Chapter 1

Epidemiology, Pathology, Management and Open Challenges of Breast Cancer in Central Sudan: A Prototypical Limited Resource African Setting

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Abstract

Little is known about breast cancer in Sudan. According to the recent data published by the Khartoum Cancer Registry, breast cancer was the most common cancer among Sudanese women. Generally, breast cancer in native African women is characterized by young age at onset, occurrence in multiparous premenopausal patients, advanced stage at diagnosis, large tumor size, high-grade and triple-negative phenotype, with correspondingly poor prognosis. In Sudan, it was reported that about 70% of the women diagnosed with breast cancer were younger than 50 years old. We present here data from local and international publications as well as primary information from the National Cancer Institute in Wad Medani (one of the only two cancer hospitals of the country, both located in Central Sudan in Khartoum and Wad Medani). We provide an up-to-date situation analysis of breast cancer in Central Sudan as an example for an African reality and the various open challenges of breast cancer in a limited resource setting. A better understanding of breast cancer in black African women is of global relevance, as there is an alarming increase in breast cancer among young black women worldwide, and these patients have the lowest survival rates.

Keywords: breast cancer, epidemiology, pathology, management, Sudan, Africa, limited resource setting

1. Introduction

Worldwide breast cancer is the most frequent cancer in women. Breast cancer is considered a biologically heterogeneous disease that is influenced by complex and still incompletely understood interactions between multiple genetic and environmental risk factors. These interactions could play an important role in the marked geographical variation of breast cancer incidence rates [1, 2]. Incidence rates are higher in the developed countries than in the developing countries and in urban versus rural areas [1–3]. In sub-Saharan Africa, low incidence of breast cancer has been documented [1–8]. This could be explained by the fact that high parity and prolonged breast-feeding, which act as protective factors [9, 10], are prevalent [9]. However, the estimated mortality rates for breast cancer in Africa are not greatly inferior to those registered in Europe. Another interesting observation is that in Africa, breast cancer tends to affect younger women [1, 2, 8, 11, 12]. A woman's age is one of the strongest risk factors for breast cancer. Its incidence rates increase steadily between 25 and 50 years of age, after which continue to rise at slower rate. In women under 20 years of age, the risk of breast cancer is very low [2, 13]. In parts of the world including sub-Saharan Africa, where life expectancy is shorter, the median age at diagnosis is 10–15 years younger than in the developed world, that is, Europe and the USA [2, 4, 11, 12, 14].

In any case, breast cancer is the most commonly diagnosed cancer among African women [15]. It has been noted that breast cancer overtook cervical cancer as the most commonly diagnosed cancer in several countries in sub-Saharan Africa, including Nigeria, Chad, Sudan, Cameroon, Central African Republic, Niger, Namibia, Congo, Kenya and Somalia [15, 16]. This was attributed to increase in the prevalence of breast cancer risk factors associated with urbanization and economic development, such as earlier menarche, later childbearing, having fewer children, obesity and increased awareness and detection [15].

Little is known about breast cancer in Sudan [17]. According to the recent data published by the Khartoum Cancer Registry, breast cancer was the most common cancer among Sudanese women [16]. During 2009–2010, the incidence rate of breast cancer was substantially higher than that of any other type of cancer in adults, males and females combined. The age-standardized rate (ASR) of breast cancer for women living in Khartoum was 66.8 per 100,000, which was higher than what was reported for women in East Africa and North Africa, but similar to those reported for Nigerian women living in Abuja or in Ibadan [16].

In the Sudan, breast cancer was the most frequent hospital-treated malignancy, accounting for about 16% (4005/25,064) of all reported cancer cases between the years 1959 and 2007 [17]. As in many African countries, this probably represents a gross underestimation due to incomplete case ascertainment and reporting [18]. In fact, accurate data are difficult to obtain in Africa because cancer registries cover only 11% of the population [19], and the quality of information about cancer types is poor [6, 20]. Mortality statistics for cancer are also inadequate. Since 1995, only three African countries (Mauritius, Egypt and South Africa) have contributed to the cancer mortality database. However, even in South Africa, death registrations for cancer were estimated to be incomplete [6]. In Sudan, precise anagraphic and clinical data are lacking, rendering it difficult, if not impossible, to make clinicopathologic correlations and to compile databases and registries. The problematic referral system has been previously described by Dafaallah et al. in the Wad Medani area, Sudan [21].

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2. Major clinicopathological features of breast cancer in Sudan

Generally, breast cancer in native African women is characterized by young age at onset, occurrence in multiparous premenopausal patients, advanced stage at diagnosis, large tumor size, high-grade and triple-negative phenotype, with correspondingly poor prognosis. The median age at diagnosis among women with breast cancer in developed countries is 61 years [22, 23]. Interestingly, a recent overview of female breast cancer statistics in the United States showed that the median age at diagnosis was somewhat younger for black women (58 years) than for white women (62 years) [24]. In Sudan, it was reported that about 70% of the women diagnosed with breast cancer were younger than 50 years (**Figure 1**) [25].

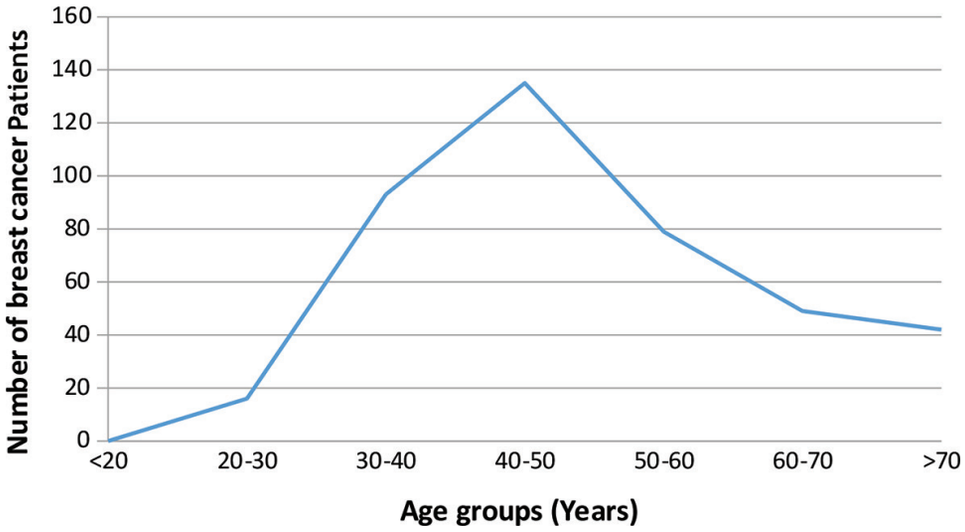

Figure 1. Age distribution of breast cancer patients treated at the NCCI-UG (Data from NCI-UG cancer registry, 2010–2011).

This could be related to the fact that Sudan has a young population structure, with 44% of the Sudanese population under 15 years of age, in addition to a relative, but significant, increase in life expectancy [26, 27]. Previous studies from other sub-Saharan countries reported that the average age of diagnosis of breast cancer among African women tends to be low. This is may be partially due to the short-life expectancy and young population structure of African women. However, the full spectrum of this phenomenon could reflect complex gene-environment interactions associated with both traditional and new lifestyles in Africa [6, 17, 19, 28–32].

Young age at breast cancer presentation in Sudanese women (**Figure 1**) appears to be contributed in minor part by genetic predisposition [13, 33, 34]. It is worth mentioning that breast cancer at a young age is generally associated with aggressive behavior, advanced stage at presentation and poorer prognosis [35].

The clinical stage of the disease at presentation is the most important factor for the outcome of the patient with breast cancer. In limited resource countries, breast cancer is typically characterized by a relatively advanced stage at presentation [33, 36–40].

Data from National Cancer Institute, University of Gezira (NCI-UG) confirm that the patients with breast cancer present in small proportion with localized disease and in large proportion with regionally diffuse and metastatic disease, as shown in **Table 1**.

Stage	Number	Percent
I	11	3
II	128	31
III	179	44
IV	93	23
Total	411	100

Source: NCI-UG cancer registry 2010–2011.

Table 1. Distribution of breast cancer patient according to clinical stage at diagnosis at NCI-UG.

It has been reported that about 80% of the breast cancer cases in Sudanese patients were diagnosed at locally advanced or metastatic stage [39]. Similar high proportions of advanced stage at diagnosis of breast cancer have been reported by several studies from other sub-Saharan African countries [36–38]. The contrary was reported from high resource countries, where 38% of the European and 30% of the US breast cancer cases have either locally advanced or metastatic disease at diagnosis [41]. Several factors may contribute to the delayed presentation of patients with breast cancer. These include lack of education, poverty, limited access to medical care and the fear of being perceived as a burden to caregivers. Other likely factors are fear of mastectomy and misconceptions about the nature or curability of the disease, which can lead women to seek alternative care instead of standard treatment [31]. About 60–75% of women in Central Sudan who develop breast cancer live in rural areas [39] and many of these women go untreated, mostly due to lack of access (financial and geographical) to health care (**Figure 2**).

Typically, in our setting, cases with breast lumps are referred by the attending physician to surgical facilities in governmental hospitals or private clinics for tissue biopsy. The average time to get the histopathology result is about 2–3 weeks [42, 43]. In Sudan, there are only two specialized treatment centers for cancer, both located in Central Sudan, that is, the Radiation and Isotopes Center, Khartoum (RICK) and the National Cancer Institute (NCI-UG) of Gezira University in Wad Medani, Gezira State, Central Sudan. Given the size of the country, this situation by itself could lead to the above-mentioned delayed presentation in which most of cancer patients come after traveling long distances from different parts of the country (**Figure 2**). Therefore, the financial aspects of investigations and treatment, alongside with the availability of boarding and lodging close to the oncology centers, represent a huge burden for the patients and their caregivers [17, 42].

Molecular profiling indicates that breast cancer is a constellation of partially diverse and clinically relevant tumor subtypes whose prevalence across populations could be influenced by

ethnicity, a complex variable combining genetic, environmental and other discriminating factors. Moreover, different breast cancer subtypes may progress along partially independent molecular pathways, which could reflect etiological and biological differences (i.e. luminal A, luminal B, Her-2/neu overexpressing, basal like, etc.) [44–46]. However, little is known about the molecular subtypes of breast cancer associated with high multiparity and lactation in non-contracepting populations, such as African populations. The molecular portrait(s) of breast tumors in Africa might be different compared to those of breast cancer in Western women [47]. Studies conducted in the USA suggest that black ethnicity adversely influences breast cancer phenotype [48]. Indeed, African Americans have been reported to manifest a higher rate of the most aggressive breast cancer subtype, that is, the basal-like subtype, associated with high grade, poor prognosis and younger age [48]. Data on the molecular subtypes of breast cancer among Sudanese patients are scarce. The basal cytokeratins, markers of the basal-like breast cancer subtype, were expressed in a fraction of cases from Central Sudan comparable to those reported for East and West African case series [49]. Lack of associations with age and tumor size may represent a special feature of basal-like breast cancer in Sudan [49].

Figure 2. A 25-year-old female with locally advanced breast cancer treated at NCI-UG. This shocking presentation demonstrates how far our patients are in term of early detection. On the other hand, the biological features of such advanced primary tumors, since several decades exceedingly rare in developed countries, are almost unknown. Hence, treatment options do not rely on scientific evidence.

Very few studies assessed the clinical and pathological characteristics of breast cancer in Sudan. One study investigated in parallel series of patients the possible differences between breast cancer in indigenous sub-Saharan African (i.e., Sudanese) versus European (i.e., Italian) women. Compared with the Italian patients, the Sudanese patients were younger and their tumors were larger, more advanced in stage, higher in grade and more frequently positive for nodal metastases. Estrogen receptor (ER) expression varied between the two series, but no significant differences were found for PgR, combined hormone receptors, Her-2/neu, CK5/6, CK17, combined basal CK status or breast cancer subtypes [33]. The study concluded that the differences between the Sudanese and the Italian breast cancer series reflected stage at

diagnosis rather than intrinsic biological characteristics [33]. This was in accordance with data reported for a breast cancer series from Nigeria, where Adebamowo and collaborators reported a high frequency of hormone receptor-positive cases, when the histopathology samples were collected under rigorous control for appropriate fixation [50]. On the contrary, studies that compared extensive series of African-American and European-American breast cancer patients found associations between aggressive estrogen receptor (ER)-negative breast cancer and both younger age at diagnosis and black ethnicity [19, 40, 48]. This suggests the possible contribution of ethnic factors to a higher burden of aggressive ER-negative breast cancer in African women. Huo et al. (2009) found that hormone receptor-negative breast cancer was predominant in a large series of 507 patients with invasive breast cancer from Nigeria and Senegal, in which only 25% of the studied cases were ER positive [40].

Similar findings were reported in studies comparing Nigerian and UK breast cancer patients. In this regards, the immunoprofile of 308 breast tumors from Nigeria, together with the patients' outcomes, was compared with a tumor grade-matched UK control group. The Nigerian women presenting with breast cancer were more frequently premenopausal, and their tumors were characterized by large primary tumor size, high tumor grade, advanced lymph node stage and higher rate of vascular invasion compared with the tumors in the UK women. In the grade-matched groups, the Nigerian breast cancers showed over representation of triple-negative and basal phenotypes and *BRCA1*-deficient breast cancer compared with the UK women, but no difference was found regarding Her-2/neu expression between the two series. The Nigerian patients showed significantly poorer outcome compared with the UK patients [47].

Elgaili et al. evaluated the clinicopathological features of breast cancer in Central Sudan and reported that estrogen and progesterone receptors expression were performed on a limited number of samples and that the majority of the tested cases resulted negative [39]. This finding was in accordance with data from other African countries, such as Tanzania, Nigeria and Kenya, where the majority of the studied breast cancers were negative for estrogen and progesterone receptors [51–54].

Huo et al. suggested that the reported high frequency of hormone receptor negativity should be interpreted with caution, as false-negative results might be introduced by antigen degradation of archival materials, besides referral, which may generate a bias towards a lower proportion of ER-positive tumors [40]. Suboptimal assays most likely contribute to the low positive estrogen and/or progesterone receptors status reported for breast cancer in Africa [55]. Moreover, the high fractions of receptors-negative cases could reflect early age at breast cancer diagnosis, in Sudan as well as elsewhere in Africa, since young breast cancer patients are more likely to have tumors with negative estrogen and/or progesterone receptors status [56, 57].

Eng et al. conducted a meta-analysis and a systematic review of the publications reporting on the frequency of breast cancer receptor-defined subtypes in indigenous populations in North and Sub-Saharan Africa and found that there was marked between-study heterogeneity in the ER+ estimates in both regions, with the majority reporting proportions between 0.40 and 0.80 in North Africa and between 0.20 and 0.70 in sub-Saharan Africa. Similarly, large between-study heterogeneity was observed for PR+ and HER2+ estimates [58]. This meta-analysis showed that the proportion of ER+ disease was lower for studies based on archived tumor

blocks compared to prospectively collected specimens and lower for series enriched in grade 3 tumors. For prospectively collected samples, the pooled proportions for ER+ and triple negative tumors were 0.59 (0.56–0.62) and 0.21 (0.17–0.25), respectively, regardless of region. This suggests that two-thirds of the African women with breast cancer have a less aggressive disease (ER+), for which targeted endocrine treatment could improve survival rates [58]. Thus, the data suggest the distribution of receptor-defined subtypes in African patients may not dramatically differ from that found in non-African patients, given the younger age structure and late presentation [58].

Nonetheless, the diversity of the African breast cancer patient population was not comprehensively represented in the case series studied thus far [40]. As a result, the impact of breast cancer with hormone receptor negativity in sub-Saharan Africa needs to be further verified, under stringent quality control, in larger and more specific studies involving different African populations [40, 58, 59].

The Ki-67 labeling index, which has been linked to patient outcome in breast cancer, is not routinely performed in Sudan and very few published reports have examined Ki-67 labeling index in African breast cancer patients. In a pilot study, the association(s) between Ki-67 labeling index and individual, pathological, clinical and immunohistochemical characteristics were investigated in 62 patients diagnosed with primary invasive breast cancer at RICK, Sudan. The results suggested a correlation with tumor differentiation and not with tumor size or any other tested marker [60].

3. Male breast cancer in Sudan

Data from Central Sudan show that to 2.3% (34/1505) of all breast cancer patients registered at NCI-UG between 1999 and 2010 are males [61], which is over two-fold higher than the proportion reported worldwide [62]. In this regard, the incidence of male breast cancer (MBC) is reportedly higher in sub-Saharan Africa [63]. In Central Sudan, the mean age at diagnosis for MBC was 56 years [61], about a decade younger than the mean age seen in developed countries [63]. The mean period between complaint awareness and MBC diagnosis was 25.3 ± 46 months. Most patients presented with a large lump (mean size, 6.8 ± 3.0 cm) or with metastatic disease (stages III/IV; 21/34, 61.8%) [61]. Because MBC is a matter of stigma in Africa, this could be a reason for late presentation, together with the same issues that apply to breast cancer in females.

4. Breast cancer genetics in Sudan

As in industrialized countries, strong genetic factors contribute to a subset of breast cancer cases in the Sudan. The germline status of the two major breast cancer susceptibility genes, *BRCA1* and *BRCA2*, was investigated in an NCI-UG breast cancer series selected based on diagnosis within 40 years of age (34 cases) or male gender (1 case). A total of 60 sequence

variants, including 5 deleterious truncating mutations (2 in *BRCA1*, 3 in *BRCA2*) and 55 variants (30 in *BRCA1*, 25 in *BRCA2*) presumed to be neutral or of little clinical significance were detected. The data suggest that in Sudan BRCA1/2 could represent an important etiological factor of breast cancer in males and young women less exposed to pregnancy and lactation [64]. Biunno et al. found 33 BRCA1 point mutations, one of which of pathogenetic relevance, in 59 Central Sudanese premenopausal breast cancer patients. The high fractions of mutations with both intercontinental and uniquely African distribution were in agreement with the high genetic diversity expected in an African population [65]. Thus, genetic variation and frequency of unique or rare mutations of uncertain clinical relevance pose significant challenges to BRCA1 testing in Sudan, as it might happen in other African contexts [34]. It is worth mentioning that a determination of BRCA1 and BRCA2 genetic mutational status will go a long way towards an effective advice on prophylaxis for breast cancer [66].

Masri et al. studied 20 unselected breast cancer patients in Sudan. They analyzed exon 11 of the BRCA2 gene and exons 5–9 of the p53 gene. They found only one somatic mutation and one polymorphism in BRCA2, without any further elaboration [67].

Hereditary breast cancer is more likely to manifest with synchronous or metachronous bilateral disease. A study from the Khartoum Teaching Hospital assessed the frequency and features of bilateral breast cancer among the patients treated during the 5-year period from 1994 to 1999. Of 521 patients treated for breast cancer, only seven (1.3%) were diagnosed with bilateral breast cancers [68].

Susceptibility to breast cancer could be predisposed by low penetrance gene polymorphisms. A single nucleotide polymorphism in the estrogen receptor gene (ESR1), C325G, implicated in breast cancer susceptibility, was genotyped in breast cancer patients and in age- and sex-matched Sudanese controls. Overall, there was a trend in the direction of an association between the CC genotype and breast cancer, which became significant in the subgroup within 50 years of age [69]. The association of the Her-2/neu Ile655Val polymorphism with breast cancer in the Sudan was also investigated [70]. Val/Val and Ile/Ile genotype frequencies were similar in patients and controls; Ile/Val had a borderline-significant association with breast cancer, not confirmed when the genotypic and allelic frequencies were stratified by age and menopausal status. Possible joint effects of Her-2/neu Ile655Val and ESR1 C325G on breast cancer risk were also investigated. The frequency of the polymorphic variants varied with ethnic origin. A significantly higher risk of breast cancer was observed among carriers of homozygous ESR1 325 CC and heterozygous Her-2/neu 655 Ile/Val [70]. These results suggest that an interaction between the ESR1 325C and Her-2/neu Ile655Val variants could contribute to breast cancer risk in Sudanese women [70].

Oncogenic viruses, such as Epstein-Barr virus (EBV), could play a role in breast carcinogenesis in Sudan. EBV genomic sequences were detected in a large fraction of tested Sudanese breast cancer specimens, suggesting an association between EBV and breast carcinoma in Sudanese patients [71].

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5. Current status of breast cancer screening in Sudan

International policies recommend screening mammography for women aged 50–69 years [72]. Other imaging modalities, such as MRI and ultrasound, are not recommended for screening in the general population. According to an analysis from the 2003 World Health Survey, only 2.2% of women age 40–69 years in limited resource settings had received any breast cancer screening. Mammography screening programs have also been estimated to cost from US$16,000 to US$37,000 per life saved, which exceeds by a significant margin the per capita health care budgets in many limited resource settings [73, 74]. Therefore, International guidelines recommend clinical breast examination (CBE) as a preferred approach to screening in settings in which mammography screening is not available [75, 76].

In Sudan, the health care system is significantly weakened by limited resources and human capacity. Resources available for health care are predominantly spent on infectious disease care, such as malaria, diarrheal diseases and tuberculosis. In our setting, the challenges of establishing national cancer screening programs include limited financial resources, shortage in trained health care professionals and social barriers that impede population enrollment into cancer screening program. In our setting, mammography machines are few. In addition, the target population is mostly young women and the available traditional film mammography machines are not efficacious for breast cancer detection in young women with dense breast.

In 2000, medical students from the Faculty of Medicine, University of Gezira, performed a breast self-examination (BSE) intervention project in "Um-Alghora," one of the poorest localities in Gezira State. During one academic semester, the students covered 200 families by training on competences of BSE. Four breast lumps were detected (two of which were fibroadenomas and two carcinomas). This project revealed that medical students, through relevant community based educational activities in preventive medicine, could have a significant effect on early detection of breast cancer by BSE [77, 78].

Given that breast cancer is the most commonly observed cancer in Sudan, an initiative for breast cancer awareness and early detection was launched in 2008, led by the National Cancer Institute, University of Gezira. Abuidris and colleagues conducted a pilot study in two localities in Gezira State, Sudan (**Figure 3**). Approximately 10,000 rural women aged 18 years or older were screened for breast cancer by using trained volunteers (**Figure 4**). Seventeen of those screened had carcinoma in situ or breast cancer, including eight with carcinoma in situ and nine with early breast cancer. In control villages, only four women self-referred for breast symptoms, three of whom had advanced-stage breast cancer [79]. Therefore, in our setting, the implementation of a cancer awareness and breast examination program that uses local volunteer women might be better used to raise awareness and encourage more women with palpable breast lumps to seek and receive early medical care.

Figure 3. Volunteers participants to the intensive training course of the breast cancer awareness and early detection initiative (March 1–5, 2009). This image shows Dr. Dafalla Abuidris, indicated by the yellow arrow, a clinical oncologist and the initiative leader. Blue arrows indicate some of the NCI-UG team members involved the in the training activities. The other women are some of the volunteers who attended the course and conducted the screening.

Figure 4. This set of images shows the context and some of the activities of the breast cancer initiative. (A) One of the poor villages in the Keremet locality, El Managil District, Gezira State, where the breast cancer initiative was launched. (B) Educational lectures conducted for the training of the volunteers at NCI-UG during March 1–5, 2009. (C) and (D) Awareness activities performed at the community level in 33 villages at the Keremet locality during 2009–2010 with the participation of the target women of the community.

6. Breast cancer management in Central Sudan

The management of patients with breast cancer requires a multidisciplinary approach to treatment (MDT). The MDT team includes a surgeon, a clinical oncologist, a pathologist, a clinical radiologist, a social worker, a nurse and a counselor. These specialists are lacking in limited-resource countries, and where they exist they tend to work in isolation, rather than in team. Therefore, almost all patients with breast cancer are treated without been seen in an MDT context. Practice guidelines that outline the optimal approach to breast cancer management have been developed by several international organizations and scientific committees, such as National Comprehensive Cancer Network (NCCN) guidelines. However, these guidelines may be inappropriate in limited resource countries for many reasons, including the extreme limitation of resources for diagnosis and treatment and the extreme shortage in trained health care providers.

The NCI-UG has a multidisciplinary breast clinic for management decisions. This clinic, established in 2002 (**Table 2**), is hosted by the Oncology Department of the NCI-UG and is attended by surgeons, oncologists, pathologists, psychologists, social workers and oncology nurses. The Gezira guidelines for the management of breast cancer, developed in 2004 and updated in 2006, are oriented towards the limited financial resources of the Sudan [80]. These guidelines represent a milestone for the improvement of breast cancer medical care in Central Sudan and are the first application of the MDT concept to patient's management in Sudan. Thus, the activities related to Gezira guidelines for management of breast cancer are part of an overall progress of the local oncology services in Central Sudan (**Table 2**). Cancer treatment is free of charge for all citizens in Sudan. Furthermore, boarding and lodging facilities close to the oncology center (NCI-UG) are available free of charge for cancer patients.

Year	Achievement
1999	Establishment of NCI-UG—formerly Institute of Nuclear Medicine & Oncology (INMO), the first center outside Khartoum (the capital city), offering radiotherapy and systemic therapy for cancer and nuclear medicine services for diagnosis
2002	Establishment of the Gezira multidisciplinary breast cancer clinic
2004	Installation of a mammography machine
2004	Development of the Gezira guidelines for management of breast cancer
2006	Update of the Gezira guidelines for management of breast cancer
2009	Establishment of hormone receptors testing using immunohistochemistry at the Department of Pathology, Faculty of Medicine, University of Gezira
2010	Development of the Sudan guidelines for management of breast cancer

Table 2. Timeline showing the overall progress of the oncology services at the NCI-U, Central Sudan.

In the next sections of diagnosis and treatment, we present and discuss the currently adopted Gezira guidelines for management of breast cancer patients [80].

6.1. Breast cancer diagnosis in Central Sudan

6.1.1. Clinical assessment

All referred breast cancer cases should undergo a thorough clinical assessment to provide guidance about the extent of the disease and the patient's fitness to tolerate cancer treatment.

6.1.2. Breast imaging

Breast ultrasound with diagnostic mammography should be part of triple assessment for all patients with breast lump. In Sudan, diagnostic breast ultrasound is often used to make a diagnosis of breast cancer, whereas diagnostic mammography is available only in few centers in Khartoum and Wad Medani (capital of the Gezira state). Therefore, triple assessment cannot be done in most parts of the country.

6.1.3. Histopathological investigations

Pathology practice in Sudan, like in other limited resource countries, has suffered from lack of funding, making it difficult for practicing pathologists to develop and apply recent technologic advances in their everyday practice [42, 43].

In Central Sudan, histopathology services are provided by the Department of Pathology, Faculty of Medicine, University of Gezira, located in Wad Medani (capital of the Gezira state), and serving the population of the Gezira state (about four million people living in an area of about 26,075 km^2; 10% of the total Sudanese population). This laboratory was established in 1978 and was the first of its kind outside Khartoum (the capital city). The average annual load during the years 2005–2009 at the above-mentioned laboratory was 5749 ± 476 and 1052 ± 128 specimens per year for histopathology and cytopathology, respectively; the overall annual load average was 6802 ± 494 [42]. There is a gross shortage of pathologists outside the capital, Khartoum. Currently, there are approximately eight anatomic pathologists serving the population of Central Sudan. Generally, there is a very poor logistic system for delivering the specimens to the laboratories. Surgical specimens are brought to the laboratory by the care givers of the patients. Buffered 10% formalin is rarely used, sometimes the specimens are received in normal saline and, rarely, in absolute ethanol [42]. Histopathologists mainly use hematoxylin-eosin routine stains. Pathologists in Gezira State depend largely on their skills in morphology (with its limitations) to classify tumors on routine stains.

According to the Gezira guidelines for management of breast cancer, the standard pathology report must include information on tumor size, lymph node status, histologic type, tumor grade, lymphovascular invasion and margin status [80]. Immunohistochemistry stains for estrogen-progesterone receptors, proliferative index (Ki67) and HER2-neu expression statuses are available, but the costs associated with testing for ER, PR and HER2 status are high, therefore these tests are not included in the primary report and are separately requested, added as extras paid by the patients. As a result, not all patients undergo hormonal receptor testing. **Figure 5** shows that 78% of the patients referred to NCI-UG in 2010–2011 had receptor

testing. Cost reduction using tissue microarray immunohistochemistry (TMA-IHC), a known cost reduction technique relative to standard whole slide IHC, is problematic when dealing with large tumors in limited resource settings, where quality control in pathology processing may be less than optimal [81]. Frozen section, fluorescence in situ hybridization (FISH) and electron microscopy services are presently not available.

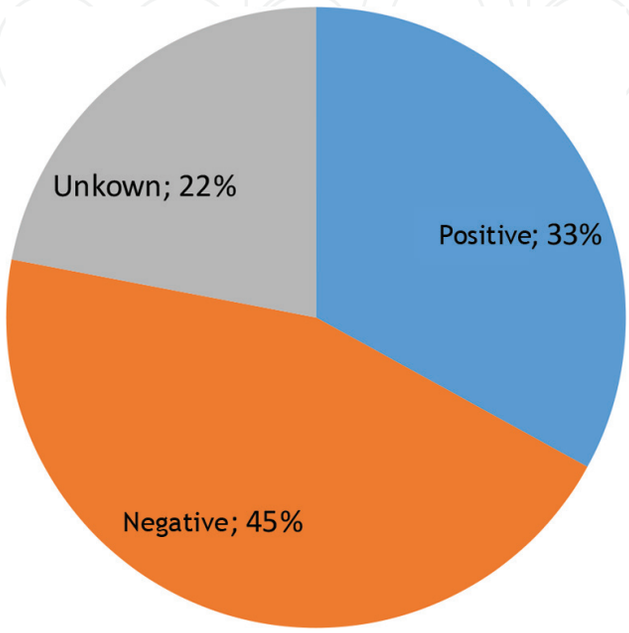

Figure 5. Distribution of breast cancer patients according to hormonal receptor status at NCI-UG (Source: NCI-UG cancer registry 2010–2011).

Because fine needle aspiration cytology (FNAC) is cheap, quick and repeatable, it was used extensively in the initial diagnosis of breast lumps. Fibroadenomas, cysts and abscesses (including antibiomas) are the most commonly diagnosed benign entities. Breast cancer initial diagnosis is usually done by FNAC, especially for late cases with ulcerations, since it is less invasive in such moribund patients with very poor general condition. In the last few years, ultrasound directed true-cut biopsies are been increasingly used initially or more commonly following FNAC.

In short, in Gezira State the preoperative diagnosis of breast cancer is based on FNAC, clinical evidence and excisional or incisional biopsy.

6.1.4. Staging investigations

In Central Sudan, diagnostic staging modalities, such as chest and skeletal radiography and liver ultrasound, are available in most tertiary hospitals. Computed tomography (CT) scans are available in two governmental institutes and in two private centers but are generally cost-prohibitive. The Department of Nuclear Medicine of the NCI-UG is the only provider of

nuclear medicine services, such as bone scan, thyroid scan, multigated acquisition (MUGA) scan and renal scan for the population of the Gezira State. Complete blood count, renal function tests and liver function tests are mandatory for newly diagnosed cases as part of staging investigation [80]. Selected blood tests (i.e. CBC, blood chemistry profile) are required for the safe administration of chemotherapy.

Despite the improved availability of pathology, radiology and nuclear medicine services, financial difficulties turn away many women with few financial resources who have breast complaints. Without adequate health insurance coverage, limited personal finances can be a significant barrier to care for many breast cancer patients regarding investigations related costs.

6.2. Treatment workup and challenges in Central Sudan

Treatment of breast cancer is dependent on the stage of the disease, age and medical state of the patient, tumor characteristics, patients' preferences and available resources. Options range from breast-conserving surgery (BCS), mastectomy, axillary clearance, chemotherapy, radiotherapy (RT), to palliative care. Treatment at an advanced stage has poor prognosis with lowest cure rates. Challenges frequently faced by oncologist treating breast cancer in Sudan are (1) most patients present with stage III or IV when they first seek medical treatment and (2) lack of adherence to treatment and inadequate follow-up because patients may have to travel long distance to receive treatment or follow-up.

6.2.1. Surgery

Breast surgery is often the initial treatment for patients who present with operable tumors. In Sudan, breast surgery is mostly performed by general surgeons. The ability to perform modified radical mastectomy (MRM) and breast-conserving surgery (BCS) is considered fundamental for surgical residence training by the Sudan Medical Specialization Board. Therefore, general surgeons in Sudan are generally well trained and have high exposure to breast surgery.

In Sudan, due to the fact that the majority of breast cancer patients present with locally advanced stage, MRM, after or without neoadjuvant chemotherapy, is the predominant surgical procedure. MRM includes removal of breast tissue, axillary tail and clearance of level I and II axillary lymph nodes. The low rate of BCS in our patients reflects the high rate of late presentation. BCS requires (1) breast imaging (mammography and ultrasound) and pathology services to ensure tumor free margins of excision, (2) surgeons experienced in achieving a good cosmetic result with negative pathologic margins of excision and (3) radiotherapy facilities. These requirements are met in our setting. Therefore, BCS is currently used as an alternative option for young patients with early breast cancer, obviously a choice that is cosmetically desirable. BCS could be a choice for patients with large tumors who achieved good response to neoadjuvant chemotherapy. Randomized trials have shown that there are no significant differences in disease-free or overall survival between patients treated by mastectomy and those treated by breast-conserving surgery and whole-breast radiotherapy [82–84]. Breast cancer peaks among Sudanese women in their 30s. Therefore, breast-conserving therapy preserves the body image and may offer better quality of life.

Reconstruction breast surgery is not an option in our setting, due to lack of plastic and reconstructive surgeons. Although sentinel lymph node (SLN) biopsy has become the preferable standard to axillary dissection in breast cancer surgery, this advanced technique is presently not available in Sudan.

6.2.2. Radiotherapy

Radiotherapy (RT) is an essential part of the multimodality treatment of breast cancer. In limited resource countries, and particularly in Sudan, the need for radiotherapy is much greater due to late presentation and inoperability of the tumors. Access to radiotherapy, however, is severely limited. Africa has less than 2% of all radiotherapy centers globally and is home to approximately 15% of the world's population, demonstrating a dire need to improve the availability of radiotherapy [85]. The NCI-UG is a governmental facility with two Co60 machines, linear accelerator machine (Linac) and a treatment planning system (**Figure 6** and **Table 3**) that treats 80–100 patients daily, about 20% of whom are breast cancer patients. Patients from different regions of Sudan are referred to NCI-UG for RT. Radiotherapy is delivered with cobalt-60 units (Co 60). The linear accelerator was installed in 2007 (VARIAN, manufactured in 2005). Energy levels of this machine are 6 and 16 MV-photons and 6, 9, 12 and 15 MeV. The machine was stored for 2 years before installation as the bunker was not constructed in time, but never treated even a single patient because of licensing issues and economic sanctions imposed to Sudan.

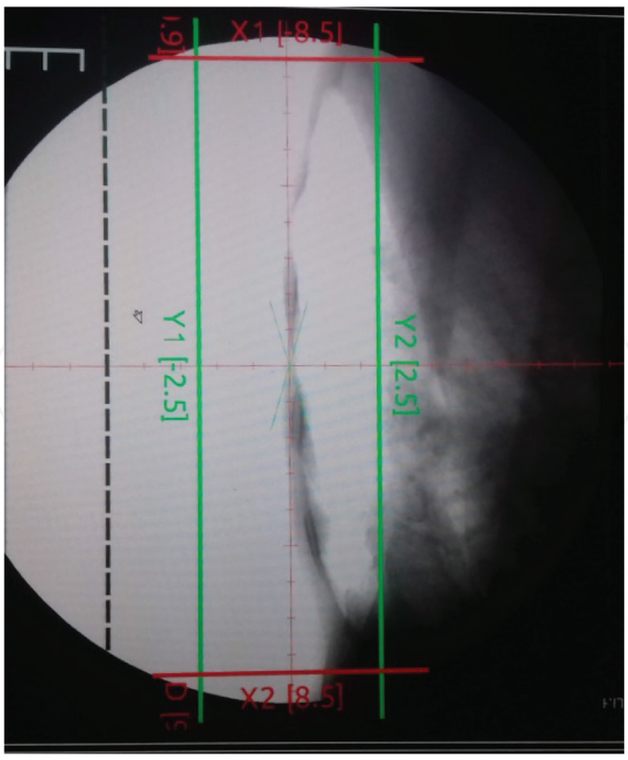

Figure 6. Simulator planning image for a chest wall radiation field at the NCI-UG.

Recourse	Counts
Clinical oncologists	4
Radiographers	10
Medical physicists	3
Engineering technicians	3
Co 60 radiotherapy machines	2
Linear accelerator[a]	1
Simulator[b]	1

[a] Non-functioning since installation in 2007.

[b] Simulator machine includes fluoroscopy and radiography option.

Table 3. Human (Staff) and physical resources (machines) at the NCI-UG.

Although linear accelerator machines (Linac) are considered preferable, cobalt machines represent a reasonable alternative in our setting because Co 60 radiotherapy machines are simpler to operate and much less expensive than Linac machines. Drawbacks of the Co 60 machines are the lower percentage depth dose and the decaying source that reduces the output, resulting in increased treatment time, which in turn reduces the patients outputs. Furthermore, the radioactive components are difficult to procure, because of the current international concerns.

The most common schedule for irradiation is 50 Gy in 25 fractions to the whole breast, administered daily, five times per week. In a large randomized trial, however, a shorter fractionation schedule (42.5 Gy in 22 days or 40 Gy in 3 weeks), more convenient and less costly, proved to be just as safe and effective [86, 87]. Thus, due to the long waiting list, cost and demand for the machine time, we considered hypo-fraction radiotherapy (treatment over 3 weeks) that simplifies the radiotherapy planning process, permitting more efficient use of our limited resources, and thus allowing the treatment of more patients with the existing equipment and personnel.

According to the Gezira guidelines for management of breast cancer, post-mastectomy irradiation is considered for patients with a tumor larger than 5 cm, or a tumor involving the chest wall or skin. It is also considered for patients with more than three positive axillary lymph nodes. Adjuvant radiotherapy is indicated for all patients who underwent BCS. Supraclavicular fossa irradiation is recommended for patients with more than three positive axillary lymph nodes. For patients with locally advanced breast cancer in which mastectomy is still not possible after initial systemic therapy, breast and regional irradiation is given, followed whenever possible by mastectomy. For patients with distant metastases, irradiation may provide relief of symptoms such as pain, bleeding, ulceration and lymphedema.

6.2.3. Chemotherapy

Systemic therapy for cancer treatment represents one of the great challenges in cancer control efforts in limited resource countries. The well-established cytotoxic chemotherapy drugs

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and endocrine therapies available for breast cancer patients in Sudan are shown in **Table 4**. At NCI-UG, a wide variety of chemotherapy regimens is in use. Anthracycline-based combination is the appropriate first-line chemotherapy for most breast cancer patients, based on significant survival benefits of the anthracycline based regimens, that is, 5-flurouracil (5FU), cyclophosphamide, doxorubicine (FAC) or 5-flurouracil (5FU), cyclophosphamide, epirubicine (FEC), when compared with 5-flurouracil (5FU) methotrexate, cyclophosphamide combinations (CMF). The anthracycline-based regimens are associated with a high risk of cardiotoxicity. Thus, CMF is still used for elderly patients with comorbidities. Taxanes-based regimens, such as cyclophosphamide, doxorubicine and taxane, are reserved for patients with extensive axillary lymphadenopathy. Systemic therapies are dispensed by a pharmacist and administered by trained nurses under supervision of a clinical oncologist. Tamoxifen is the most widely used endocrine therapy for breast cancer patients and a large proportion of postmenopausal patients are treated with aromatase inhibitors either alone or sequential with Tamoxifen. Furthermore, Tamoxifen is prescribed empirically for breast cancer patients with unknown hormone receptors.

Drug	Dose
Doxorubicin	60 mg/m^2
Epirubicin	100 mg/m^2
Cyclophosphamide	600 mg/m^2
5FU	600 mg/m^2
Methotrexate	40 mg/m^2
Docetaxel	100 mg/m^2
Paclitaxel	175 mg/m^2
Carboplatin	AUC 6
Cisplatin	50 mg/m^2
Capecitabine	1250 mg/m^2
Gemicitabine	1000 mg/m^2
Novalbine	25 mg/m^2
Tamoxifen	20 mg P.O
Anastrazole	1 mg P.O
Letrozole	2.5 mg P.O
G-CSF	5 mcg/kg

[a]These drugs were included in the 2014 WHO model list for essential medicine.

Table 4. List of available cancer drugs for breast cancer patients at the NCI-UG[a].

The choice of chemotherapy and hormonal therapy for breast cancer depends on the indication in the Gezira guidelines for management of breast cancer.

6.2.4. Targeted therapy agents

In our setting, Trastuzumab is the only available targeted therapy. However, the costs to the patients and issues related to insurance coverage limit patient access to this drug. Therefore, Trastuzumab is not included in the WHO model list for essential medicines, and HER2 targeted therapy is not considered as a priority in our limited resource setting by health care policy makers and insurance companies. Another limitation is that HER2 borderline cases (IHC score 2+) cannot be reassessed due to the unavailability of the fluorescence in situ hybridization (FISH) technique [88].

6.2.5. Palliative care services

The NCI-UG palliative care service was established in 1999 for pain control, stoma care and wound care. The available pain medications are paracetamol, nonsteroidal anti-inflammatory drugs, tramadol and morphine (both intravenous and oral). These medications are provided free of charge. However, these services remain grossly inadequate and represent a further area of priority, which led to the establishment of the Gezira palliative care program in 2015, to provide palliative care at home for terminal-stage cancer patients.

7. Conclusions, future perspectives and open challenges

Sudan and many other sub-Saharan African countries need to face alarming increases in cancer incidence [19, 28–30, 32, 89]. This situation impacts on the above-mentioned African health care crisis. At the same time, there is a very scarce and often incorrect perception of cancer as a disease in many African communities [13, 19, 28–30, 32, 37, 90–92]. In Sudan, breast cancer, particularly in premenopausal women, is increasingly recognized as an emerging health problem. Overall, the features of breast cancer in the Sudan may reflect population structure and reproductive factors resulting in low postmenopausal breast cancer incidence. On the other hand, the available data indicate that the Sudanese breast cancer series are enriched with cases of male breast cancer and early onset female breast cancer, particularly in parous women, suggesting specific risk factors [17, 64]. Information on breast cancer incidence in our limited resource setting is lacking due to lack of population cancer registry. In Sudan, as suggested by hospital-based case series the burden of disease is clearly increasing and breast cancer may account for large proportion of cancer load. Population-based studies, however, are needed to determine the true incidence of the disease, which, in present contest, is difficult to evaluate. It is probable that the breast cancer cases arising in Sudanese women derive from poorly understood interactions between strong genetic and environmental factors, which may include factors promoted by pregnancy and lactation. Moreover, an understanding of the above-mentioned complex situation is primarily important in view of the need of developing ad hoc designed preventive and therapeutic strategies. This requires local political will, painstaking development of infrastructures, trained personnel and focused international support [33, 43, 93]. Finally, but not lastly, a better understanding of breast cancer in black African women is of global crucial relevance, as there is an alarming increase in breast cancer among young black women worldwide and these patients have the lowest survival rates.

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References

[1] Igene, H., *Global health inequalities and breast cancer: an impending public health problem for developing countries.* Breast J, 2008. **14**(5): 428–34.

[2] Bray, F., P. McCarron, and D.M. Parkin, *The changing global patterns of female breast cancer incidence and mortality.* Breast Cancer Res, 2004. **6**(6): 229–39.

[3] Parkin, D.M., et al., *Global cancer statistics, 2002.* CA Cancer J Clin, 2005. **55**(2): 74–108.

[4] Veronesi, U., et al., *Breast cancer.* Lancet, 2005. **365**(9472): 1727–41.

[5] Ferlay, J., et al., *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide*. 2004, IARC Press: Lyon.

[6] Parkin, D.M., et al., *Cancer in Africa: Epidemiology and Prevention*. 2003, Lyon: IARC Press.

[7] Parkin, D.M. and C.S. Muir, *Cancer incidence in five continents. Comparability and quality of data.* IARC Sci Publ, 1992(120): 45–173.

[8] Sighoko, D., et al., *Population-based breast (female) and cervix cancer rates in the Gambia: evidence of ethnicity-related variations.* Int J Cancer, 2010. **127**(10): 2248–56.

[9] Huo, D., et al., *Parity and breastfeeding are protective against breast cancer in Nigerian women.* Br J Cancer, 2008. **98**(5): 992–6.

[10] Enger, S.M., et al., *Breastfeeding history, pregnancy experience and risk of breast cancer.* Br J Cancer, 1997. **76**(1): 118–23.

[11] Basro, S. and J.P. Apffelstaedt, *Breast cancer in young women in a limited-resource environment.* World J Surg, 2010. **34**(7): 1427–33.

[12] Baltogiannis, G. and D.H. Roukos, *Letter to the editor: Breast cancer in young women in Africa: are there genetic and clinical differences with European ancestry patients?* World J Surg, 2010. **34**(8): 1982–3.

[13] Awadelkarim, K.D., et al., *Hereditary breast cancer in Sub-Saharan Africa.* Curr Women's Health Rev, 2012. **8**(1): 44–54.

[14] Vorobiof, D.A., F. Sitas, and G. Vorobiof, *Breast cancer incidence in South Africa.* J Clin Oncol, 2001. **19**(18 Suppl): 125S–127S.

[15] Jemal, A., et al., *Cancer burden in Africa and opportunities for prevention.* Cancer, 2012. **118**(18): 4372–84.

[16] Saeed, I.E., et al., *Cancer incidence in Khartoum, Sudan: first results from the Cancer Registry, 2009-2010.* Cancer Med, 2014. **3**(4): 1075–84.

[17] Awadelkarim, K.D., R. Mariani-Costantini, and N.E. Elwali, *Cancer in the Sudan: an overview of the current status of knowledge on tumor patterns and risk factors.* Sci Total Environ, 2012. **423**: 214–228.

[18] Adesunkanmi, A.R., et al., *The severity, outcome and challenges of breast cancer in Nigeria.* Breast, 2006. **15**(3): 399–409.

[19] Porter, P., *"Westernizing" women's risks? Breast cancer in lower-income countries.* N Engl J Med, 2008. **358**(3): 213–6.

[20] Parkin, D.M., *The evolution of the population-based cancer registry.* Nat Rev Cancer, 2006. **6**(8): 603–12.

[21] Dafallah, S.E., E.M. Yousif, and A.A. Idris, *Analysis of documents used in referral system in Wad Medani, Sudan.* Saudi Med J, 2005. **26**(1): 148–50.

[22] Howlader N, N.A., Krapcho M, et al., *SEER Cancer Statistics Review, 1975-2012, based on Nov 2014 SEER data submission.* 2015, National Cancer Institute: Bethesda, MD.

[23] Altekruse, S.F., et al., *SEER Cancer Statistics Review, 1975-2007, http://seer.cancer.gov/csr/1975_2007/*. 2010, National Cancer Institute: Bethesda, MD.

[24] DeSantis, C.E., et al., *Breast cancer statistics, 2015: Convergence of incidence rates between black and white women.* CA Cancer J Clin, 2016. **66**(1): 31–42.

[25] Salim, O.H., et al., *Breast cancer in Africa, are we dealing with a different disease.* Sudan Med J 2014. **50**(1): 1–12.

[26] Sudan Demographic and Health Survey, *Sudan Demographic and Health Survey 1989/1990*. 1991, Department of Statistics, Ministry of Economic and National Planning, Khartoum, Sudan and Institute for Resource Development/Macro International, Inc., Columbia, Maryland, USA: Khartoum, Sudan. p. 1–145.

[27] The Republic of Sudan, *Country Report, The Fourth Meeting of the Follow-up Committee on the Implementation of Dakar/Ngor Declaration and the Programme of Action of the International Conference on Population and Development, 28–31 January.* 2002: 1–16.

[28] Ikpatt, O.F., et al., *Breast cancer in Nigeria and Finland: epidemiological, clinical and histological comparison.* Anticancer Res, 2002. **22**(5): 3005–12.

[29] Morris, K., *Cancer? In Africa?* Lancet Oncol, 2003. **4**(1): 5.

[30] Gondos, A., et al., *Cancer survival in Kampala, Uganda.* Br J Cancer, 2005. **92**(9): 1808–12.

[31] Hamad, H.M., *Cancer initiatives in Sudan.* Ann Oncol, 2006. **17 Suppl 8**: viii32–viii36.

[32] Kerr, F. and D. Kerr, *Do we bear any moral responsibility for improving cancer care in Africa?* Ann Oncol, 2006. **17**(12): 1730–1.

[33] Awadelkarim, K.D., et al., *Pathological, clinical and prognostic characteristics of breast cancer in Central Sudan versus Northern Italy: implications for breast cancer in Africa.* Histopathology, 2008. **52**(4): 445–56.

[34] Biunno, I., et al., *BRCA1 point mutations in premenopausal breast cancer patients from Central Sudan.* Fam Cancer, 2014. **13**(3): 437–44.

[35] Swanson, G.M., and Chen-Sheng Lin., *Survival patterns among younger women with breast cancer: the effects of age, race, stage, and treatment.* J Nat Cancer Inst 1993. **Monographs, 16**: 69–77.

[36] Amir, H., et al., *TNM classification and breast cancer in an African population: a descriptive study.* Cent Afr J Med, 1997. **43**(12): 357–9.

[37] Ekortarl, A., P. Ndom, and A. Sacks, *A study of patients who appear with far advanced cancer at Yaounde General Hospital, Cameroon, Africa.* Psychooncology, 2007. **16**(3): 255–7.

[38] Sarre, B., et al., *Epidemiological, therapeutic and prognostic aspects of breast cancer: about 473 cases collected in Hopital Principal de Dakar.* Dakar Med, 2006. **51**(2): 92–6.

[39] Elgaili, E.M., et al., *Breast cancer burden in central Sudan.* Int J Womens Health, 2010. **2**: 77–82.

[40] Huo, D., et al., *Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer.* J Clin Oncol, 2009. **27**(27): 4515–21.

[41] Sant, M., et al., *Breast carcinoma survival in Europe and the United States.* Cancer, 2004. **100**(4): 715–22.

[42] Awadelkarim, K.D., A.A. Mohamedani, and M. Barberis, *Role of pathology in Sub-Saharan Africa: an example from Sudan.* Pathol Lab Med Int, 2010. **2**: 49–57.

[43] Mariani-Costantini, R., et al., *Building Sustainable Capacity for Disease Diagnosis in Sub-Saharan Africa: Case Studies of Cooperation in Diagnostic Pathology*, in *New Knowledge in a New Era of Globalization*, P. Pachura, Editor. 2011, InTech Open Access Publisher Rijeka: Croatia. p. 243–266.

[44] Perou, C.M., et al., *Molecular portraits of human breast tumours.* Nature, 2000. **406**(6797): 747–52.

[45] Sorlie, T., et al., *Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications.* Proc Natl Acad Sci U S A, 2001. **98**(19): 10869–74.

[46] Sorlie, T., et al., *Repeated observation of breast tumor subtypes in independent gene expression data sets.* Proc Natl Acad Sci U S A, 2003. **100**(14): 8418–23.

[47] Agboola, A.J., et al., *Molecular characteristics and prognostic features of breast cancer in Nigerian compared with UK women.* Breast Cancer Res Treat, 2012. **135**(2): 555–69.

[48] Carey, L.A., et al., *Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study.* Jama, 2006. **295**(21): 2492–502.

[49] Awadelkarim, K.D., et al., *Basal-like phenotype in a breast carcinoma case series from Sudan: prevalence and clinical/pathological correlations.* Pathol Res Int, 2011. **2011 (Article ID: 806831)**: 1–10.

[50] Adebamowo, C.A., et al., *Immunohistochemical and molecular subtypes of breast cancer in Nigeria.* Breast Cancer Res Treat, 2008. **110**(1): 183–8.

[51] Mbonde, M.P., et al., *Expression of estrogen and progesterone receptors in carcinomas of the female breast in Tanzania.* Oncol Rep, 2000. **7**(2): 277–83.

[52] Burson, A.M., et al., *Clinical and epidemiologic profile of breast cancer in Tanzania.* Breast Dis, 2010. **31**(1): 33–41.

[53] Ikpatt, O.F. and R. Ndoma-Egba, *Oestrogen and progesterone receptors in Nigerian breast cancer: relationship to tumour histopathology and survival of patients.* Cent Afr J Med, 2003. **49**(11-12): 122–6.

[54] Bird, P.A., A.G. Hill, and N. Houssami, *Poor hormone receptor expression in East African breast cancer: evidence of a biologically different disease?* Ann Surg Oncol, 2008. **15**(7): 1983–8.

[55] Raina, V., et al., *Clinical features and prognostic factors of early breast cancer at a major cancer center in North India. 2005;42.* Indian J Cancer, 2005. **42**: 40–45.

[56] Albain, K.S., D.C. Allred, and G.M. Clark, *Breast cancer outcome and predictors of outcome: are there age differentials?* J Natl Cancer Inst Monogr, 1994(16): 35–42.

[57] Kroman N1, J.M., Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M., *Factors influencing the effect of age on prognosis in breast cancer: population based study.* BMJ, 2000. **320**(7233): 474–479.

[58] Eng, A., V. McCormack, and I. dos-Santos-Silva, *Receptor-defined subtypes of breast cancer in indigenous populations in Africa: a systematic review and meta-analysis.* PLoS Med, 2014. **11**(9): e1001720.

[59] Mohammed, S.I. and J.B. Harford, *Sorting reality from what we think we know about breast cancer in Africa.* PLoS Med, 2014. **11**(9): e1001721.

[60] Awadelkarim, K.D., et al., *Ki-67 labeling index in primary invasive breast cancer from Sudanese patients: a pilot study.* ISRN Pathol, 2012. **2012 (Article ID: 232171)**: 1–6.

[61] Elhaj, A., A.I. Ismaeel, and K.D. Awadelkarim, *Male breast cancer patients: a retrospective study of patients characteristics and treatment outcome at the National Cancer Institute (NCI-UG)—Central Sudan.* Pan Arab J Oncol, 2012. **5**(1): 18–22.

[62] Pant, K. and U. Dutta, *Understanding and management of male breast cancer: a critical review.* Med Oncol, 2008. **25**(3): 294–8.

[63] Niewoehner, C.B. and A.E. Schorer, *Gynaecomastia and breast cancer in men.* BMJ, 2008. **336**(7646): 709–13.

[64] Awadelkarim, K.D., et al., *BRCA1 and BRCA2 status in a Central Sudanese series of breast cancer patients: interactions with genetic, ethnic and reproductive factors.* Breast Cancer Res Treat, 2007. **102**(2): 189–99.

[65] Fackenthal, J.D. and O.I. Olopade, *Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations.* Nat Rev Cancer, 2007. **7**(12): 937–48.

[66] Oluwagbemiga, L.A., A. Oluwole, and A.A. Kayode, *Seventeen years after BRCA1: What is the BRCA mutation status of the breast cancer patients in Africa?—a systematic review.* Springerplus, 2013. **1**(1): 83.

[67] Masri, M.A., et al., *Minor role for BRCA2 (exon11) and p53 (exon 5-9) among Sudanese breast cancer patients.* Breast Cancer Res Treat, 2002. **71**(2): 145–7.

[68] Khairy, G.A., et al., *Bilateral breast cancer. Incidence, diagnosis and histological patterns.* Saudi Med J, 2005. **26**(4): 612–5.

[69] Siddig, A., et al., *Estrogen receptor alpha gene polymorphism and breast cancer.* Ann N Y Acad Sci, 2008. **1138**: 95–107.

[70] Siddig, A., et al., *HER-2/neu Ile655Val polymorphism and the risk of breast cancer.* Ann N Y Acad Sci, 2008. **1138**: 84–94.

[71] Yahia, Z.A., et al., *Epstein Barr virus: a prime candidate of breast cancer aetiology in Sudanese patients.* Infect Agent Cancer, 2014. **9**(1): 9.

[72] Fletcher, S.W. and J.G. Elmore, *Clinical practice. Mammographic screening for breast cancer.* N Engl J Med, 2003. **348**(17): 1672–80.

[73] Galukande, M. and E. Kiguli-Malwadde, *Rethinking breast cancer screening strategies in resource-limited settings.* Afr Health Sci, 2010. **10**(1): 89–92.

[74] Harford, J.B., *Breast-cancer early detection in low-income and middle-income countries: do what you can versus one size fits all.* Lancet Oncol, 2011. **12**(3): 306–12.

[75] Yip, C.H., et al., *Guideline implementation for breast healthcare in low- and middle-income countries: early detection resource allocation.* Cancer, 2008. **113**(8 Suppl): 2244–56.

[76] WHO Position Paper on Mammography Screening, in *WHO Guidelines Approved by the Guidelines Review Committee*. 2014: Geneva.

[77] AbdElrahman, S.H. and M.A.A. Yousif, *Self examination of the breast for early detection of breast cancer: the role of medical students in the faculty of medicine – University of Gezira – Sudan.* Sudanese J Publ Health, 2006. **1**(1): 36–42.

[78] AbdElrahman, S.H., I.M. Elbashir, and A.A. Mohamadani, *The prevention of cancer through community-based interventionS (CBIS) in low-resource populations in Gezira state, Central Sudan*, in *27th Annual Meeting of the Internal Association of Cancer Registries*. 2005: Entebbe, Uganda.

[79] Abuidris, D.O., et al., *Breast-cancer screening with trained volunteers in a rural area of Sudan: a pilot study.* Lancet Oncol, 2013. **14**(4): 363–70.

[80] Elhaj, A.M., A.A. Elshaikh, and A.A. Mohammadani, *National guidelines for management of breast cancer: for enforcement or persuasion?* Sudan Med J, 2012. **48**(3): 213–218.

[81] Awadelkarim, K.D., et al., *Tissue microarray (TMA) versus whole section immunohistochemistry in the assessment of ER/PR and Her-2/neu status in a breast cancer series from Sudan.* Breast J, 2013.

[82] Fisher, B., et al., *Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer.* N Engl J Med, 2002. **347**(16): 1233–41.

[83] van Dongen, J.A., et al., *Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial.* J Natl Cancer Inst, 2000. **92**(14): 1143–50.

[84] Veronesi, U., et al., *Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer.* N Engl J Med, 2002. **347**(16): 1227–32.

[85] Preker, A., et al., *Scaling up health professional education: opportunities and challenges for Africa*, in *Force for Scaling Up Education and Training for Health Workers, Global Health Workforce Alliance, World Bank*, 2008: Washington, D.C.

[86] Deantonio, L., et al., *Hypofractionated radiation therapy for breast cancer: Long-term results in a series of 85 patients.* Tumori, 2016: 0.

[87] Whelan, T.J., et al., *Long-term results of hypofractionated radiation therapy for breast cancer.* N Engl J Med, 2010. **362**(6): 513–20.

[88] Wolff, A.C., et al., *American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer.* Arch Pathol Lab Med, 2007. **131**(1): 18–43.

[89] Parkin, D.M., et al., *Changing cancer incidence in Kampala, Uganda, 1991-2006.* Int J Cancer. **126**(5): 1187–95.

[90] Nyagol, J., 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, 2006. **28**(2): 97–103.

[91] Oluwatosin, O.A., *Rural women's perception of breast cancer and its early-detection measures in Ibadan, Nigeria.* Cancer Nurs, 2006. **29**(6): 461–6.

[92] Dye, T.D., et al., *Complex care systems in developing countries: breast cancer patient navigation in Ethiopia.* Cancer. **116**(3): 577–85.

[93] Awadelkarim, K.D., *Research infrastructure: use foreign aid to help African science.* Nature, 2013. **495**(7440): 174.

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