Chapter 6
Breast Cancer in Sub-Saharan Africa

Matthew Evans and Abeer M. Shaaban

Abstract Breast cancer is poised to become one of the biggest public health concerns in Sub-Saharan Africa by the mid-twenty-first century. Three factors conspire to propel breast cancer to the forefront of disease burden in the region. Firstly, as Sub-Saharan African demographics rapidly come to resemble those of Western societies, rates of the disease are set to surge in the coming decades. Secondly, there is evidence that breast cancer in Sub-Saharan African women is a distinct – and overall more aggressive – disease than that seen in the West, with higher rates of adverse histological and molecular features and poor outcome. Finally, on top of the above, is the irony that the very societies being presented with these challenges are those least able to confront them effectively: with little health infrastructure and poor levels of public health awareness. Here, we provide an overview of the epidemiology, molecular biology and challenges of breast cancer diagnosis and management in Sub-Saharan Africa. This should not, however, be cause for resignation. Examples abound of practical initiatives in Sub-Saharan Africa which have driven monumental improvements in outcomes for breast cancer patients. Furthermore, increasing interest in the biology of this unique disease has already begun to deliver palpable benefits to its sufferers, and has the potential to overcome the challenges which it poses.

Keywords Breast cancer • Sub-Saharan Africa • Diagnosis • Oestrogen receptor • HER2

6.1 Introduction

Breast cancer is an increasingly important health problem in Sub-Saharan Africa (SSA). While the continent was formerly dominated by cervical cancer and Kaposi's sarcoma, improvements in anti-retroviral therapy and increasing life expectancy

M. Evans, MA, KS, AKC • A.M. Shaaban, MBBCh, PhD, FRCPath, Dip Health Res (✉)
Department of Histopathology and Cancer Siences, Queen Elizabeth Hospital Birmingham and University of Birmingham, Birmingham, UK
e-mail: Matthew.Evans@uhb.nhs.wwuk; Abeer.Shaaban@uhb.nhs.uk

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have caused breast cancer to become the second commonest cause of cancer death in Africa (Jemal et al. 2012; Chokunonga et al. 2013). Rates have almost doubled in Uganda over the last 20 years, and 20% increases have been reported in Gambia and Mali (Jemal et al. 2012; Sighoko et al. 2013).

6.2 Epidemiology

Due to a paucity of cancer registry coverage across SSA only estimates of cancer prevalence are available. GLOBOCAN 2012 estimates an age-standardised rate of 33.8 per 100,000, which only narrowly falls short of the 34.8 cervical cancer cases (Ferlay et al. 2013). On current trends, the incidence of breast cancer in SSA is projected to double by 2035 (Fig. 6.1).

By international standards, breast cancer in SSA is not common (Chokunonga et al. 2013; Rambau et al. 2011), with an incidence approximately one quarter that of the US (Fig. 6.2), (Huo et al. 2009). This difference may be at least partly racially-driven: it has been shown that white South Africans have a rate of breast cancer more than six times that of their black counterparts (Vorobiof et al. 2001), and similar findings have been reported in the US (Stark et al. 2010; Fregene and Newman 2005; Adebamowo et al. 2008). In both societies, though, the effects of socioeconomic inequality are difficult to disentangle.

SSA breast cancer may be more aggressive than in the West. It is notable that, despite dramatic differences in incidence, the mortality rates from breast cancer are very similar in the US and SSA (Fig. 6.3), (Huo et al. 2009). Moreover, higher mortality rates have been reported in US African-Americans, compared to Caucasians (Stark et al. 2010; Fregene and Newman 2005). The aggressive inflammatory breast cancer has also been reported to be more common in African women (McCormack et al. 2013).

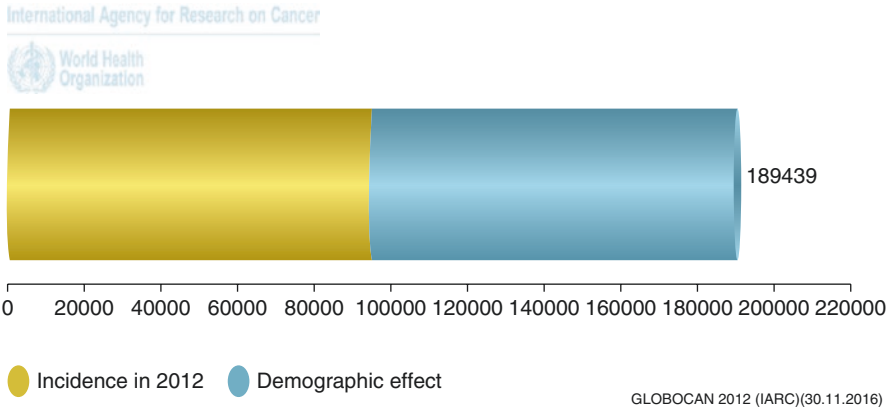

Fig. 6.1 Current incidence and projected number of new cancer in sub-Saharan Africa by 2035 (Ferlay et al. 2013)

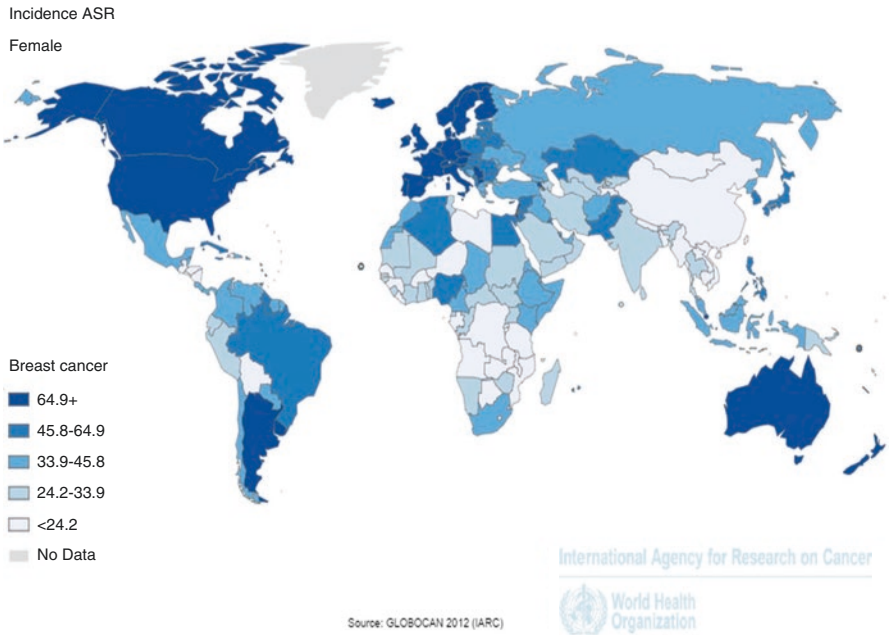

Fig. 6.2 Low incidence of breast cancer in sub-Saharan Africa (Ferlay et al. 2013)

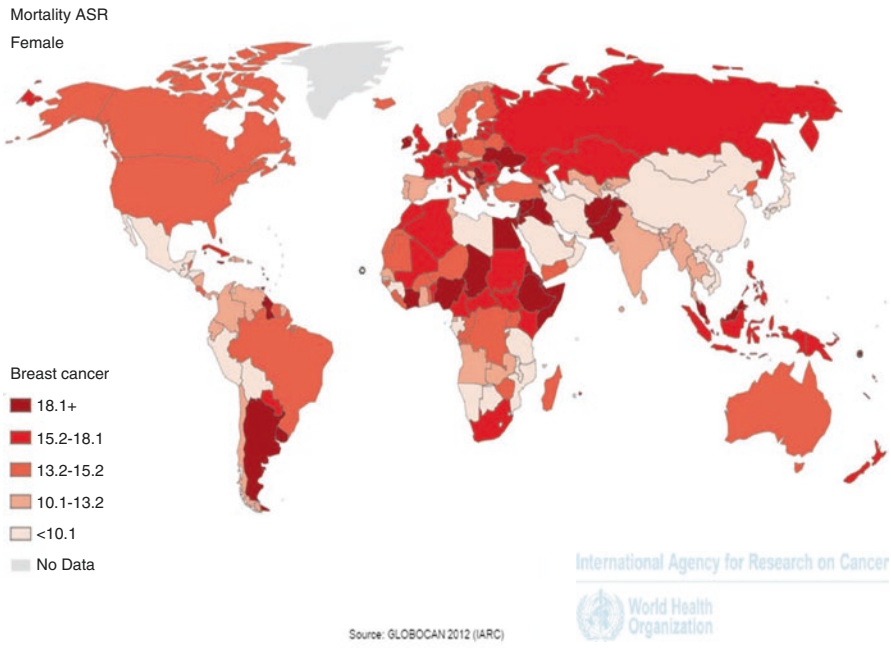

Fig. 6.3 High rates of breast cancer mortality in sub-Saharan Africa (Ferlay et al. 2013)

The mean age of SSA women with breast cancer has consistently been shown to be approximately 10–15 years lower than their European and Northern American counterparts (Rambau et al. 2011), with the disease affecting predominantly pre-menopausal women in much of the region (Sighoko et al. 2013; Chokunonga et al. 2013; Titloye et al. 2016). Evidence that this is racially-driven derives from studies of African-American women, who also develop breast cancer at a younger age than Caucasians (Fregene and Newman 2005; Stark et al. 2010). However, many investigators have suggested that this phenomenon is simply a reflection of the fact that few women in SSA live beyond their sixth decade, artificially reducing the mean age of women afflicted by breast cancer (Gukas et al. 2005; Akarolo-Anthony et al. 2010). Interestingly, with rapid increases in life expectancy across SSA, it has been noted that most of the rising incidence of the disease is being driven by increased rates in older women (Parkin et al. 2009; Chokunonga et al. 2013; Akarolo-Anthony et al. 2010); if these trends continue, it is plausible that the demographics of breast cancer in SSA will come to resemble those of Western societies.

Although data are scarce, it is worth recognising that rates of male breast cancer in SSA have consistently been shown to be significantly higher than in Western societies. Studies in Ghana, Nigeria, Tanzania and Uganda have identified rates of 2.4–8.6% (Akosa et al. 2005; Gakwaya et al. 2008; Kidmas et al. 2005), compared to less than 1% in Caucasian populations (Speirs and Shaaban 2009).

6.3 Risk Factors

It is widely-accepted that breast cancer risk is correlated with lifetime exposure to oestrogen; thus, the traditional reproductive patterns of women in SSA – late menarche, multiple pregnancies from an early age, and exclusive breastfeeding for more than a year – may have been responsible for the historically low incidence of the disease (Okobia et al. 2006b). Many investigators have demonstrated that breast cancer in SSA is associated with delayed first pregnancy, reduced numbers of pregnancies, and reduced duration of breastfeeding (Akarolo-Anthony et al. 2010; Parkin et al. 2009; Chokunonga et al. 2013; Huo et al. 2008; Okobia et al. 2006b; Adebamowo et al. 2002). Interestingly, some studies have shown that early first pregnancy is paradoxically associated with increased cancer risk in pre-menopausal SSA women. This has been explained by the fact that there is a known, transient increase in breast cancer risk following pregnancy (Sighoko et al. 2013; Jordan et al. 2013); historically, interparous intervals in SSA have been short and women have not survived long after menopause, meaning that they suffer from the increased post-parous cancer risk without ever benefiting from the long-term protective effect – this may contribute to the low mean age of breast cancer in SSA (Huo et al. 2008; Okobia et al. 2006b). It is to be noted that the protective effect of pregnancy and breast feeding relates to oestrogen receptor positive breast cancer and has no

effect on reducing the likelihood of hormone receptor negative breast cancer (Phipps et al. 2011).

Given rapid improvements in nutrition in the region, anthropometric risk factors have been examined with increasing interest. Contradictory findings have been reported in relation to the relationship between breast cancer and obesity in SSA (Chokunonga et al. 2013; Adebamowo et al. 2002). A possible reason for this is that patients often present with advanced disease, commonly associated with cachexia, rendering cause and effect difficult to disentangle (Brinton et al. 2014; Okobia et al. 2006b). Other researchers have found that high hip-to-waist ratios are more strongly correlated with an increased risk of breast cancer (Okobia et al. 2006b) and, importantly, that this effect is seen both in early- and late-stage cancers (Adebamowo et al. 2002).

Interestingly, it has been proposed that a high BMI in early life is associated with a subsequent increased breast cancer risk (Jordan et al. 2013) and several studies have identified a positive relationship between height and breast cancer risk (Adebamowo et al. 2002). Adult height is strongly related to nutritional status in childhood which is, itself, related to age of menarche. As nutrition improves in SSA, the age of menarche has fallen and this has been associated with increased cancer risk (Akarolo-Anthony et al. 2010; Parkin et al. 2009; Huo et al. 2008; Adebamowo et al. 2008).

6.4 Clinical and Pathological Features

Almost without exception, studies have shown that the breast cancers of SSA women are larger and more advanced than those in their Western counterparts. Mean tumour size has been reported to be 3–7 cm (Brinton et al. 2014; Rambau et al. 2011; Stark et al. 2010; Titloye et al. 2016), and 53–91% of patients have presented at stage III or IV (Brinton et al. 2014; Kantelhardt et al. 2014; Rambau et al. 2011). Investigators have reported 70–92% of patients having lymph node metastases at presentation (Ikpatt et al. 2002a; Rambau et al. 2011; Brinton et al. 2014), 39–46% of women having fungating cancers (Clegg-Lamptey and Hodasi 2007; Adesunkanmi et al. 2006) and 13% having distant metastases (Adesunkanmi et al. 2006).

Of course, that this truly reflects a greater degree of biological aggressiveness cannot necessarily be assumed; relatively poor access to quality diagnostics and treatment undoubtedly allows tumours to progress by the time of presentation. Two early findings, however, lend some weight to the suggestion that SSA breast cancer is indeed intrinsically more aggressive: that 81% of women even with a less than 3 month symptom history had stage III or IV disease at presentation (Hassan et al. 1992), and that 77.7% black South African women presented with stage III or IV disease compared to 30.7% of their white counterparts (Vorobiof et al. 2001).

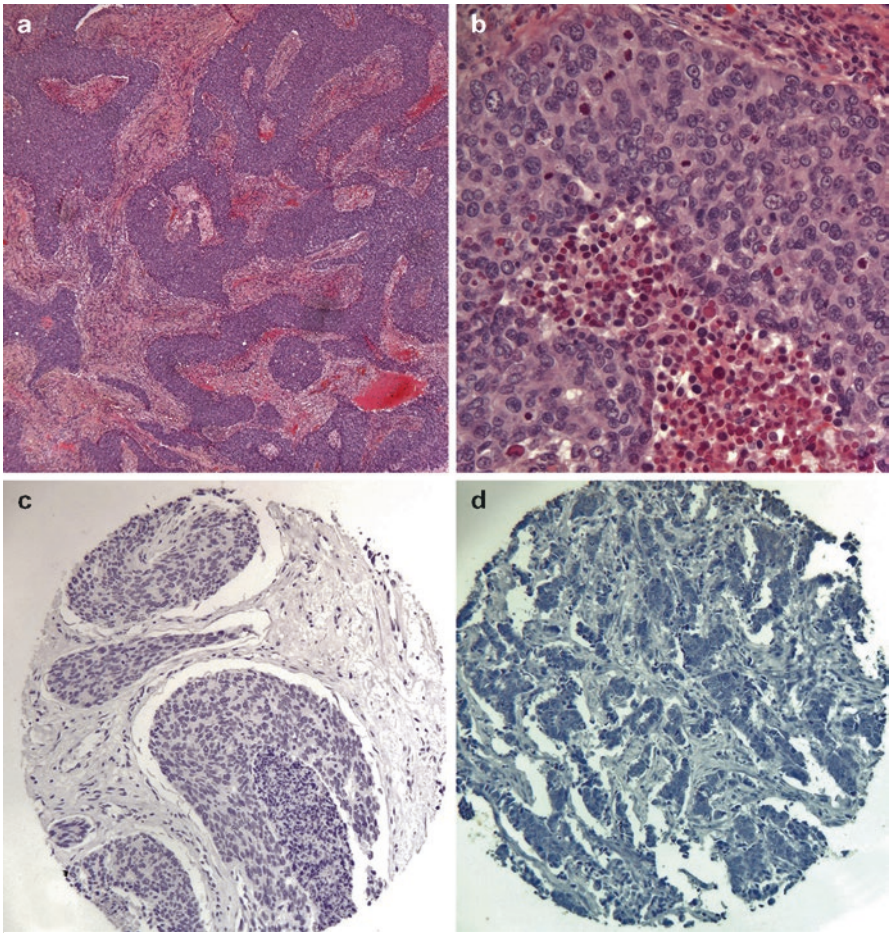

Fig. 6.4 Typical morphological and immunohistochemical features of sub-Sarahran breast cancer. (**a**) Low-power appearance of a typical high-grade tumour showing a syncytial growth pattern. (**b**) High-power appearance showing large pleomorphic nuclei with conspicuous mitoses and stromal chronic inflammation. (**c**) Tissue microarray showing oestrogen receptor (ER) negativity. (**d**) Tissue microarray showing HER2 negativity

From a pathological perspective, grade 3 cancers constitute the majority of tumours in most series (Brinton et al. 2014), (Fig. 6.4a, b). Studies examining histological types of breast cancer have presented complex, often contradictory results, owing perhaps to relatively small numbers of cases. In all studies, ductal carcinoma of no special type (NST) has been the most common subtype, accounting for up to 92.7% of cases (Gukas et al. 2005). It is difficult to comment on the incidence of more uncommon subtypes, but a fairly consistent feature in the literature is the underrepresentation of lobular carcinoma, making up only 0–5.2% of cases (Ikpatt et al. 2002b; Kantelhardt et al. 2014; Adebamowo et al. 2008; Rambau et al. 2011;

Clegg-Lamptey and Hodasi 2007; Titloye et al. 2016); it has been suggested that this reflects the fact that lobular carcinoma is generally a disease of older women who are less represented in SSA cohorts (Gukas et al. 2005). Given the lack of mammographic screening, it is unsurprising that isolated DCIS diagnoses are rare in SSA (Rambau et al. 2011; Bird et al. 2008).

6.5 Molecular Biology

Improved understanding of the molecular biology of breast cancer, and the relationship of molecular markers with biological behaviour, has led to a conception of breast cancer as a constellation of related but distinct diseases. Breast cancer has been classified into five taxonomic subtypes (Perou et al. 2000) which are related to protein expression on immunohistochemistry, based on hormone receptor, HER2, proliferation index and basal marker expression. A summary of the prevalence of these molecular subtypes across various ethnic backgrounds is presented in Table 6.1.

The luminal subtype, which is characterised by ER and PR expression, is dominant in Caucasian populations, but is relatively uncommon in SSA (Bird et al. 2008; Stark et al. 2010; Gukas et al. 2005; Ikpatt et al. 2002b). Instead, SSA populations are dominated by triple-negative and HER2+ subgroups. However, it has been noted that techniques used to assess immunohistochemical status in older studies have been suboptimal: many rely on the use of archival material in which antigen degradation is well-recognised, use of large resection specimens rather than biopsy material is frequent, under- and over-fixation are both common, and robust internal quality control is often lacking (Adebamowo et al. 2008; Akarolo-Anthony et al. 2010; Brinton et al. 2014; McCormack et al. 2013). Ironically, recent studies which

Table 6.1 Summary of molecular profiles of breast cancer in the UK, sub-Saharan Africa and African-Americans in the US

Study	Galukande et al. (2014)		Titloye et al. (2016)	Adebamowo et al. (2008)	Galukande et al. (2014)	Ihemelandu et al. (2007)	
Location	UK	Nigeria	Nigeria	Nigeria	Uganda	USA	
Population	Not stated	Not stated	Black African	Not stated	Not stated	African Americans	
Age	32% ≤ 50 years	61% ≤ 50 years	85% ≤ 50 years	Not stated	Mean age 45 years	≤ 65 years old	< 35 years only
Luminal A	76	26	15	78	38	55	26
Luminal B	5	5	5	3	5	12	14
HER2	5	19	20	4	22	12	4
Triple-negative	10	38	60	16	34	21	57

have adhered meticulously to immunohistochemical protocols have continued to identify variable proportions of the different molecular profiles (Adebamowo et al. 2008; Huo et al. 2009; Titloye et al. 2016).

Possible explanations for these confusing findings have been proffered. Firstly, marked differences in molecular profiles have been reported across SSA, with ER negative cancer rates of 37% in the south and 65–75% in the east (Kantelhardt et al. 2014); thus, the locale of a particular study, and potentially the ethnic sub-groups/tribal origin included, may have a significant impact. Secondly, it is known that breast cancers in younger women are more likely to under-express ER and PR and to show HER2 amplification; given that SSA women with breast cancer are significantly younger than those in North America and Europe, it is perhaps as much for demographic as biological reasons that luminal subtypes appear to be so uncommon, compared to triple-negative and HER2+ groups (Galukande et al. 2014; McCormack et al. 2013). In addition, some studies include only a small number of patients rendering the results rather variable.

Despite all the above confounding factors, there is evidence to support the proposition that luminal subtypes are less common in SSA women compared with Caucasians. The largest study to date, examining 880 tumours, showed a predominance of the triple negative phenotype (Titloye et al. 2016), (Fig. 6.4c, d). Studies in South Africa (McCormack et al. 2013) and the US (Stark et al. 2010; Ihemelandu et al. 2007) have shown, even when matched for age and stage, that black women have lower hormone receptor expression rates than white women.

6.6 Diagnosis

There is no systematic mammographic screening system in SSA, and therefore patients present only in the symptomatic setting (Daramola et al. 2016). Breast self-examination is infrequently practiced (Clegg-Lamptey et al. 2009b; Okobia et al. 2006a), partly explaining the advanced nature of cancers at presentation.

Furthermore, numerous studies have identified a short mean interval of 10–15 months between symptom onset and cancer diagnosis (Pace et al. 2015; Clegg-Lamptey et al. 2009b; Brinton et al. 2014; De Ver Dye et al. 2011; Clegg-Lamptey and Hodasi 2007; Bird et al. 2008). There are many reasons for this. Surveys conducted across SSA have implicated lack of knowledge of the significance of symptoms, initial use of spiritual healing and herbs, fear of mastectomy, a belief that no effective treatment is available and stigmatism from the community (De Ver Dye et al. 2011; Clegg-Lamptey et al. 2009a). Systemic problems such as lack of medical staff, distance to medical centres, prohibitive costs of medical appointments, long delays in referrals, and failures on the part of medical staff to recognise the symptoms of cancer have also been identified (Pace et al. 2015; Gakwaya et al. 2008).

In much of SSA, extensive use is made of Fine Needle Aspiration Cytology (FNAC) in initial diagnosis of breast cancer (Clegg-Lamptey and Hodasi 2007); unlike core biopsies, this is a cheap, fast technique which requires relatively little

laboratory infrastructure and few specialist staff (Kingham et al. 2013). In addition to having high sensitivity for breast cancer diagnosis, the cytological material can also be used for hormone receptor assessment (Kantelhardt et al. 2014). Generally, biopsy is reserved for equivocal cases. FNAC however cannot differentiate between in-situ and invasive carcinoma and is less reliable for hormone receptor and HER2 assessment, and so only core biopsy is recommended for the primary diagnosis of breast cancer in Western countries (Ellis et al. 2016). Mammographic and ultrasound imaging are not typically used unless a mass is not palpable or breast-conserving surgery is likely. The remainder of the work-up typically involves a chest X-ray, liver function tests, liver ultrasound and bone scanning to detect distant metastases (Clegg-Lamptey and Hodasi 2007).

A review of breast cancer reporting practices in Nigeria revealed some shortcomings in the quality and completeness of histopathology reports (Daramola et al. 2016). Less than a third of reports indicated the histological type of cancer, and in just under half of these cases, the histological type was found to be inaccurate on review. Although most cancers were graded, many had been under-graded, with poor-quality fixation being partly responsible for the discrepancies. Only 40% of reports made any reference to lymph node status. Given that subsequent therapeutic decisions hinge on accurate histological information, improved training and quality assurance are required as a matter of urgency. In particular, attention to good fixation of fresh specimens, a simple, non-costly process, will improve the quality of histological sections and hence the accuracy of histological assessment.

6.7 Treatment

The mainstay of breast cancer treatment in SSA is surgery. Given that many of these tumours are large at presentation, this may be preceded by neoadjuvant chemotherapy (Clegg-Lamptey and Hodasi 2007; Kingham et al. 2013). Mastectomy is by far the most common form of surgery, making up approximately 80% of all procedures (Clegg-Lamptey et al. 2009a; Gakwaya et al. 2008; Clegg-Lamptey and Hodasi 2007). There are several reasons for this: the large cancers which typify the disease in SSA are generally not amenable to breast-conserving surgery (Clegg-Lamptey and Hodasi 2007); many of these operations are toilet mastectomies performed for palliative reasons; and poor availability of radiotherapy and pre-operative imaging leave mastectomy the only practicable option (Kingham et al. 2013). Indeed, it has been acknowledged that the rate of mastectomies in SSA is excessively high, and has the counterproductive effect of discouraging women from seeking medical help (Gakwaya et al. 2008).

The use of hormonal therapy in SSA is as controversial as rates of receptor positivity. Many investigators have identified frequent empirical use of Tamoxifen (Bird et al. 2008; Kingham et al. 2013; Clegg-Lamptey et al. 2009a; Adesunkanmi et al. 2006). The rationale for this is clear: immunohistochemistry is prohibitively expensive for most SSA women but Tamoxifen is cheap. On the assumption that most

breast cancers express hormone receptors (which is true in Caucasian women), only a minority would fail to benefit from empirical Tamoxifen. As previously discussed, though, rates of hormone receptor positivity in SSA may well be lower than in the West. Indeed, several authors have argued that the status quo is likely harmful and that up-front hormone receptor testing ought to be implemented (Bird et al. 2008; Galukande et al. 2014), at least for younger women whose cancers are less likely to express hormone receptors (Kantelhardt et al. 2014). Efforts to set up and standardise hormone receptor and HER2 testing in SSA are ongoing and several regional centres have already been set up in African countries such as Nigeria. This has been largely via links between SSA and Western countries including in person and remote training of African pathologists on histological assessment and molecular marker testing (Rotimi et al. 2017).

Radiotherapy is frequently advised because of the high rates of locally-advanced cancers, but in one series only one third of women attended their appointments (Adesunkanmi et al. 2006). The reasons for this are legion, but surely an important factor is the need to travel long distances to cancer centres for such treatment due to its scarcity. Indeed, little more than a third of SSA countries have radiotherapy facilities, placing this essential modality out of reach for the majority of women in the region (Abdel-Wahab et al. 2013). Other more targeted treatments such as trastuzumab are generally poorly-available and too expensive for the majority (Pace and Shulman 2016); in any case, testing for HER2 status is not done as routine on breast tumours, which is of particular concern given that HER2+ rates are relatively high in SSA.

However, although poor availability and affordability of key treatment modalities are serious problems in SSA, it is dwarfed by the issue of poor patient adherence to treatment. The scale is extraordinary: in one series, 12.7% of patients defaulted prior to any treatment, 9.5% defaulted during or after neoadjuvant chemotherapy, and tragically 3.8% defaulted and later returned with stage IV cancer (Clegg-Lamptey and Hodasi 2007). Several surveys have identified fear of mastectomy as the major factor driving this behaviour (Clegg-Lamptey et al. 2009a, b; Okobia et al. 2006a).

It is little surprise that breast cancer in SSA has a very poor prognosis. Reliable data is difficult to source, but 5-year survival rates in Gambia and Nigeria have been estimated to be 12% and 8–15%, respectively (Gukas et al. 2005; Unger-Saldaña 2014). Even in relatively affluent South Africa, black women have survival rates of only 64%, compared to 80% for their white counterparts (Vorobiof et al. 2001).

6.8 Conclusion

Much remains unknown in relation to breast cancer in SSA. A great deal of the difficulty in assessing the disease's epidemiology and clinical course lies in disentangling the complex issues of socioeconomic disadvantage and unique demographics from biological factors. Robust cancer registry data is required to provide tools for

evidence-based management strategies. What can be stated with certainty at the moment though, is that women with breast cancer in SSA are young, tend to present with large and advanced cancers, and frequently have poor outcomes.

Though the picture at present is grim, there is cause for optimism. It has been shown that improvements in cancer awareness, faster referrals and better diagnostic and treatment facilities in Soweto have been associated with a noticeable decline in women presenting with late-stage cancers (McCormack et al. 2013). Even more promisingly, a Ugandan study found that use of multidisciplinary teams and guideline-based management algorithms have achieved 5-year survival rates of 74% for early- and 39% for late-stage cancers (Gakwaya et al. 2008). SSA Pathologists and clinicians are striving to make progress in improving their diagnostic accuracy and quality of care. Combatting this disease will by no means be a simple task, but it is clear that this challenge is in no way insuperable.

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