DOWNSTAGING BREAST CANCER IN SUB-SAHARAN AFRICA: A REALISTIC TARGET?

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Most breast cancer patients in high-income countries have a good prognosis. However, patients in sub-Saharan Africa (SSA) have poor prognosis largely because of advanced stage at presentation. Current evidence is consistent with the poor breast cancer survival in SSA being largely driven by long delays to diagnosis rather than a higher prevalence of aggressive disease subtypes, indicating that downstaging may be a viable and effective approach to reducing mortality from the disease in the region.

A diagnosis of breast cancer in most high-income countries has extremely good prognosis in the vast majority of women *(1)*, but in many sub-Saharan African (SSA) countries its prognosis is extremely poor *(2–4)*. In most settings at least 25% of women die within two years of diagnosis *(3–5)*. The need to improve survival rates in affected SSA women is unquestionable, but strategies require sound epidemiologic evidence on fundamental features of this cancer, particularly in relation to the well-established heterogeneity of this tumour. Breast cancer comprises several subtypes – the potential to diagnose early will largely depend on the predominant subtypes present.

Herein, we highlight key features of the epidemiology of breast cancer in SSA. We then address the question of whether downstaging (Box), as an essential component of early curative treatment, is a realistic target, by first examining the dominant subtypes in SSA, the challenges in determining them and whether they and/or other factors influence advanced disease stage at diagnosis. These "fundamentals" of breast cancer in SSA would shed light on the potential to improve survival, and lead to today's pertinent question of how to achieve this within resource-limited settings. Throughout, we acknowledge the diversity of SSA populations, culturally, spatially and in access to healthcare.

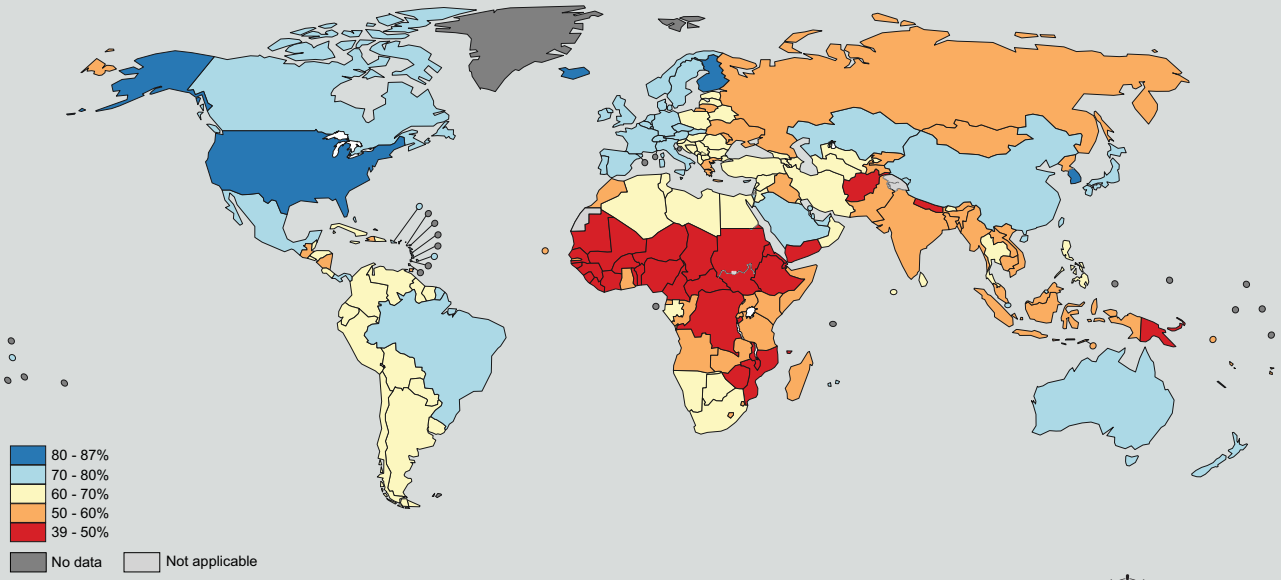
Box: Downstaging symptomatic disease versus screening for asymptomatic disease

- Downstaging, also known as downwards stage migration, refers to the process of ensuring that symptomatic women, i.e. those with a palpable cancer or other clinically-detectable symptom, are diagnosed with earlier, and potentially curable, breast cancer rather than later, mainly incurable, disease.
- Screening aims to detect pre-clinical cancer lesions in asymptomatic women, i.e. women who have no clinically-detectable disease, through the use of mammography, often in combination with other imaging modalities (e.g. ultrasound).

Breast cancer burden in SSA

Like in many other parts of the world, breast cancer is the most common cancer in women in SSA *(6)*. However, in contrast to high-income countries, where in 2012 there was on average one breast cancer death for every four women newly-diagnosed with breast cancer, in SSA this ratio was one breast cancer death for every two new diagnoses, reflecting the poor survival from this disease in the region (Figure 1). In that year 48,000 SSA women died from breast cancer and 94,000 women were diagnosed with breast cancer *(6)*. Future projections of incidence and mortality of breast cancer will depend greatly on SSA's demographic transitions. After retractions at the height of the HIV/AIDS epidemic, today SSA's population growth rates and life-expectancy are increasing at the fastest rates in the world *(7)*. As a consequence, at 2012 age-specific mortality

Figure 1: Five-year breast cancer survival worldwide and in Africa as estimated by its proxy (1- mortality/incidence)



rates, a projected 81,000 breast cancer deaths, that is 11% of global breast cancer deaths will occur in SSA in 2030 *(6)*. This death toll may be higher if there are, as are expected from fertility and lifestyle-related changes, increases in age-specific breast cancer incidence rates, but deaths could be avoided if survival rates are improved.

The SSA-wide picture has considerable between-setting differences. In 2012, estimated incidence rates were highest in South Africa, Mauritius and Nigeria and were at least two-times lower in countries such as Swaziland, The Gambia and Guinea *(6)*. Estimates of incidence time trends are scarce, but the few available – e.g. from Uganda, Malawi and South Africa – show ~5% increases in rates per year *(8–10)*. Poor health information systems have also hindered survival studies. Losses to follow-up of over 40% at three years are common, and this yields very unreliable 5-year survival estimates. For instance, 5-year survival estimates from Ethiopia have ranged from 27% to 46% *(3)*. Nevertheless, five-year survival, as estimated by 1-mortality/incidence *(11)*, also displays regional variations: estimates are higher in Southern Africa than in some Western African populations (Figure 1).

Is breast cancer in SSA a more aggressive disease?

It is often stated that breast cancer in SSA is a more aggressive disease than elsewhere. This perception stems from two main observations. Firstly, the average age at breast cancer diagnosis is ~10 years younger in SSA than in western countries (~50 years in SSA *(6)* vs. 63 years in the United States *(6, 12)*). *This* has been interpreted by some as an indication that the disease in SSA is a more aggressive fast-growing one and of a different fundamental etiological origin. However, as breast cancer incidence rates in young, as in older, age-groups are actually lower in SSA than in high-income countries *(6)*, the shift towards an earlier age at diagnosis is likely to simply reflect the much younger population of the region (~89.4% women in SSA were aged <50 years in 2017 vs. ~57.9% in more developed regions of the world *(13)*). In other words, a larger proportion of breast cancers occur at young pre-menopausal ages in SSA because women in these age-groups represent a larger proportion of the population in that region. Second, most breast cancers in SSA are diagnosed at advanced stages. This then leads to poorer outcomes as treatment options are more limited and less effective. Half of the studies included in a recent systematic review *(14)* reported that 70% or more of breast cancer patients were diagnosed at an advanced stage (TNM stages III and IV *(15)*), and although advanced stage may indicate the predominance of a more biologically aggressive form of disease, it may also be a consequence of long delays between onset of symptoms and diagnosis. These two possibilities are discussed below.

Breast cancer subtypes are usually identified in the clinical setting by immuno-histochemistry (IHC), which stains cancer cells according to the presence of estrogen (ER), progesterone (PR) and human epidermal growth factor-2 (HER2) receptors. ER-positive (ER+) cancers depend on oestrogen for their growth, so they can be treated with drugs to reduce either the effect of this hormone (e.g. tamoxifen) or its levels (e.g. aromatase inhibitors), and usually have a better prognosis *(16)*. Women with HER2-positive (HER2+) cancers have a worse prognosis, but they respond to immunotherapy (i.e.

trastuzumab) in combination with chemotherapy *(16)*. Cancers with no positive ER, PR or HER2 receptors, the so-called "triple negative" cancers, are some of the most aggressive forms of the disease for which there are no targeted treatments *(16)*.

The relative proportions of breast cancer subtypes in SSA are central to the potential for, and strategies needed, to reduce breast cancer deaths in the region. Subtypes differ by environmental and lifestyle risk factors *(17)*, in the contribution of inherited genetic mutations *(18)*, in tumour growth rates pre-diagnosis – the speed of which determines the time window for down-staging – and, post-diagnosis, in disease aggressiveness and prognosis *(19)*, and the choice and costs of targeted treatment modalities *(16)*. If the predominant tumours are aggressive subtypes, the time window for downstaging (i.e. for early diagnosis of symptomatic disease; Box 1) would be short. On the other hand, if the predominant tumours are less aggressive subtypes, the window of opportunity for downstaging may be wider allowing for interventions to accelerate presentation and diagnosis, allowing earlier treatment that may cure the patient or significantly improve quality of life where cure is not possible.

ER+ subtypes account for ~80% of all breast cancers among White women (i.e. those of European ancestry) in the United States, but for a smaller proportion (~65%) among United States Black women *(20)*. In SSA, some studies, albeit not all, have reported lower proportions of ER+ disease *(21)*. These somewhat alarming results from small studies are often quoted, but, as outlined below, the overall picture differs. The reliability of ER testing is highly dependent on the quality of the procedures used for tissue sample collection, fixation, and receptor testing. Poor quality procedures (e.g. delays in processing tissue samples, inadequate fixation and dehydration procedures) lead to false ER-negative results. A recent systematic review *(21)* found marked between-study heterogeneity in the reported proportion of ER+ tumours in the region, with studies based on suboptimal procedures (e.g. archival tissue blocks) yielding lower ER+ frequency estimates whilst those based on better-quality (e.g. prospectively-collected) samples showing that two-thirds of breast cancers in SSA Black women were ER+, a frequency similar to that found among United States Black women. Further, in South Africa, from a nationwide study with receptor testing conducted under the same conditions and in the same laboratories, Black women had only a small excess of ER- disease; percentage of ER- disease was 34% compared to 25% in White women *(22)*. Whilst this difference is important, and needs to be understood, the overlap of subtypes between the groups is notably large: 90% of Black patients have the same breast cancer subtype as their White counterparts.

The systematic review mentioned above *(21)* highlighted the paucity of data on breast cancer subtypes in SSA, cautioning against any generalizations. High-quality procedures for tissue sample collection, processing and receptor testing, are needed for the histological diagnosis and receptor subtyping of breast cancer in SSA. These are already available in Southern Africa, but in Western and Eastern Africa only once this resource is widely available will it be possible to accurately determine the receptor-defined subtype distribution in SSA, and whether it varies across the region. Nevertheless, despite current uncertainties, the existing evidence points to the subtype distribution in many SSA settings not being greatly different from that seen in high-income countries, with most disease being ER+ and, hence likely to be less aggressive, with a long window for downstaging interventions, and potential curability.

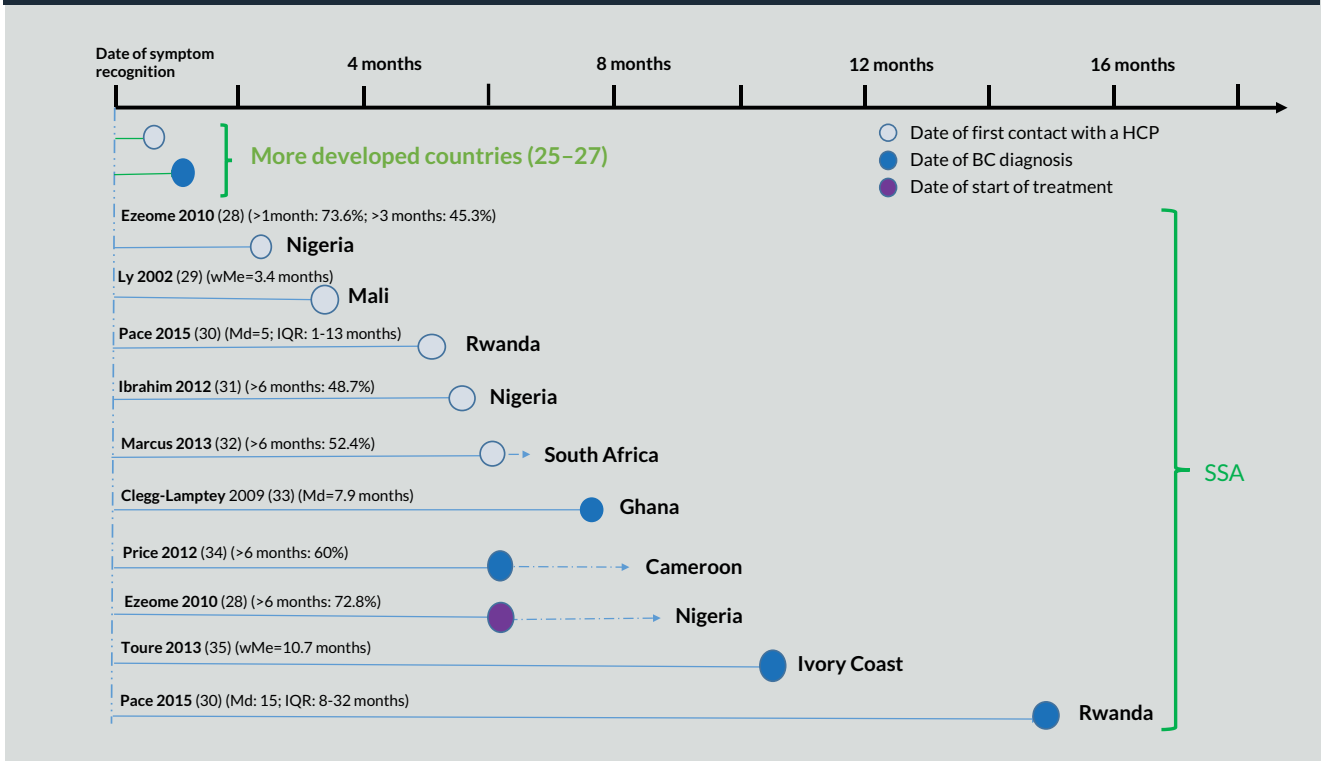
Delays to diagnosis

Time to diagnosis of breast cancer comprises several components. A simplistic partition of this timeline starts at the (unobservable) time from clinical onset of symptoms, i.e. time when lesions become symptomatic and therefore clinically detectable, to their recognition by the woman; the time from symptom recognition to her first contact with a healthcare provider; and the time from first contact with a provider to a definitive diagnosis of breast cancer *(23)*. There is strong evidence that a delay from symptom recognition to diagnosis of more than three months is associated with later stage at presentation and poorer survival *(24)*. In high-income countries, the time interval from symptom recognition to a diagnosis is often less than 30 days *(25–27)*. In contrast, in SSA, these delays are often greater than 6 months *(28–35)* (Figure 2). These long delays are consistent with breast cancers in SSA comprising predominantly slow-growing, less aggressive, ER+ subtypes. Most SSA studies reported average tumour sizes between 4 to 8 cm *(14)*. Tumour growth models *(36)* predict that it would take ~12 and ~22 months for a tumour of 2 cm, the average size when a tumour becomes palpable, to grow to 4 cm and 6 cm respectively (Figure 3). These models are for other populations; nevertheless, their estimates provide a rough indication of the likely duration of the time window for downstaging the disease. Furthermore, reported delay times from SSA studies in Figure 2 are not widely different from model-expected times. This thus suggests a considerable time window representing a realistic opportunity to ensure women receive an earlier diagnosis of palpable disease.

Challenges to early breast cancer diagnosis and treatment

Several studies have shown that early stage breast cancer in SSA *(3–5)*, as elsewhere *(37)*, is associated with better survival

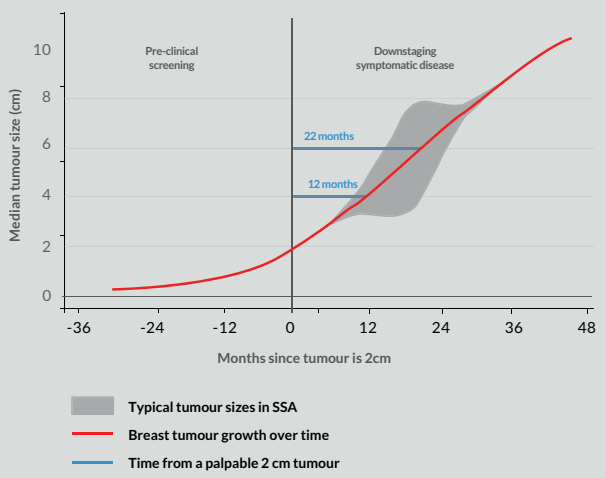
Figure 2: Reported delays in the presentation, diagnosis and treatment of breast cancer in sub-Saharan Africa (modified from Espina et al. *(53)*) and, for comparison, in more developed countries. (IQR: inter-quartile range; Md: median; Me: mean: wMe: weighted mean. A dashed line indicates that the estimate from the original publication shown here is likely to be an underestimation of the true average delay)



than late stage disease, consistent with early diagnosis and treatment leading to reductions in mortality from this disease.

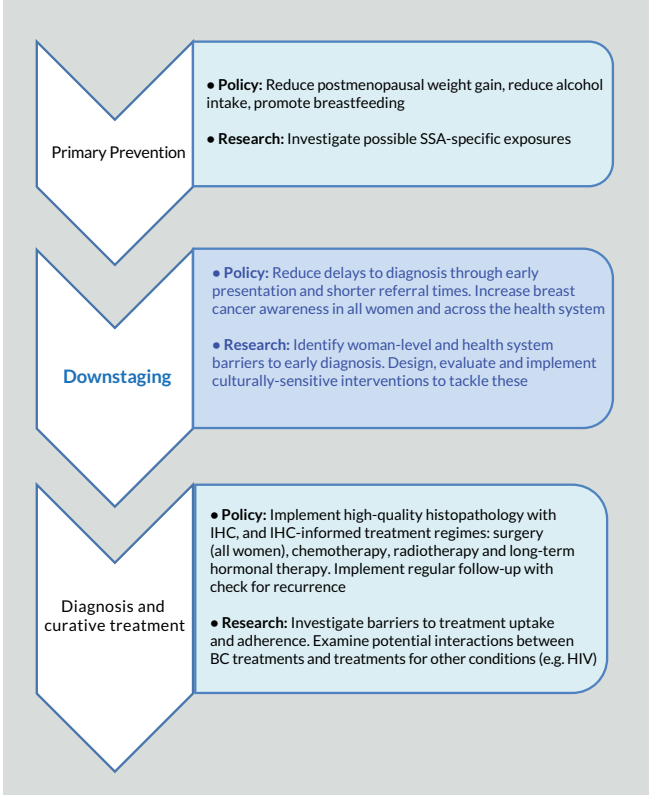
Downstaging of symptomatic breast cancer, rather than screening of asymptomatic women, should be the priority in the region. Mammography screening is advocated for early breast cancer diagnosis in settings where breast cancer stage at diagnosis distributions reflect short intervals between a clinically-detectable symptom (e.g. a palpable lump) and breast cancer diagnosis, and where health systems can support wide-scale screening. Several reasons argue against this approach in SSA settings. Firstly, as the incidence of breast cancer in SSA is lower than in high-income countries, the yield of a screening programme will be low, that is, a large number of women would need to be screened to detect a true case of breast cancer thus shifting the balance between its benefits and harms towards the latter, and reducing its cost-effectiveness. Secondly, the aim of screening is to detect asymptomatic tumours before they give rise to symptoms or become palpable (Box 1); however, substantial delays to diagnosis in SSA occur after a tumour is palpable and, hence, clinically detectable (Figure 2). Thirdly, the implementation and running of a screening programme requires considerable levels of funding, administrative capability as well as infrastructure and technical resources; these are simply not available in low-resource settings such as those in SSA. Fourthly, screening can reduce breast cancer mortality only if women with suspicious

Figure 3: Average modelled breast tumour growth curves in western populations. The long delay times to diagnosis (Figure 2) and the large tumour sizes seen in SSA are not inconsistent with this model



screen-detected lesions, many of which will not be malignant breast cancer, have timely access to appropriate diagnosis and treatment. The addition of women with suspicious screen-detected lesions to those with symptomatic disease would place significant additional burden on already over-stretched healthcare systems in the region. It is worth noting that even in countries with a population-based mammographic screening programme, which has reached a high coverage, the majority of breast cancer patients present symptomatically (e.g. only 32% of all breast cancers in the United Kingdom in 2007 were

Figure 4: Breast cancer control in sub-Saharan Africa: policy recommendations and research priorities (BC: breast cancer; HIV: human immunodeficiency virus; IHC: immuno-histochemistry; SSA: sub-Saharan Africa



screen-detected; 56% among those in the target age-group 50–69 years *(38)*). There is currently no conclusive evidence that screening asymptomatic women with low-technology approaches such as breast self-examination (BSE) or clinical breast examination (CBE) leads to reductions in breast cancer mortality mortality *(39)*, albeit CBE may be useful for downstaging symptomatic disease (as discussed below).

How can downstaging be achieved? The Breast Health Global Initiative and the Breast Cancer Initiative 2.5 recommend a stratified approach, with a phased implementation, for low-resource settings *(40, 41)*. The first phase should focus on tackling health-system related barriers to early diagnosis of symptomatic breast cancer through, the provision of adequate training to healthcare professionals, development of standardized diagnostic and treatment guidelines and protocols as well as implementation of clear patient navigation pathways to ensure faster referral to tertiary care services. Initiatives to increase breast cancer awareness in the population should be promoted in addition to ensuring that the health system will be able to cope with the increasing demand in diagnostic capability that they will generate. Studies in rural Sudan *(42)* and Tanzania *(43)*, as in India *(44)*, have shown that breast cancer awareness campaigns coupled with CBE (performed by trained non-medical volunteers) are effective in downstaging the disease in these settings where the majority of women present with advanced disease. Given that no conclusive evidence currently exists, a pertinent question is whether such downstaging will translate into mortality reductions. Some of these ongoing studies will be able to provide an answer to this question in the near future.

Early diagnosis must be coupled with early treatment if reductions in mortality are to be achieved. As no single subtype is rare in SSA, making IHC routinely available should be a priority unless robust local evidence suggests otherwise. In SSA settings where IHC testing is not available it may be reasonable to assume, on the basis of current evidence, that the majority of patients would benefit from anti-hormonal treatments particularly as they are low cost, easy to administer and have few side effects.

Research priorities for downstaging breast cancer

Research priorities for downstaging need to be established within a broader framework for breast cancer control in SSA (Figure 4). Appropriate recognition of breast cancer symptoms, improved access to health facilities and timely diagnosis of symptomatic patients are essential to downstage breast cancer in SSA. Understanding the influence of the factors that influence a woman's journey to breast cancer diagnosis and treatment is vital to the development of effective interventions. Studies in SSA *(45–47)* have found that delays to diagnosis are associated with a combination of woman-level (e.g. low educational level, poor socioeconomic status, living in a rural area, poor breast cancer awareness, belief in traditional or spiritual medicine) and health system-related factors (e.g. distance to nearest healthcare provider, number of healthcare providers visited prior to diagnosis, health professionals with poor breast cancer knowledge, unavailability of suitable diagnostic facilities, lack of appropriate referral pathways). However, the relative importance of these factors is likely to vary from setting to setting as a result of differences in sociocultural norms, economic development and healthcare systems. This is currently being investigated in the multi-country African Breast Cancer – Disparities in Outcomes (ABC-DO) study, a study on the determinants of breast cancer survival in five SSA countries (Namibia, Nigeria, South Africa, Uganda and Zambia) *(48)*. Findings from this study, which will become available within the next two years, will provide a first indication of the extent to which woman-level and health system barriers to early diagnosis differ across settings in the region, as well as of their impact on stage at diagnosis and survival, and will provide the necessary evidence-base to design appropriate interventions for downstaging breast cancer. Such interventions will need to be properly evaluated not only in terms of their effectiveness in reducing stage at breast cancer diagnosis but, crucially, also on whether they

will ultimately translate into reductions in mortality from the disease.

For downstaging to reduce mortality from breast cancer it needs to be coupled with early treatment. Research on the factors that influence timely access to appropriate treatment regimens, and their uptake and adherence *(49–52)*, is crucial. Accurate determination of the distribution of receptor-defined subtypes of breast cancer across the region should be regarded as a priority. Ideally, high-quality IHC should be available in clinical settings as part of the routine management of breast cancer patients to inform treatment choices but achieving this would not be trivial (e.g. need for well-equipped pathological laboratories, adequately trained technicians and pathologists). In the absence of this, large multi-country studies based on a common high-quality control protocol, which properly addresses the analytical issues which have plagued previous IHC studies, will help to assess the extent to which there is heterogeneity across the region (e.g. by sub-region, ethnicity) and would provide the necessary evidence-base to monitor trends in the subtype distribution as women adopt more westernisced risk profiles (e.g. smaller family sizes, high BMI).

Finally, setting up and maintaining high-quality health information systems is essential for measuring the breast cancer burden in the population, monitoring future trends, and for proper evaluation of interventions that are rolled out into the community. Recent technological developments (e.g. in m-health) may help to achieve this in low-resource settings, particularly for patient follow-up which has been notoriously difficult to implement in SSA settings. ■

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