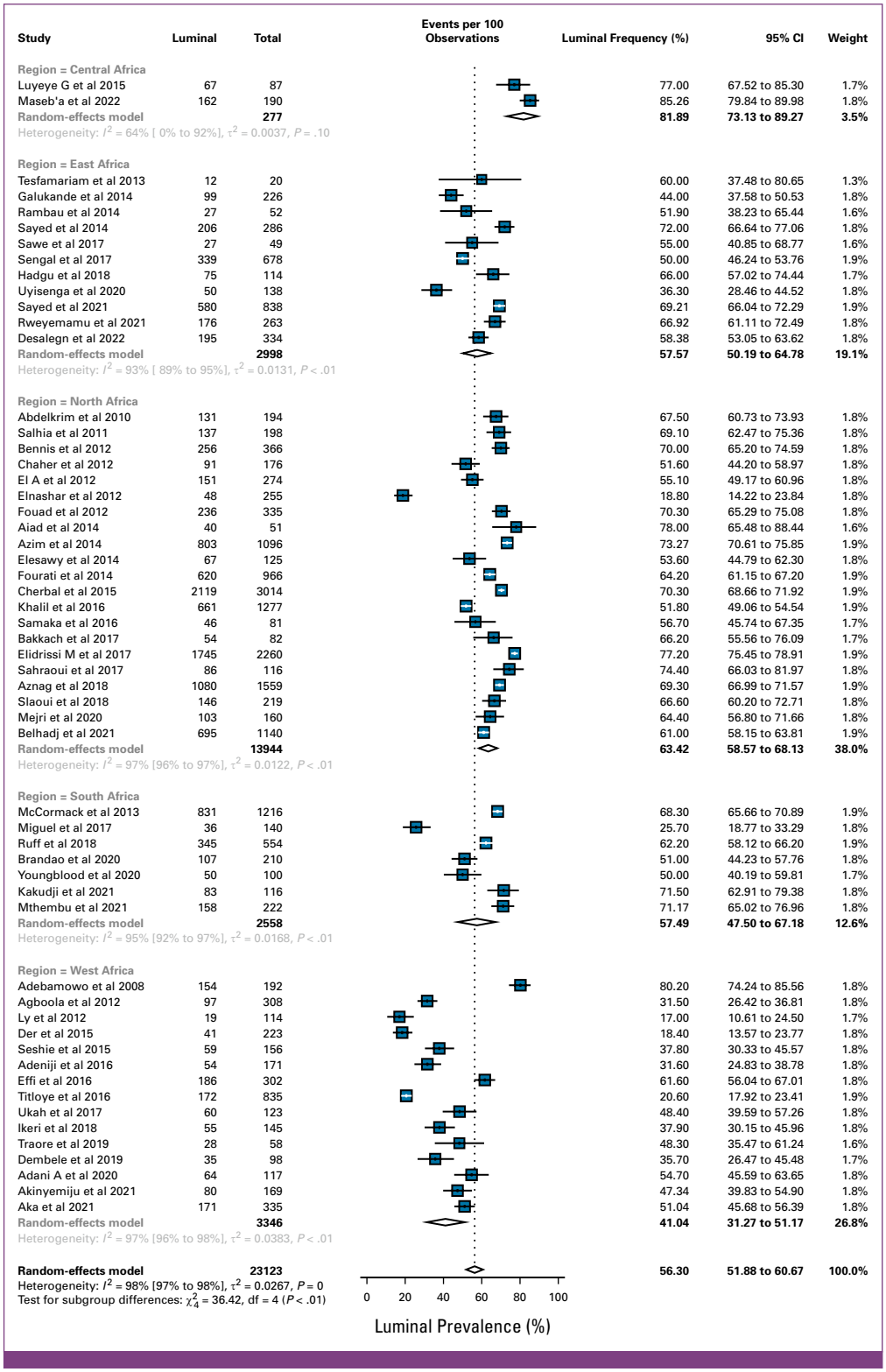

FIG 3. Pooled luminal frequency stratified by regions.

for molecular subtype analysis (Data Supplement, Table S2). Africa still lags in integrating genomic markers for BC care and management.[30] Thus, IHC, which combines ER, PR, HER2, and Ki-67 (a human nuclear antigen proliferative marker), has become the surrogate method in most African countries.[31]

From our results, the combined luminal subtype frequency was highest in Northern Africa (63.42%) compared with other regions (41.04%-63.42%). This corroborates the report of El Fatemi et al[32] suggesting a dominant Lum B subtype in this region. When pooled by individual countries

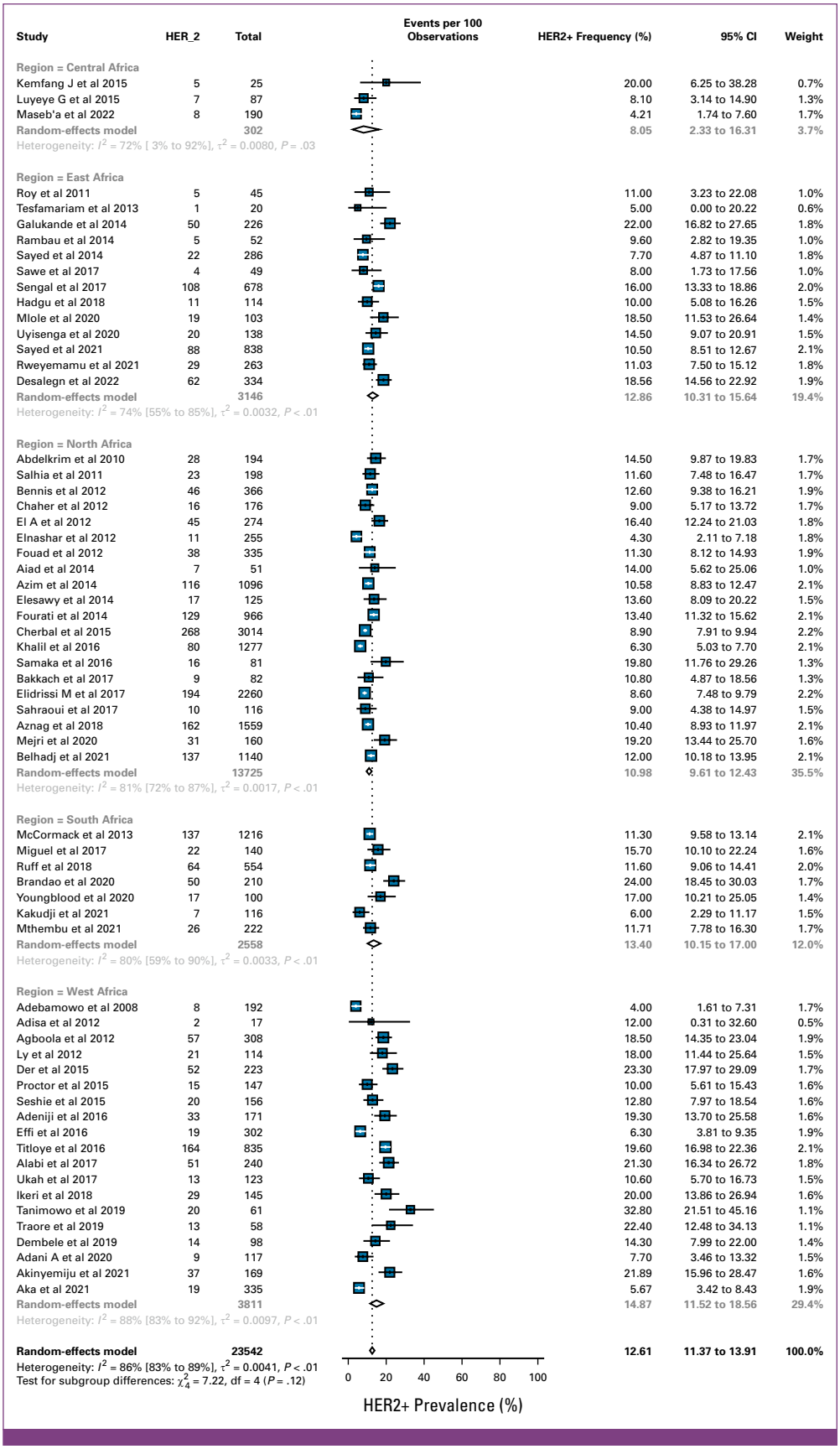

FIG 4. Pooled HER2+ frequency stratified by regions. HER2+, human epidermal growth factor receptor 2–positive.

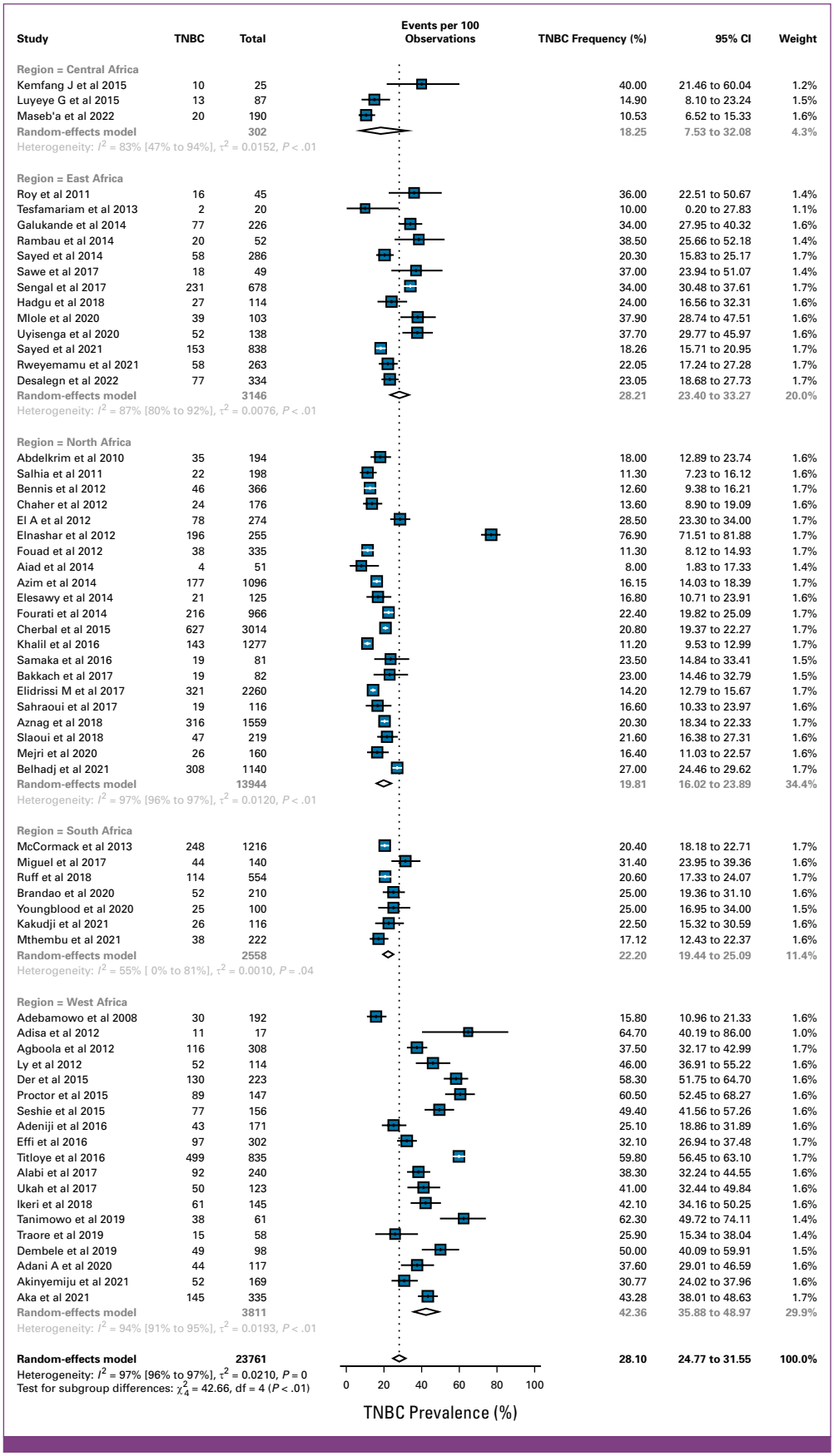

FIG 5. Pooled TNBC frequency stratified by regions. TNBC, triple-negative breast cancer.

(Data Supplement, Table S3), Kenya and South Africa showed high frequencies (68.44% and 67.65, respectively) of the luminal subtype. The luminal subtype is associated with a favorable prognosis and a lower risk of metastasis to distant organs.[33] This favorable biology may account for lower mortality in Kenya and South Africa compared with other countries in the 2020 GLOBOCAN data.[1] It is, however, important to note, as suggested by Hamidi et al,[34] that the low rate of mortality in Northern Africa is boosted by the more advanced screening, diagnostic, and treatment facilities available to countries in this region.

The reported frequency of HER2+ tumors was generally low in all African regions with an even distribution across all regions. This finding contrasts with observations among African American women who have been shown to have a higher risk of presenting with HER2+ BC.[15,35] Several factors contribute to this discrepancy, including under-reporting because of the high cost and unavailability of anti-HER2 agents, as well as the misclassification of HER2 status because of the limited use of FISH to confirm equivocal IHC scores.[36-38] Adani-Ifè et al[39] stressed the need for better facilities in Togo as most HER2 tests were obtained using the American Society for Oncology scoring rather than using FISH. Additionally, a review of 20 cancer registries in sub-Saharan African (SSA) countries revealed that only eight centers provided HER2 testing.[40] Similarly, Olasehinde et al[41] studied an institutional database in Nigeria and found that HER2 testing was performed through staining as facilities for FISH were unavailable. These observations corroborate our finding that only four of the publications reviewed for this article used FISH. These findings underscore the need for capacity and infrastructure development across Africa for proper subtyping of BC, thereby identifying women who can benefit from targeted treatment with anti-HER2/neu agents.

The overall pooled TNBC frequency was 28.10% with regional variations. West Africa had the highest frequency (42.36%) compared with other regions (18.25%-28.21%). These results agree with previous findings of high TNBC prevalence in West Africa.[2,25,42] Pooling by individual countries showed that Ghana, Mali, and Nigeria had the highest cases of TNBC with 56.17%, 47.85%, and 40.32%, respectively. These results are consistent with previous findings of a higher prevalence of TNBC in West Africa, which may account for worse outcomes of BC in this region.[2,25,42] Newman et al[43] found higher TNBC in Ghanaian and African American women than the Whites and noticed a correlation between West African ancestry and the risk of developing the TNBC subtype.

The lack of IHC monitoring is a common challenge in most African countries. A review of 20 registries in SSA showed that only about half of these centers had standby laboratories for IHC testing. Additionally, three of these centers had to rely on obtaining IHC results from other countries, while one center could not obtain IHC results at all.[40] Furthermore, a review of records from an institutional database in Nigeria showed that of 607 patients diagnosed with BC between 2010 and 2018, only 131 patients had undergone IHC tests.[41] Similarly, in some countries such as Ethiopia and Guinea, IHC is not carried out because of the unavailability of facilities.[44] A study conducted by Traoré et al[45] in Guinea revealed that out of 569 breast tumors diagnosed between 2007 and 2016, IHC testing was only carried out on 56 of these cases. In a study that combined data from five SSA countries (Namibia, Nigeria, Uganda, South Africa, and Zambia), it was found that IHC testing is a routined point of care in Namibia and South Africa. However, in Uganda, Nigeria, and Zambia, IHC monitoring is not a standard point of care and when required, it is organized out of pocket. As a consequence, evidence-based decisions are not routinely made for patients with BC in many African countries.[46]

A significant limitation encountered when attempting to stratify the Lum A and B subtypes for this scoping review lies in the inconsistency of biomarkers across various research papers. This necessitated the combination of Lum A and Lum B as luminal for this scoping review.

Overall, our data further support the existing evidence of great variability among the African population. This underscores the need for a genetic and evidence-based approach in stratifying African populations in the studies designed to understand the genetic drivers of disparities in BC burden.[47,48] A huge disparity exists in BC care and management between developed countries and countries in Africa.

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DATA SHARING STATEMENT

All data used in the analysis are available on request. All relevant data to the study have been included in the article or uploaded as supplementary information.

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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

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

Solomon O. Rotimi
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