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REVIEW

Breast cancer in Africa: prevalence, treatment options, herbal medicines, and socioeconomic determinants

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Abstract Breast cancer is the leading cause of cancer-related deaths in women worldwide. GLOBOCAN estimated about 1.7 million new cases of breast cancer diagnoses worldwide and about 522,000 deaths in 2012. The burden of breast cancer mortality lies in the developing low-income and middle-income countries, where about 70% of such deaths occur. The incidence of breast cancer is also rising in low-income and middle-income countries in Africa as trend towards urbanization, and adoption of Western lifestyles increases. In general, the triple-negative breast cancer (TNBC) subtype tends to be frequent in women of African ancestry. What are the factors contributing to this prevalence? Are there genetic predispositions to TNBC in African women? This review addresses these questions and provides an update on the incidence, survival, and mortality of breast cancer in Africans, with a focus on sub-Saharan Africans. We have also addressed factors that could account for ethical disparities in incidence and mortality. Further, we have highlighted challenges associated with access to essential drug and to healthcare treatment in some African countries and outlined alternative/herbal treatment methods that are increasingly implemented in Africa and other developing nations.

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Introduction

Cancer is a group of diseases characterized by abnormal cells that grow and invade healthy cells in the body and is amongst the leading cause of death worldwide. According to GLOBOCAN estimates in 2012, an estimated 14.1 million new cancer cases were diagnosed and a staggering mortality of about 8.2 million from cancer were reported worldwide in 2012 [1, 2]. Lung cancer remains the leading cause of cancer-related deaths worldwide, followed by breast cancer [1]. However, breast cancer is the most frequently diagnosed cancer in females and the leading cause of death in females worldwide [1]. With nearly 1.7 million new cases in 2012 and almost 522,000 deaths globally [3], there is not only an urgent need for efficient and alternative treatment methods, but also improved awareness of the disease. Breast cancer incidence rates in women vary by more than tenfold among continents and mortality rates vary about fourfold. The highest rates occur in Western Europe and North America, and the lowest rates in Africa and Asia. Mortality rates among African American women are the highest, whereas the lowest mortality rates exist among Korean women [2]. Studies have shown that on average, African American and African women for instance develop breast cancer a decade earlier than Caucasians [4–7]. The age-standardized breast cancer incidence rate by continent is about 70.08 in Europe, 47.50 in the Americas, 57.5 in Oceania, 37.5, in Asia and 28.66 in Africa, while the mortality rate is about 15.93 in Europe,

13.94 in America, 18.07 in Oceania, 13.21 in Asia and 13.72 in Africa [2, 8, 9]. Five-year survival rates however vary from around 80% in high-income countries to 60% in middle-income countries and 40% in low-income countries [10]. This review examines the current state of breast cancer in African and African-American women, with emphasis on breast cancer management in Africa, as well as alternative methods used for the treatment of breast cancer in Africa.

Breast cancer incidence and mortality in African and African American women

Data compiled from 26 African countries in 2012 indicate that breast cancer accounts for 25% of all cancer diagnosis and 20% of all cancer deaths in women [3, 11]. The incidence of breast cancer in sub-Saharan African women is relatively low (less than 40 per 100,000 women), compared with that of women from the North America and Northern Europe (95 and 100 cases per 100,000 persons, respectively) [3, 12]. However, there is considerable regional variation in incidence rates in Africa, ranging from 26.8 to 30.4 per 100,000 women in Central and East Africa, to nearly 40 per 100,000 in southern African and western African countries [12]. The incidence in sub-Saharan Africa is projected to double by 2050 [13]. For instance, according to a report by the national cancer prevention and control strategy for Zimbabwe, the five most common cancers in black women were cervical cancer (33.9%), breast cancer (9.7%), Kaposi sarcoma (9.6%), eye (8.7%), and non-Hodgkin lymphoma (4.1%). Zimbabwe with a population of about 13 million, recorded 246 registered cases of breast cancer in 2005, and this figure rose to 487 in 2013 [13]. Although only a few African countries maintain breast cancer registries, GLOBOCAN data projected that about 94,000 women in Africa developed breast cancer in 2012 [3].

Breast cancer is the most commonly diagnosed cancer among African-American women, with an estimated 30,700 new cases and about 6310 deaths anticipated in 2016 [14]. Data from the American Cancer Society reveal that the lifetime probability (%) of developing or dying from breast cancer differs based on race/ethnicity in American. 11.1% (i.e., 1 in 9 cases) of African-American women are at risk of developing breast cancer, which is slightly lower than the probability in White women at 13.1% (1 in 8). However, the risk of dying from breast cancer is higher in African-American women (3.3%; 1 in 31), compared with 2.7% (1 in 37) in White women [14]. The incidence rate among African-American women has increased steadily since the 1980s, largely due to more frequent mammography screening [14–19]. However, a slight decrease in the incidence rate in White women in the 2000s was attributed to a drop-in use of hormone replacement therapy [17].

Although the incidence rate of breast cancer is lower in Africa than the rest of the world, the mortality rate in the continent remains the highest [20, 21]. GLOBOCAN data for sub-Saharan Africa in 2012 showed that 94,000 women developed breast cancer and 48,000 died from it. In addition, the burden of breast cancer in sub-Sahara Africa is projected to double between 2012 and 2030 due to population aging and expansion [6, 20]. Mortality rates vary in different African countries. Certain African countries such as Nigeria, Egypt, and Ethiopia are reported to have the highest mortality rates [21, 22]. Data compiled by the Global Health Data Exchange on the total population indicate that in Zimbabwe for example, the average annual breast cancer mortality rate is about 2.5 per 100,000 people [23]. Death rates for breast cancer among African Americans based on a 2008–2012 statistics was estimated at 31 per 100,000 according to the National Center for Health Statistics, Centers for Disease Control and Prevention as provided by the Surveillance, Epidemiology, and End Results Program [14, 16].

Common molecular subtypes of breast cancer in African and African-American women

The World Health Organization (WHO) describes at least 17 distinct histological types of breast cancer. These include invasive ductal carcinoma, invasive lobular carcinoma, tubular carcinoma, invasive cribriform carcinoma, medullary carcinoma, mucinous carcinoma, neuroendocrine carcinoma, invasive papillary carcinoma, invasive micropapillary carcinoma, apocrine carcinoma, metaplastic carcinoma, lipid-rich carcinoma, secretory carcinoma, oncocytic carcinoma, adenoid cystic carcinoma, acinic-cell carcinoma, glycogen-rich clear cell carcinoma, and sebaceous carcinoma [24–26]. However, studies based on gene expression profiling identified four main intrinsic molecular subtypes of breast cancer known as luminal A, luminal B, HER2-enriched and triple-negative breast cancer (TNBC) [27–30] (Fig. 1). Luminal breast cancers constitute about 70% of hormone receptor (HR)+ breast cancers and have more favorable prognosis [31]. Luminal A cancers express high levels of ER and progesterone receptor (PR), and low levels of HER2 whereas, luminal B cancers are ER+, and express high HER2 levels [31, 32]. Luminal B cancers also display higher expression of proliferation genes than luminal A and are therefore higher in grade [31, 32]. HER2-enriched breast cancer constitutes 15–25% of invasive breast cancers, and have poor prognosis. TNBC are characterized by the absence of ER, PR and HER2 overexpression. However, the stratification of TNBC is

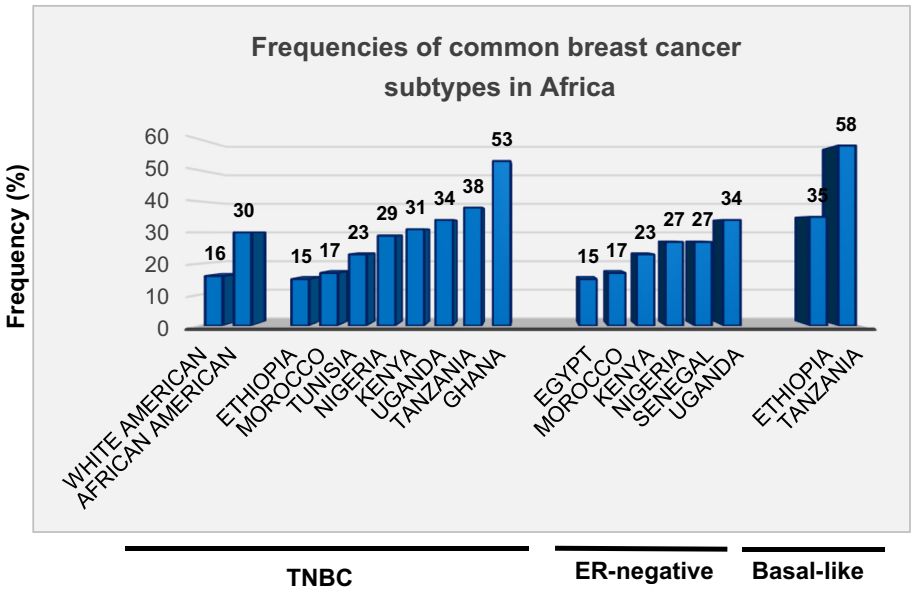

Fig. 1 Reported frequencies of TNBC, ER-negative, and basal-like breast cancers: The graph shows frequencies of these cancers in some Africans and African American populations compared with the White American population

complex [33]. TNBC can be further classified under basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory, mesenchymal (M), M stem-like and luminal androgen receptor subtypes [34]. The M group has been reported to have the worst outcome [31, 32, 34, 35]. TNBC generally represents approximately 15–20% of all newly diagnosed breast cancers, but has the worse prognosis compared with the other subtypes, accounting for a disproportionate number of breast cancer-related deaths each year [36]. Several studies have reported a markedly higher proportion of TNBC in indigenous African populations, accounting for the generally poor survival reported for breast cancer patients in Africa [21, 37, 38]. The incidence of TNBC was also found to be higher in African American women as well as western and sub-Saharan African women in comparison with American, European, and East African women, and this was suggested to be associated with a genetic predisposition to mammary carcinogenesis although no common germline mutation in women of African ancestry has been identified [39].

Prevalence of triple-negative breast cancer in African and African-American women

Clinicopathological characteristics of TNBCs include early onset, large mean tumor size, high grade, and higher incidence of node positivity at the time of diagnosis [40]. Thus, the TNBC status is an independent risk factor for increased propensity for metastases and relapse. This poor prognosis is compounded by the fact that at the molecular level, TNBCs are more heterogeneous compared to HER2+ and ER+ subtypes and therefore lack druggable target(s) [41].

Although adequate population-based data on breast cancer in African countries in general are limited, where available, various studies corroborate that the frequency of TNBCs were significantly higher in sub-Saharan African countries, compared to the western Caucasian countries [39]. It is estimated that about half of sub-Saharan African breast cancer cases diagnosed to be TNBC [42]. The rate of TNBC is especially higher among the younger African women; however, the average age of onset of breast cancer diagnosis is in the late 40s [5–7]. TNBC was reported to account for 53.2% breast cancer cases in Ghanaian women, 29.8% in African Americans, and as low as 15.5% White Americans [43] (Fig. 1). TNBC frequency in Ethiopians was also low at 15.0%. In a Nigerian-based study, analysis of 82 breast cancer patients analyzed between 2013 and 2014, revealed that 31.70% (26/82) of the patients were triple-negative, which is about 10% higher than the global incidence [36, 43]. In a study on Moroccan patients, TNBC was diagnosed in 16.50% of the 152 breast cancer cases analyzed [44]. In general, African American or West African women from Nigeria, Mali, Senegal and Ghana, both display higher frequencies in TNBC/ER−/BL breast cancers, compared with East African countries like Ethiopia. This is can be explained by population migration during the trans-Atlantic slave trade era where individuals from West African countries were transported to North America [39].

BRCA1 and BRCA2 mutations in African and African American women

Hereditary breast cancers are known to account for 2–10% of all cases of breast cancer diagnosis [45]. Pathogenic germline mutations (protein-truncating, disease-associated missense,

and splice variants) within the breast cancer-susceptible genes, *BRCA1* and *BRCA2* [46], especially in TNBCs, are one of the major culprits. More than 2000 different mutations have been reported in *BRCA1* and *BRCA2* genes including deletions, insertions, and numerous single nucleotide substitutions [47]. *BRCA1* and *BRCA2* are in fact the best-known genes linked to breast cancer risk [46]. Malone et al. reported that *BRCA1* mutations are more common in Caucasians (2.9% of breast cancer cases) than African Americans (1.4% of cases) [48]. The prevalence of *BRCA1* mutations in Caucasian American breast cancer patients of Ashkenazi Jewish origin is the highest at 10.2%, compared with mutations in non-Jewish populations, which accounts for 2.0% of all cases [48]. *BRCA2* mutations on the other hand were found to be slightly more prevalent in African Americans (2.6%) versus Caucasians (2.1%) cases [48].

Some of the *BRCA1* and *BRCA2* mutations are founder mutations and the three most common founder mutations occur in Ashkenazi Jews (Jews of Eastern European descent), and include 185delAG and 5382insC (*BRCA1*) and 6174delT (*BRCA2*) [49] (Table 1). Other common *BRCA1* mutations in various ethnic groups include 5382insC, C61G and 4153delA in Polish, 2804delAA in Dutch, 1081delG in Chinese, 4153delA and 5382insC in Russian, Q563X, 3166ins5, 1201del1 and 2594delC in Swedish, 2800delAA in Scottish, 4184del4 in English, and C4446T in French Canadian (reviewed in [50]). The 6174delT, 5573insA, 8765delAG, 2157delG, 999del5 and 4486delG are some of the *BRCA2* founder mutations in Ashkenazi-Jewish, Dutch, French-Canadian, English and Icelandic ethnic groups, respectively (reviewed in [50]) (Table 1).

Compared to the White population, fewer studies have reported specific mutations in the *BRCA1* and *BRCA2* genes in the Black population (Table 2) [51, 52]. There are few reports on *BRCA1* and *BRCA2* genetic testing and limited information on mutation/genetic diversity in *BRCA1* and *BRCA2* genes in most African populations. Shen et al. screened 54 African American breast cancer patients for common mutations in the *BRCA1* gene and identified one novel frameshift mutation (3331 insG) and three missense sequence variants (A3537G, A3667G, and C4009T) on exon 11 at low frequency [53]. None of the Ashkenazi Jewish founder mutations were found in the African American cohort in this study. A literature-based study in 2003 by Olopade et al. [54] revealed that over 50% of all *BRCA1* and *BRCA2* mutations were unique to Africans or African Americans. The study found that recurrent mutations were dispersed, with only two pathogenic *BRCA1* mutations (943ins10 and M1775R), for example, detected in three or more unrelated families. However, *BRCA1* mutations (943ins10, 1832del5, and 5296del4) were associated by haplotype studies and therefore could have ancestral roots. Of particular importance, the 943ins10 mutation was associated with a single haplotype identified in seven African-American women and is speculated to originate from one family which immigrated from the Ivory Coast in West Africa [55]. Diez et al. reported a novel c.1949_1950delTA mutation in the *BRCA1* gene in a Senegalese woman with TNBC and with a family history of breast cancer [56].

A c.798_799delTT *BRCA1* mutation identified in 11 North African families, and accounted for 22% of total identified *BRCA1* mutations in genetic screening in North African countries, including Morocco, Algeria, Tunisia, and Libya, suggesting that this mutation may arise from a founder allele [57]. A survey in Sudan involving 47

Table 1 Examples of BRCA1 and BRCA2 founder mutations

Population	BRCA1	BRCA2	References
Ashkenazi Jewish	185delAG, 532inC	617delIT	[51, 54, 55]
Dutch	del3,8kbEx8-13, del5, 10bpEx22, 204delAA	5573insA	[125]
French Canadian	R1443X, C4446T	8765delAG	[52]
Icelandic	185del AG, 5454 delC	999del5, 4486delG	[52]
Egypt	c.789_799delTT	999del5	[126–128]
Morocco		ND	[126–128]
Western Cape of South Africa		599del4	[126–128]
Polish	5382C, C61G, 4153delA	ND	[52]
Chinese	1081delG	ND	[52]
Russia	4153delA, 5382insC	ND	[52]
Sweden	Q563X, 3166ins5, 1201del1, 2594delG	ND	
Scottish/English	2800delAA/4184del4	ND/2157delG	[52]

ND not determined

Table 2 *BRCA1* and *BRCA2* mutations reported in African and African Americans

Population	BRCA1	BRCA2	References
Nigeria	c.5277+480_5332+672del	ND	[129]
Egypt	185del AG, 5454 del C, 330dupA, 4160delAG, 2789delG, 5385insC, c. 4041delAG	999 del 5	[126]
Tunisia	c.2551delG, c.5266dupC, c.798_799delTT	1537del4, 5909insA, c.211dupA	[130, 131]
Algeria	c.46_74del29, c.798_799delTT, c.1016dupA	ND	[56]
Morocco	c.789_799delTT,c.5095C>T, c.4942A>T, c.2805delA/2924delA	ND	[127, 128]
Western Cape of South Africa	c.1504_1508del	c.2826_2829del, c.6447_6448dup, c.5771_5774DEL	[132]
Africa American	185delAG, 5382insC, 943ins10, 1832del5, 5296del4, c.1949_1950delTA	5999Ddel4	[56, 60, 133]

ND not determined

subjects with family history of breast cancer and 20 control subjects (with no family history), found *BRAC1* and *BRCA2* mutations in 51% of those with a family history, and 20% of the control group [53]. The majority of the *BRCA1* mutations detected occurred in exon 11. Only 2 *BRCA2* mutations were found, and both in the control group [53]. Genetic analysis of breast cancer samples from North African patients led to the identification of a potential founder allele (c.798_799delTT) that occurred in two Algerian families and in two families from Tunisia [58]. However, no solid founder mutations have been identified in the few studies conducted so far which indicated a high frequency of *BRCA1* mutations in African women (Table 3). Given the economic constraints inherent to some African countries, there is an urgent need for a concerted effort to improve screening programs and individual testing throughout the continent to determine the impact of germ line mutations among African breast cancer patients.

Breast screening and diagnosis

High mortality rates of breast cancer in Africa have been linked to inadequate screening and diagnostic services [1, 2, 59]. Most African countries are yet to implement a national breast cancer screening program. Screening and early diagnosis have been shown to significantly reduce the high rate of breast cancer mortality in developed countries [6, 60]. Three main methods are used today to screen breast cancer worldwide: mammography, clinical breast examination by trained personnel, and self-breast examination [56, 60]. Mammography is widely used and proven to be the most effective method. For instance, studies conducted in Australia, the US and some European nations showed a clear reduction in breast cancer mortality rates when mammogram was used for screening breast cancer patients [56]. However, most African and less developed countries have limited access to mammography. For example, a study in Uganda showed that only four mammogram machines were available for a population of 6–7 million eligible women and the service was unaffordable for the average Uganda women [60, 61]. Furthermore, mammography is recommended for screening of women between 40 and 69 years [6] and not for women below the age of 35 year because the denser breast in younger women makes it difficult to distinguish normal tissues from abnormal tissues on the X-ray film [61]. Since breast cancer incidence is higher among young African women, when compared to women from Western countries, their ineligibility for mammography puts them at a higher risk of displaying more advanced tumors at the time of diagnosis [6, 61].

Due to the limited access to mammography, many African countries have resorted to the use of ultrasonography. Ultrasonography has been shown to increase the rate of breast cancer diagnosis especially in women that have denser breasts or in cases where negative result was obtained with mammogram [56]. In addition, sonography itself is cost effective and therefore highly used in many African countries such as Nigeria, Uganda, and Egypt [62–65]. However, there is inadequate information on whether the use of ultrasonography is linked to reduced rates of breast cancer mortality [56]. A study in Malawi concluded that clinical breast examination by trained personnel was a cost-effective method for breast cancer screening [66]. In Morocco and Ghana, clinical breast examination has also improved early breast cancer diagnosis especially among lay women and people that lack access to mammogram and sonography [6, 67].

Table 3 Major molecular subtypes of breast cancer

	Major molecular subtypes of breast cancer			
	Luminal A	Luminal B	HER2+	Basal-like (triple-negative or TNBC)
Characteristics	ER/PR+, HER2−	ER/PR+, HER2+	HER2 overexpression	ER/PR/HER− (TNBC)
Genetics			*erbB2/HER2* gene amplification chromosome 17q12	*BRCA1* and *BRCA2*, etc.
Approximate incidence (% of cases)	73	10	13	5
Therapy	Targeted	Targeted	Targeted	Chemotherapy
Drug examples	Tamoxifen, fulvestrant, aromatase inhibitors (anastrozole, letrozole, or exemestane)	Tamoxifen, fulvestrant, aromatase inhibitors (anastrozole, letrozole, or exemestane) and HER2-targeted drugs	Trastuzumab/Herceptin, tyrosine kinase inhibitors (lapatinib, dasatinib, imatinib, etc.)	Cytotoxics such as doxorubicin, paclitaxel, cyclophosphamide, and carboplatin
Prognosis	Favorable	Poorer than luminal A; better than HER2 or TNBC	Aggressive, but better prognosis because of availability of combination therapy	Aggressive and unfavorable because of lack of target therapy

Breast self-examination is another method that is highly recommended by physicians in many African countries for because it is free, painless and easy to practice [64, 68]. There is however limited information on the effect of breast self-examination in the reduction of breast cancer mortality. Despite the awareness of breast cancer and the advantages of breast self-examination in Africa, only few women are reported to conduct self-examination [68, 69]. The reluctance to perform breast self-examination by some of these women was based on the sociocultural environment in which they live [68]. For others, it was simply because of fear instigated by their perceptions of breast cancer as a lethal disease [70].

Conventional breast cancer therapy

Since the late 1970s there has been a steady increase in the number of treatment options for breast cancer [71]. Nowadays, there is an assortment of targeted therapies and other strategies including surgery, radiation and chemotherapy. The selection of a breast cancer treatment plan is based on the identification of the molecular subtype of the patient, which can be ER+, HER2+, or triple-negative. While various targeted treatment options are available for ER+ and HER2+ breast cancers, TNBCs, which lack a characterized target, can only be treated by chemotherapy. All these therapies however can be applied as neoadjuvant or adjuvant therapy, that is before or after surgery, respectively [71].

ER+ targeted therapy (hormonal therapy)

Endocrine therapy for ER+ breast cancers is the most commonly used therapy that targets the ER protein itself or its ligand, estrogen. ER is part of the estrogen signaling pathway. Estrogen binds to the hydrophobic pocket of ER, inducing receptor resulting in conformational changes and receptor-dimer formation, all of which enable ER to regulate the transcription of genes involved in cell growth and proliferation. There are different classes of endocrine treatments. These include selective ER modulators such as tamoxifen, and selective ER degraders such as fulvestrant, and aromatase inhibitors (AIs) [71]. Tamoxifen is a partial agonist that binds competitively with estrogen in the same hydrophobic pocket in ER, but induces a different conformational change that suppresses the ability of the ER to bind to its target gene [72]. Tamoxifen was approved by the Food and Drug Administration (FDA) in 1977 as the front-line drug for the treatment of metastatic ER+ breast cancers. Fulvestrant is a pure antagonist that induces the degradation of the ER protein. The drug was approved by the FDA for the treatment of ER+ metastatic breast cancer in 2002 [71]. AIs reduce the amount of estrogen in the body by blocking the activity of aromatase, an enzyme that catalyzes the conversion of androgen into estrogen. AIs such as anastrozole (FDA approval, 1996) and letrozole (FDA approval, 2005) have proven to be extremely effective in the treatment of breast cancer among postmenopausal women [73].

HER2+ targeted therapy

HER2 overexpression is historically associated with poor outcomes [74]. The development of a HER2-targeted agent, trastuzumab (sold under the brand name Herceptin), has considerably improved prognosis of patients with HER2+ breast cancer [75]. The drug was approved by the FDA in combination with paclitaxel as a first-line treatment of HER2+ metastatic breast cancers, and as a single agent for second and third-line therapy. Trastuzumab became the first therapeutic antibody targeted against an oncogene to receive FDA approval. Trastuzumab was shown to significantly improve median survival by about 5 months from 20.3 to 25.1 months [74]. Several other newer HER2-targeted agents, including lapatinib, pertuzumab, and trastuzumab-emtansine (T-DM1), have also been clinically beneficial in the treatment of HER2+ breast cancers [71, 76, 77]. Neoadjuvant treatment of early-stage HER2+ breast cancers with a combination of trastuzumab and sequential chemotherapy, followed by breast surgery, radiotherapy (if recommended), is currently the standard approach. This has dramatically improved survival rates in the HER2+ subgroup to nearly 40–75% over 10 years [78, 79].

Treatment of triple-negative breast cancers

No targeted therapies are available for TNBCs. These cancers are typically treated with a combination of therapies such as surgery, radiation therapy, and chemotherapy [71]. Radiation therapy is also routinely given to patients who received lumpectomy, while chemotherapeutics are administered as neoadjuvant or adjuvant therapy [71]. According to the American Cancer Society (https://www.cancer.org/), the most common chemotherapeutic drugs for adjuvant and neoadjuvant treatment used in combination therapy include: anthracyclines, such as doxorubicin (Adriamycin) and epirubicin (Ellence); taxanes, such as paclitaxel (Taxol) and docetaxel (Taxotere); 5-fluorouracil; cyclophosphamide (Cytoxan) and carboplatin (Paraplatin). In cases of advanced metastasis, breast cancer drugs such as platinum agents (cisplatin, carboplatin), vinorelbine (Navelbine), capecitabine (Xeloda), liposomal doxorubicin (Doxil), gemcitabine (Gemzar), mitoxantrone (Novantrone), ixabepilone (Ixempra), albumin-bound paclitaxel (nab-paclitaxel or Abraxane), and eribulin (Halaven) are available choices.

Surgery

Limited resources for complementary neoadjuvant or adjuvant therapy in sub-Saharan Africa has contributed to the application of surgery as the primary modality for the management of resectable breast cancer. Mastectomy is considered culturally objectionable in some African countries, and therefore compliance by the patients varies from country to country. For example, the refusal rates in countries like Eritrea and Cameroon are fewer compared to Nigeria for example [80]. About 35% of all breast cancer cases reported in Nigeria are treated surgically, and this rate is almost 100% in Cameroon for resectable cases [12, 80]. It is reported that up to 75% of women in Africa display very advanced disease at the time of diagnosis and this rate is as high as 81% in the Democratic Republic of Congo and 90% in Niger [81, 82]. About 85% of breast cancer patients undergo mastectomy usually because of the advanced stage of the disease or simply due to lack of other modalities of treatment. In sharp contrast, mastectomy rates in Europe are 30% [83]. Lack of or poor access to radiation facilities in Africa is the rate-limiting step for breast conservation in many African countries [12]. Even countries in like Tunisia, where radiotherapy facilities are available, the breast conservation rate is less than 20% [84, 85].

Access to therapeutic drugs breast cancer treatment in Africa

Breast cancer patients in Africa face unique challenges beyond the pathology of the disease because of the lack of adequate social and economic resources. Besides, there is a steady rise in the cost of new and more effective systemic therapies for breast cancer. These challenges are compounded by inadequate allocation of funds for healthcare in general [11]. The high cost of treatment, severe clinical side effects, and esthetic side effects such as hair loss from chemotherapy, greatly contribute to the elevated noncompliance rates in many countries in Africa [86–88]. In Cameroon, a third of patients are reported to delay the first two cycles of chemotherapy because of limited financial resources [86]. Non-adherence to chemotherapy schedules has also been documented in Nigeria [89].

The price difference between generic and brand name drugs is significant and this fact underscores the importance of increasing access of generic drugs to low–middle-income countries (LMICs). Although the patents for most chemotherapy drugs such as paclitaxel, cyclophosphamide, carboplatin and cisplatin, carboplatin have expired, there are considerable price discrepancies observed in the products. According to a report prepared for OXFAM (Oxford Committee for Famine Relief: www.oxfam.org) by Ellen 't Hoen (an activist for global access to essential drugs) [90], the drug with the highest cost per treatment is imatinib with low, medium, and high cost per treatment of $28295, $37259, and $46224, respectively. On the other hand, the cost per treatment for tamoxifen, ranging from $16 to $548,

is the lowest (Fig. 2). Although the patent for tamoxifen expired in 2002, the drug has one of the highest price range [91]. The buyers median price of tamoxifen is 0.0897 US$/tablet [91]; however, the high/low ratio price of tamoxifen can be as high as 33 (Fig. 3) [91]. Further, the indicative cost per treatment of paclitaxel can be as low as $658 in some regions of the world and 19 times more ($12,250) in other areas (www.oxfam.org). These high ratio values cannot be accounted for by the drug's patent status alone since the patent for tamoxifen, for example, expired in 2002, yet the drug has the highest high/low price ratio when compared with other drugs [92]. The lower cost of essential drugs in some nations may be attributed to government-imposed subsidy regulations that allow for affordable public healthcare.

Both tamoxifen and trastuzumab used for the treatment of ER and HER2+ breast cancers, respectively, are included in the WHO essential drug list [93]. However, the cost and access to targeted therapy medication for breast cancer is still a concern in many LMIC including many sub-Saharan African countries. While generic tamoxifen is now readily available and at very low cost or even free in some countries, the cost of trastuzumab is still astronomically high even for high-income countries [94] (Fig. 4). For example, the average price for one trastuzumab injection in South Africa is $2115, while the average UK retail price and UK hospital price are $631 and $317, respectively. The average cost per injection of trastuzumab in US clinic is about $3000. The annual cost per year for trastuzumab injections can be as high as $54,000 and $49,000 in China and US, respectively. This treatment costs over $46,000 in South Africa and about $25,000 in the UK (www.oxfam.org) (Fig. 4). A lower cost of the generic drug between $11,000 and $24,000 can be found in India where Indian generic manufacturers, for example, Emcure Pharmaceuticals Ltd., lowered the general price trastuzumab by as much as 30% [95]. While breast cancer mortality rates in wealthy countries are declining because of early diagnosis and the availability of treatment opportunities, the prognosis is dire in LMIC in African, where there is limited access to and affordability of effective treatment.

Alternative treatment strategies for breast cancer in Africa

Socioeconomic factors and the high cost of available therapeutic drugs have largely contributed to the rising incidence of breast cancer in Africa. However, the popularization of herbal medicine for the treatment of various ailments provides hope and urgently needed alternatives to conventional medicine. There are reports that indicate that

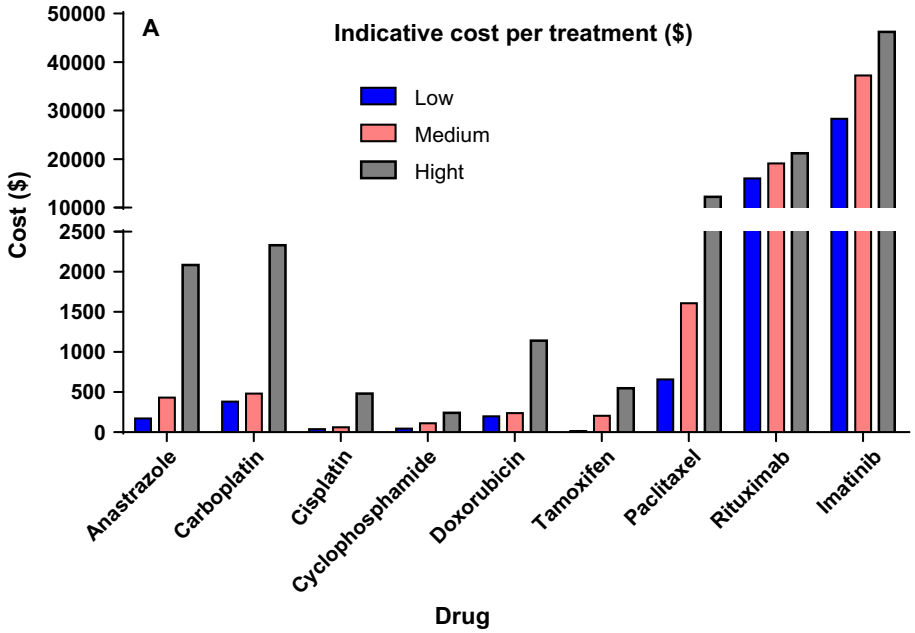

Fig. 2 Relative cost per treatment of indicated drugs ($): the low, medium, and high cost. Reported by Global Task Force on Expanded Access to Cancer Care and Control, and adapted from ACCESS TO CANCER TREATMENT: "A study of medicine pricing issues with recommendations for improving access to cancer medication." A report prepared for OXFAM by Ellen 't Hoen, LLM: Medicines Law and Policy. *Please note: Estimated costs for anastrozole, imatinib, and tamoxifen are per year, and these costs can fluctuate depending on duration of the particular treatment course. The chemotherapy is usually a multi-regimen treatment and therefore the total treatment costs will vary depending on the prescribed regimen. Also see [95] and http://gtfccc.harvard.edu/fs/docs/icb.topic1063570.files/ccd_report_111027.pdf for further details

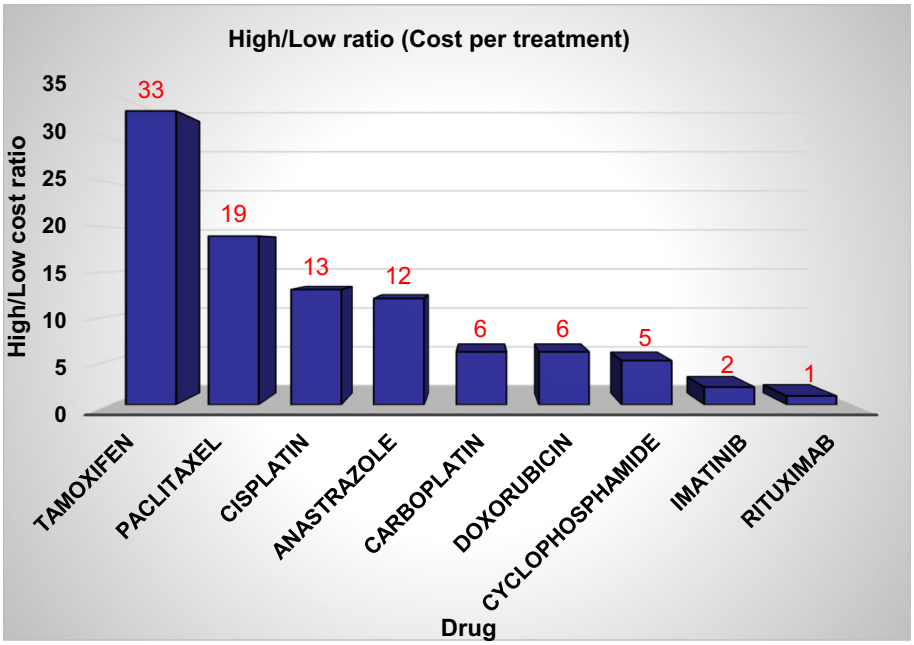

Fig. 3 High/low ratio of the relative cost per treatment of indicated drugs: the ratio ranges from 1 (rituximab) to 33 (tamoxifen). For additional information, see http://gtfccc.harvard.edu/fs/docs/icb.topic1063570.files/ccd_report_111027.pdf for further details

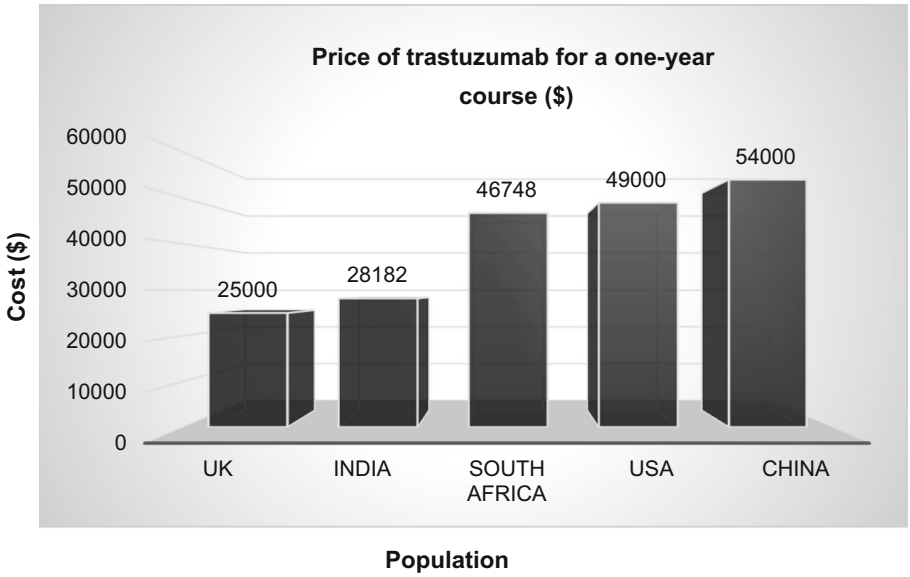

Fig. 4 Price of trastuzumab for a 1-year course ($): trastuzumab is not on the WHO model list of essential medicines (EML) and so the cost of the drug per year is considerable higher than those of other drugs on the WHO EML. The cost can be as high as $54,000 in China and less than 20,000 in India. Adapted from Ellen 't Hoen [90]. For additional information, also see: http://gtfccc.harvard.edu/fs/docs/icb.topic1063570.files/ccd_report_111027.pdf. Also see: 'Roche dropping Herceptin price in India by 30%' http://www.fiercepharma.com/story/roche-droppingherceptin-price-india-30/2013-03-01; and for Biocon launch on Herceptin biosimilar in India see: http://www.pharmatimes.com/article/14-01-20/Biocon_to_launch_world_s_first_Herceptin_biosimilar_in_India.aspx#ixzz3QbEB6lAv

some natural dietary agents in fruits, spices, and vegetables, and plant-derived phytochemicals exhibit health promoting effects, including the ability to prevent and/or suppress the progression of various types of cancers including breast cancer [96–99]. Numerous plant extracts have been tested in a variety of in vitro and in vivo model systems against different types of cancers. These plants have been shown to exhibit chemopreventive and chemotherapeutic effects due to their high levels of alkaloids, terpenes, benzopyrans, coumarins, diarylheptanoids, flavonoids, indoles, xanthonoids, proteins, polysaccharides, carotenoids, and stilbenes contents [100–102]. It is estimated that about 60% of breast cancer patients already use complementary alternative therapies in combination with conventional anti-cancer drugs [100]. Phytochemicals, for example, are known to possess anti-oxidant activity, but at

relatively higher concentrations can act as pro-oxidant by generating reactive species that induce DNA fragmentation of cancerous cells or by preventing the activation of pro-carcinogens [103–106].

Africa is known for its large diversity of medicinal plants for the treatment of various ailments including cancer. The increasing use of medicinal plants has generated considerable interest, not only among members of the scientific community, but also among the general public [101, 102, 107]. Although many African plant extracts have been reported to exhibit anticancer activity, those used for the specific treatment of breast cancer are scarce. Table 4 contains a list of some plants whose extracts have displayed promising results in experimental studies. These plant extracts are administered in different forms to treat breast cancer [102]. In Kenya for instance, the stem bark of *Tabernaemontana stapfiana* is dried and pounded into powder, mixed with alcohol and applied topically once a day for a month [102]. The dried leaves powder of *Glycine wightii*, known to have high penetrative ability, is also

Table 4 Promising plant extracts with anti-breast cancer activity

Plant species	Plant part(s) or type	Breast cancer cell type/animal model	Pharmacological target/mechanism of action	References
Ganoderma lucidum	Mushroom	Breast cancer cell lines; mice	Inhibit the release of IL-8, IL-6, MMP-2 and MMP-9; Wnt/β-catenin signaling; downregulates the ER	[121, 129]
Azadirachta indica	Leaves	Rats	– Upregulates proapoptotic genes – Upregulates p53, B cell lymphoma-2 protein (Bcl-2)-associated X protein (Bax), Bcl-2-associated death promoter protein (Bad) caspases – Upregulates phosphatase and tensin homolog gene (PTEN), as well as c-Jun N-terminal kinase (JNK)	[134]
Hwanggeum chal sorghum	Whole plant	MCF-7 MDA-MB 231 Mice	– Blocks Jak/STAT signaling pathways – Down-regulates the expression of STAT5b/IGF-1R and STAT3/VEGF – Down-regulate the expression of VEGF-R2 – Down-regulate the expression of cell cycle regulators (cyclin D, cyclin E, and pRb) – Induces G1 phase arrest and migration inhibition	[135]
Boswellia serrata	Gum resin exudate	Rats	– Induces cell death by inhibiting the phosphorylation of ERK-1 and ERK-2 – Induces apoptotic pathways	[135, 137]
Momordica charantia	Leaves	Fruit	– Upregulates the expression of tumour suppressor gene – Modulates signal transduction	[138]
Ocimum sanctum	Leaves	MCF-10 DCIS	– Inhibits cell proliferation and migration – Increases ROS generation – Causes induction of COX-2 protein	[139]
Acokanthera oppositifolia	Stems	MCF-7	Inhibit cell proliferation	[102]
Xanthium strumarium	Stems	MCF-7		
Oncosiphon piluliferum[a]	Whole plants	MCF-7		
Kigelina africana[a]	Roots	MCF-7		
Parinari capensis[a]	Whole plants	MCF-7		
Sansevieria pearsonii[a]	Roots	MCF-7		
Pelargonium acraeum[a]	Whole plants	MCF-7		

[a] Plants that showed total growth inhibition at concentration ranging from 6.25 to 8.92 μg/mL

applied topically [102], whereas, the *Tragia brevipes* powder is infused and orally taken daily [102]. It is important to note that these practices are undertaken by communities living in and around the tropical rainforest, and in regions where there is limited access to any form of surgery or to standard clinical care. This has led to a great appreciation for alternative medicinal practices, even though the efficacy of the products used has not been clinically validated.

The clinical benefits of herbal medications have however been well documented in other parts of the world, including China (for review, see [108]). For example, a study by Piao et al. [109] demonstrated that breast cancer patients that underwent conventional chemotherapy in combination with the standardized aqueous mistletoe extract from China saw significantly improved quality of life and reduced occurrence of adverse effects in comparison to patients that received conventional chemotherapy alone, or those co-treated with lentinan [110]. The beneficial effect of this plant extract was attributed to its ability to modulate the immune system [110]. A similar conclusion was made when breast cancer patients were treated with chemotherapy in combination with *Shenqi Fuzheng* injection [111]. The *Shenqi Fuzheng* injection is formulated from two kinds of Chinese medicinal herbs (*huangqi* and *dangshen*), and was approved by the State FDA of the People's Republic of China in 1999 primarily as an anti-tumor injection [112]. Clinical trials on the use of *Shenqi Fuzheng* injection in combination with platinum-based chemotherapy for the treatment of advanced non-small cell lung cancer have demonstrated improved tumor response and reduced the toxicity from standard platinum-based chemotherapy [113]. *Shenqi Fuzheng* injection combined with chemotherapy has also been shown to be effective in the treatment of breast cancer in a mechanism that is reported to involve improved immunity [111, 114–116].

Other Chinese traditional herbs such as *Salvia miltiorrhiza* (Danshen) and *Coriolus versicolor* (Yunzhi) have also been shown to modulate the immune system in breast cancer patients' post-treatment [117]. *Ganoderma lucidum*, also commonly known as Reishi or Lingzhi, has been used as a potent medicinal mushroom for more than 2000 years in China [118]. A high dietary intake of Reishi has been found to be negatively associated with the risk of developing breast cancer [119]. Further, many studies have reported that Reishi has anti-cancer activities in in vivo and in vitro breast cancer models. [118, 120–132]. The results of a case–control study in over 2000 patients in China revealed that the intake of fresh or dried mushrooms alone or in combination with green tea reduced the risk of breast cancer in women and had a positive effect on suppressing malignancy [133]. All these studies validate a potential use of Reishi in breast cancer patients as an adjunct to chemotherapy or radiotherapy. It has been reported that almost all breast cancer patients in China use herbal medicine as part of their cancer therapy to boost their immune system [134], and to improve quality of life after operation [135].

Conclusion and future

Breast cancer incidence in African countries is rising [6, 101, 102, 136, 137], and it is presently considered as the leading cause of cancer in women [138, 139]. This increase is due to socioeconomic factors compounded by the: (i) lack of resource and/or treatment facilities; (ii) limited access to early detection; (iii) delay in seeking diagnosis, which result in a high proportion of women with disease at the late-stage; (iv) high cost of available chemotherapeutic drugs; (v) lack of effective national awareness campaigns; and (vi) increasing urbanization. Herbal medicine in Africa is an under-explored alternative to treatment and its future use as an affordable adjunctive therapy for breast cancer will be especially beneficial for African countries and other low-income countries.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108
2. Torre LA, Siegel RL, Ward EM, Jemal A (2016) Global Cancer Incidence and Mortality Rates and Trends–An Update. Cancer Epidemiol Biomarkers Prev 25:16–27
3. Ferlay J, Soerjmataram I, Ervik M, Dikshit R, Eser S, Mathers C (2013) GLOBOCAN 2012 cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. International Agency for Research on Cancer, Lyon
4. Aziz H, Hussain F, Sohn C, Mediavillo R, Saitta A, Hussain A, Brandys M, Homel P, Rotman M (1999) Early onset of breast carcinoma in African American women with poor prognostic factors. Am J Clin Oncol 22:436–440

5. Abdulrahman GO Jr, Rahman GA (2012) Epidemiology of breast cancer in europe and Africa. J Cancer Epidemiol 2012:915610
6. Brinton LA, Figueroa JD, Awuah B, Yarney J, Wiafe S, Wood SN, Ansong D, Nyarko K, Wiafe-Addai B, Clegg-Lamptey JN (2014) Breast cancer in Sub-Saharan Africa: opportunities for prevention. Breast Cancer Res Treat 144:467–478
7. Ly M, Antoine M, Dembele AK, Levy P, Rodenas A, Toure BA, Badiaga Y, Dembele BK, Bagayogo DC, Diallo YL et al (2012) High incidence of triple-negative tumors in sub-saharan Africa: a prospective study of breast cancer characteristics and risk factors in Malian women seen in a Bamako university hospital. Oncology 83:257–263
8. Donepudi MS, Kondapalli K, Amos SJ, Venkanteshan P (2014) Breast cancer statistics and markers. J Cancer Res Ther 10:506–511
9. Dubey AK, Gupta U, Jain S (2015) Breast cancer statistics and prediction methodology: a systematic review and analysis. Asian Pac J Cancer Prev 16:4237–4245
10. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T et al (2008) Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol 9:730–756
11. Kantelhardt EJ, Muluken G, Sefonias G, Wondimu A, Gebert HC, Unverzagt S, Addissie A (2015) A Review on Breast Cancer Care in Africa. Breast Care (Basel) 10:364–370
12. Vanderpuye V, Grover S, Hammad N, PoojaPrabhakar N, Simonds H, Olopade F, Stefan DC (2017) An update on the management of breast cancer in Africa. Infect Agents Cancer. doi:10.1186/s13027-017-0124-y
13. Chokunonga E, Borok MZ, Chirenje ZM, Nyakabau AM, Parkin DM (2013) Trends in the incidence of cancer in the Black population of Harare, Zimbabwe 1991-2010. Int J Cancer 133:721–729
14. DeSantis CE, Siegel RL, Sauer AG, Miller KD, Fedewa SA, Alcaraz KI, Jemal A (2016) Cancer statistics for African Americans, 2016: progress and opportunities in reducing racial disparities. CA Cancer J Clin 66:290–308
15. Boring CC, Squires TS, Health CW Jr (1992) Cancer statistics for African Americans. CA Cancer J Clin 42:7–17
16. DeSantis C, Naishadham D, Jemal A (2013) Cancer statistics for African Americans, 2013. CA Cancer J Clin 63:151–166
17. Ghafoor A, Jemal A, Cokkinides V, Cardinez C, Murray T, Samuels A, Thun MJ (2002) Cancer statistics for African Americans. CA Cancer J Clin 52:326–341
18. Wingo PA, Bolden S, Tong T, Parker SL, Martin LM, Heath CW Jr (1996) Cancer statistics for African Americans, 1996. CA Cancer J Clin 46:113–125
19. American-Cancer-Society (2016) Cancer facts and figures for African Americans, p 38
20. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. Journal international du cancer 136:E359–E386
21. Eng A, McCormack V, dos-Santos-Silva I (2014) Receptor-defined subtypes of breast cancer in indigenous populations in Africa: a systematic review and meta-analysis. PLoS Med 11:e1001720
22. Tetteh DA, Faulkner SL (2016) Sociocultural factors and breast cancer in sub-Saharan Africa: implications for diagnosis and management. Womens Health (Lond) 12:147–156
23. GHDx, I. Global health data exchange. http://ghdx.healthdata.org/
24. World-Health-Organization (2012) WHO classification of tumours of the breast. International Agency for Research on Cancer (IARC), Lyon
25. Weigelt B, Geyer FC, Reis-Filho JS (2010) Histological types of breast cancer: how special are they? Mol Oncol 4:192–208
26. Weigelt B, Reis-Filho JS (2009) Histological and molecular types of breast cancer: is there a unifying taxonomy? Nat Rev Clin Oncol 6:718–730
27. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752
28. Prat A, Perou CM (2011) Deconstructing the molecular portraits of breast cancer. Mol Oncol 5:5–23
29. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS et al (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 98:10869–10874
30. Brenton JD, Carey LA, Ahmed AA, Caldas C (2005) Molecular classification and molecular forecasting of breast cancer: ready for clinical application? Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23:7350–7360
31. Cho N (2016) Molecular subtypes and imaging phenotypes of breast cancer. Ultrasonography 35:281–288
32. Hon JD, Singh B, Sahin A, Du G, Wang J, Wang VY, Deng FM, Zhang DY, Monaco ME, Lee P (2016) Breast cancer molecular subtypes: from TNBC to QNBC. Am J Cancer Res 6:1864–1872
33. Prat A, Karginova O, Parker JS, Fan C, He X, Bixby L, Harrell JC, Roman E, Adamo B, Troester M et al (2013) Characterization of cell lines derived from breast cancers and normal mammary tissues for the study of the intrinsic molecular subtypes. Breast Cancer Res Treat 142:237–255
34. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA (2011) Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 121:2750–2767
35. Ahn SG, Kim SJ, Kim C, Jeong J (2016) Molecular Classification of Triple-Negative Breast Cancer. J Breast Cancer 19:223–230
36. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA (2007) Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 13:4429–4434
37. Bird PA, Hill AG, Houssami N (2008) Poor hormone receptor expression in East African breast cancer: evidence of a biologically different disease? Ann Surg Oncol 15:1983–1988
38. Huo D, Ikpatt F, Khramtsov A, Dangou JM, Nanda R, Dignam J, Zhang B, Grushko T, Zhang C, Oluwasola O et al (2009) Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. J Clin Oncol 27:4515–4521
39. Newman LA, Kaljee LM (2017) Health disparities and triple-negative breast cancer in African American women: a review. JAMA Surg. doi:10.1001/jamasurg.2017.0005
40. Hubalek M, Czech T, Muller H (2017) Biological Subtypes of Triple-Negative Breast Cancer. Breast Care 12:8–14
41. Hahnen E, Hauke J, Engel C, Neidhardt G, Rhiem K, Schmutzler RK (2017) Germline Mutations in Triple-Negative Breast Cancer. Breast Care (Basel) 12:15–19
42. Der EM, Gyasi RK, Tettey Y, Edusei L, Bayor MT, Jiagge E, Gyakobo M, Merajver SD, Newman LA (2015) Triple-Negative Breast Cancer in Ghanaian Women: the Korle Bu Teaching Hospital Experience. Breast J 21:627–633
43. Obomaa YI, Susana BE, Elesha SO, Jonathan M (2017) Breast cancer biomarkers at Niger delta university hospital: comparisons with national and international trends and clinical significance. Pathophysiology. doi:10.1016/j.pathophys.2017.05.002

44. Rais G, Raissouni S, Aitelhaj M, Rais F, Naciri S, Khoyaali S, Abahssain H, Bensouda Y, Khannoussi B, Mrabti H et al (2012) Triple negative breast cancer in Moroccan women: clinico-pathological and therapeutic study at the National Institute of Oncology. BMC Womens Health 12:35
45. Campeau PM, Foulkes WD, Tischkowitz MD (2008) Hereditary breast cancer: new genetic developments, new therapeutic avenues. Hum Genet 124:31–42
46. Pruss D, Morris B, Hughes E, Eggington JM, Esterling L, Robinson BS, van Kan A, Fernandes PH, Roa BB, Gutin A et al (2014) Development and validation of a new algorithm for the reclassification of genetic variants identified in the BRCA1 and BRCA2 genes. Breast Cancer Res Treat 147:119–132
47. Karami F, Mehdipour P (2013) A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int. doi:10.1155/2013/928562
48. Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ, Marchbanks PA, Simon MS, McDonald JA, Norman SA et al (2006) Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in White and Black American women ages 35 to 64 years. Cancer Res 66:8297–8308
49. Antoniou AC, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Olsson H, Johannsson O, Borg A, Pasini B et al (2005) Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies. J Med Genet 42:602–603
50. Nagy R, Sweet K, Eng C (2004) Highly penetrant hereditary cancer syndromes. Oncogene 23:6445–6470
51. Lawal AO, Atoyebi O, Adesunkanmi AK (2012) Seventeen years after BRCA1: what is the BRCA mutation status of the breast cancer patients in Africa? A systematic review. Springerplus. doi:10.1186/2193-1801-1-83
52. Oluwagbemiga LA, Oluwole A, Kayode AA (2012) Seventeen years after BRCA1: what is the BRCA mutation status of the breast cancer patients in Africa? A systematic review. Springerplus. doi:10.1186/2193-1801-1-83
53. Elnour AM, Elderdery AY, Mills J, Mohammed BA, Elbi-etAbdelaal D, Mohamed A, Elhassan K, Hady A, Wahab A, Cooper A (2012) BRCA 1 & 2 mutations in Sudanese secondary school girls with known breast cancer in their families. Int J Health Sci (Qassim) 6:8
54. Olopade OI, Fackenthal JD, Dunston G, Tainsky MA, Collins F, Whitfield-Broome C (2003) Breast cancer genetics in African Americans. Cancer 97:236–245
55. Stoppa-Lyonnet D, Laurent-Puig P, Essioux L, Pages S, Ithier G, Ligot L, Fourquet A, Salmon RJ, Clough KB, Pouillart P et al (1997) BRCA1 sequence variations in 160 individuals referred to a breast/ovarian family cancer clinic. Institut Curie Breast Cancer Group. Am J Hum Genet 60:1021–1030
56. Lauby-Secretan B, Loomis D, Straif K (2015) Breast-cancer screening-viewpoint of the IARC Working Group. N Engl J Med 373:1479
57. Laraqui A, Uhrhammer N, Rhaffouli HE, Sekhsokh Y, Lahlou-Amine I, Bajjou T, Hilali F, El Baghdadi J, Al Bouzidi A, Bakri Y et al (2015) BRCA genetic screening in Middle Eastern and North African: mutational spectrum and founder BRCA1 mutation (c.798_799delTT) in North African. Dis Markers. doi:10.1155/2015/194293
58. Uhrhammer N, Abdelouahab A, Lafarge L, Feillel V, Ben Dib A, Bignon YJ (2008) BRCA1 mutations in Algerian breast cancer patients: high frequency in young, sporadic cases. Int J Med Sci 5:197–202
59. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386
60. Panieri E (2012) Breast cancer screening in developing countries. Best Pract Res Clin Obstet Gynaecol 26:283–290
61. Galukande M, Kiguli-Malwadde E (2010) Rethinking breast cancer screening strategies in resource-limited settings. Afr Health Sci 10:89–92
62. Denewer A, Hussein O, Farouk O, Elnahas W, Khater A, El-Saed A (2010) Cost-effectiveness of clinical breast assessment-based screening in rural Egypt. World J Surg 34:2204–2210
63. Agodirin SO, Ojemakinde OM, Bello TO, Oguntola AS, Aremu AA, Ojemakinde KO, Adeoti ML, Agbakwuru EA (2012) Ultrasound-guided wire localization of lesions detected on screening mammography in Osogbo, Nigeria and its impact on breast conservative surgery. Ann Afr Med 11:91–95
64. Koon KP, Lehman CD, Gralow JR (2013) The importance of survivors and partners in improving breast cancer outcomes in Uganda. Breast 22:138–141
65. Batsis C (2011) Two-stage breast cancer screening in the developing world. World J Surg 35:698–699
66. Gutnik L, Lee C, Msosa V, Moses A, Stanley C, Mzumara S, Liomba NG, Gopal S (2016) Clinical breast examination screening by trained laywomen in Malawi integrated with other health services. J Surg Res 204:61–67
67. El Fakir S, Najdi A, Khazraji YC, Bennani M, Belakhel L, Abousselham L, Lyoussi B, Bekkali R, Nejjari C (2015) Breast cancer screening in Morocco: performance indicators during two years of an organized programme. Asian Pac J Cancer Prev 16:6285–6288
68. Suh MA, Atashili J, Fuh EA, Eta VA (2012) Breast self-examination and breast cancer awareness in women in developing countries: a survey of women in Buea, Cameroon. BMC Res Notes 5:627
69. Pengpid S, Peltzer K (2014) Knowledge, attitude and practice of breast self-examination among female university students from 24 low, middle income and emerging economy countries. Asian Pac J Cancer Prev 15:8637–8640
70. Oladimeji KE, Tsoka-Gwegweni JM, Igbodekwe FC, Twomey M, Akolo C, Balarabe HS, Atilola O, Jegede O, Oladimeji O (2015) Knowledge and beliefs of breast self-examination and breast cancer among market women in Ibadan, South West, Nigeria. PLoS ONE 10:e0140904
71. Lukong KE (2017) Understanding breast cancer—the long and winding road. BBA Clin 7:64–77
72. Plouffe L Jr (2000) Selective estrogen receptor modulators (SERMs) in clinical practice. J Soc Gynecol Investig 7:S38–S46
73. Chumsri S, Howes T, Bao T, Sabnis G, Brodie A (2011) Aromatase, aromatase inhibitors, and breast cancer. J Steroid Biochem Mol Biol 125:13–22
74. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M et al (2011) Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273–1283
75. Singh JC, Jhaveri K, Esteva FJ (2014) HER2-positive advanced breast cancer: optimizing patient outcomes and opportunities for drug development. Br J Cancer 111:1888–1898
76. Dieras V, Vincent-Salomon A, Degeorges A, Beuzeboc P, Mignot L, de Cremoux P (2007) Trastuzumab (Herceptin) and breast cancer: mechanisms of resistance. Bull Cancer 94:259–266
77. Junttila TT, Li G, Parsons K, Phillips GL, Sliwkowski MX (2010) Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. Breast Cancer Res Treat. doi:10.1007/s10549-010-1090-x
78. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE, Martino S, Mamounas EP, Kaufman PA, Wolmark N

(2011) Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 29:3366–3373
79. Wuerstlein R, Harbeck N (2017) Neoadjuvant therapy for HER2-positive breast cancer. Rev Recent Clin Trials. doi:10.2174/1574887112666170202165049
80. Langenhoven L, Barnardt P, Jacobson J (2016) Phenotype and treatment of breast cancer in HIV-positive and -negative women in Cape Town, South Africa. J Glob Oncol 2:284–291
81. Islami F, Lortet-Tieulent J, Okello C, Adoubi I, Mbalawa CG, Ward EM, Parkin DM, Jemal A (2015) Tumor size and stage of breast cancer in Cote d'Ivoire and Republic of Congo—results from population-based cancer registries. Breast 24:713–717
82. Zouladeny H, Dille I, Wehbi NK, Kim J, Soliman AS (2015) Epidemiologic and clinical profiles of breast diseases in Niger. Int J Cancer Oncol. doi:10.15436/2377-0902.15.015
83. Bhikoo R, Srinivasa S, Yu TC, Moss D, Hill AG (2011) Systematic review of breast cancer biology in developing countries (part 2): Asian subcontinent and South East Asia. Cancers (Basel) 3:2382–2401
84. Maalej M, Frikha H, Ben Salem S, Daoud J, Bouaouina N, Ben Abdallah M, Ben Romdhane K (1999) Breast cancer in Tunisia: clinical and epidemiological study. Bull Cancer 86:302–306
85. Maalej M, Hentati D, Messai T, Kochbati L, El May A, Mrad K, Romdhane KB, Ben Abdallah M, Zouari B (2008) Breast cancer in Tunisia in 2004: a comparative clinical and epidemiological study. Bull Cancer 95:E5–E9
86. Price AJ, Ndom P, Atenguena E, Mambou Nouemssi JP, Ryder RW (2012) Cancer care challenges in developing countries. Cancer 118:3627–3635
87. Jakesz R (2008) Breast cancer in developing countries: challenges for multidisciplinary care. Breast Care (Basel) 3:4–5
88. Maree JE, Mulonda JK (2017) Caring for patients with advanced breast cancer: the experiences of Zambian nurses. Asia Pac J Oncol Nurs 4:23–28
89. Adisa AO, Gukas ID, Lawal OO, Adesunkanmi ARK (2010) Breast cancer in Nigeria: is non-adherence to chemotherapy schedules a major factor in the reported poor treatment outcome? Breast J 16:206–207
90. 't Hoen E (2013) A victory for global public health in the Indian Supreme Court. J Public Health Policy 34:370–374
91. Hanlon M, Zhang R (2013) Price discrimination in essential medicines: evidence from International Drug Price Indicator Guide data. Int Health 5:58–63
92. Knaul F, Frenk J, Shulman L (2011) Closing the cancer divide: a blueprint to expand access in low and middle income countries. President and Fellows of Harvard College
93. Mayor S (2015) WHO includes 16 new cancer drugs on list of essential medicines. Lancet Oncol 16:757
94. Aitelhaj M, Lkhoyaali S, Rais G, Boutayeb S, Errihani H (2016) First line chemotherapy plus trastuzumab in metastatic breast cancer HER2 positive—observational institutional study. Pan Afr Med J 24:324
95. 't Hoen E (2015) A study of medicine pricing issues with recommendations for improving access to cancer medication. OXFAM: ACCESS TO CANCER TREATMENT, p 54
96. Zhang G, Wang Y, Zhang Y, Wan X, Li J, Liu K, Wang F, Liu K, Liu Q, Yang C et al (2012) Anti-cancer activities of tea epigallocatechin-3-gallate in breast cancer patients under radiotherapy. Curr Mol Med 12:163–176
97. Huang J, Yang B, Xiang T, Peng W, Qiu Z, Wan J, Zhang L, Li H, Li H, Ren G (2015) Diallyl disulfide inhibits growth and metastatic potential of human triple-negative breast cancer cells through inactivation of the beta-catenin signaling pathway. Mol Nutr Food Res 59:1063–1075
98. Abu Sayeed M, Bracci M, Lazzarini R, Tomasetti M, Amati M, Lucarini G, Di Primio R, Santarelli L (2017) Use of potential dietary phytochemicals to target miRNA: promising option for breast cancer prevention and treatment? J Funct Foods 28:177–193
99. Kim SH, Singh SV (2015) The role of polycomb group protein Bmi-1 and Notch4 in breast cancer stem cell inhibition by benzyl isothiocyanate. Breast Cancer Res Treat 149:681–692
100. Farzaei MH, Bahramsoltani R, Rahimi R (2016) Phytochemicals as adjunctive with conventional anticancer therapies. Curr Pharm Des 22:4201–4218
101. Fouche G, Cragg GM, Pillay P, Kolesnikova N, Maharaj VJ, Senabe J (2008) In vitro anticancer screening of South African plants. J Ethnopharmacol 119:455–461
102. Ochwang'i DO, Kimwele CN, Oduma JA, Gathumbi PK, Mbaria JM, Kiama SG (2014) Medicinal plants used in treatment and management of cancer in Kakamega County, Kenya. J Ethnopharmacol 151:1040–1055
103. Hadi SM, Asad SF, Singh S, Ahmad A (2000) Putative mechanism for anticancer and apoptosis-inducing properties of plant-derived polyphenolic compounds. IUBMB Life 50:167–171
104. Orhan IE, Kartal M, Gulpinar AR, Cos P, Matheeussen A, Maes L, Tasdemir D (2013) Assessment of antimicrobial and antiprotozoal activity of the olive oil macerate samples of *Hypericum perforatum* and their LC-DAD-MS analyses. Food Chem 138:870–875
105. Bachmeier B, Nerlich AG, Iancu CM, Cilli M, Schleicher E, Vene R, Dell'Eva R, Jochum M, Albini A, Pfeffer U (2007) The chemopreventive polyphenol curcumin prevents hematogenous breast cancer metastases in immunodeficient mice. Cell Physiol Biochem 19:137–152
106. Weng CJ, Yen GC (2012) Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives. Cancer Treat Rev 38:76–87
107. Nwodo JN, Ibezim A, Simoben CV, Ntie-Kang F (2016) Exploring cancer therapeutics with natural products from African medicinal plants, Part II: alkaloids, terpenoids and flavonoids. Anticancer Agents Med Chem 16:108–127
108. Li X, Yang GY, Li XX, Zhang Y, Yang JL, Chang J, Sun XX, Zhou XY, Guo Y, Xu Y et al (2013) Traditional Chinese medicine in cancer care: a review of controlled clinical studies published in Chinese. PLoS ONE. doi:10.1371/journal.pone.0060338
109. Piao BK, Wang YX, Xie GR, Mansmann U, Matthes H, Beuth J, Lin HS (2004) Impact of complementary mistletoe extract treatment on quality of life in breast, ovarian and non-small cell lung cancer patients. A prospective randomized controlled clinical trial. Anticancer Res 24:303–309
110. Büssing A (2000) Mistletoe: the genus *Viscum*. Medicinal and aromatic plants—industrial profiles, p 280
111. Dai Z, Wan X, Kang H, Ji Z, Liu L, Liu X, Song L, Min W, Ma X (2008) Clinical effects of Shenqi Fuzheng injection in the neoadjuvant chemotherapy for local advanced breast cancer and the effects on T-lymphocyte subsets. J Tradit Chin Med 28:34–38
112. Dong J, Su SY, Wang MY, Zhan Z (2010) Shenqi Fuzheng, an injection concocted from Chinese medicinal herbs, combined with platinum-based chemotherapy for advanced non-small cell lung cancer: a systematic review. J Exp Clin Cancer Res 29:137
113. Dedong C, Huilin X, Anbing H, Ximing X, Wei G (2016) The effect of ShenQi FuZheng injection in combination with chemotherapy versus chemotherapy alone on the improvement of efficacy and immune function in patients with advanced non-small cell lung cancer: a meta-analysis. PLoS ONE 11:e0152270

114. Huang ZF, Wei JS, Li HZ (2008) Effect of Shenqi Fuzheng injection combined with chemotherapy on thirty patients with advanced breast cancer. Zhongguo Zhong Xi Yi Jie He Za Zhi 28:152–154
115. Li HS, Yang B, Su XC (2009) Effect of Shenqi Fuzheng injection on repairing the immune function in patients with breast cancer. Zhongguo Zhong Xi Yi Jie He Za Zhi 29:537–539
116. Lv Y, Zhang G, Ma Y, Ma M, Liao R, Xiang J, Chen R, Yan X, Bie F, Huang M et al (2015) Shenqi Fuzheng injection combined with chemotherapy for breast cancer: a meta-analysis of randomized controlled trials. Evid Based Complement Altern Med 2015:635858
117. Wong CK, Bao YX, Wong ELY, Leung PC, Fung KP, Lam CWK (2005) Immunomodulatory activities of Yunzhi and Danshen in post-treatment breast cancer patients. Am J Chin Med 33:381–395
118. Kladar NV, Gavaric NS, Bozin BN (2016) Ganoderma: insights into anticancer effects. Eur J Cancer Prev 25:462–471
119. Shin A, Kim J, Lim SY, Kim G, Sung MK, Lee ES, Ro J (2010) Dietary mushroom intake and the risk of breast cancer based on hormone receptor status. Nutr Cancer Int J 62:476–483
120. Bao PP, Lu W, Cui Y, Zheng Y, Gu K, Chen Z, Zheng W, Shu XO (2012) Ginseng and *Ganoderma lucidum* use after breast cancer diagnosis and quality of life: a report from the Shanghai Breast Cancer Survival Study. PLoS ONE 7:e39343
121. Barbieri A, Quagliariello V, Del Vecchio V, Falco M, Luciano A, Amruthraj NJ, Nasti G, Ottaiano A, Berretta M, Iaffaioli RV et al (2017) Anticancer and anti-inflammatory properties of *Ganoderma lucidum* extract effects on melanoma and triple-negative breast cancer treatment. Nutrients. doi:10.3390/nu9030210
122. Gonul O, Aydin HH, Kalmis E, Kayalar H, Ozkaya AB, Atay S, Ak H (2015) Effects of *Ganoderma lucidum* (higher Basidiomycetes) extracts on the miRNA profile and telomerase activity of the MCF-7 breast cancer cell line. Int J Med Mushrooms 17:231–239
123. Hu H, Ahn NS, Yang X, Lee YS, Kang KS (2002) *Ganoderma lucidum* extract induces cell cycle arrest and apoptosis in MCF-7 human breast cancer cell. Int J Cancer 102:250–253
124. Jiang J, Slivova V, Harvey K, Valachovicova T, Sliva D (2004) *Ganoderma lucidum* suppresses growth of breast cancer cells through the inhibition of Akt/NF-kappaB signaling. Nutr Cancer 49:209–216
125. Jiang J, Slivova V, Sliva D (2006) *Ganoderma lucidum* inhibits proliferation of human breast cancer cells by down-regulation of estrogen receptor and NF-kappaB signaling. Int J Oncol 29:695–703
126. Kim TH, Kim JS, Kim ZH, Huang RB, Chae YL, Wang RS (2016) Induction of apoptosis in MCF7 human breast cancer cells by Khz (fusion of *Ganoderma lucidum* and *Polyporus umbellatus mycelium*). Mol Med Rep 13:1243–1249
127. Loganathan J, Jiang J, Smith A, Jedinak A, Thyagarajan-Sahu A, Sandusky GE, Nakshatri H, Sliva D (2014) The mushroom *Ganoderma lucidum* suppresses breast-to-lung cancer metastasis through the inhibition of pro-invasive genes. Int J Oncol 44:2009–2015
128. Lu QY, Sartippour MR, Brooks MN, Zhang Q, Hardy M, Go VL, Li FP, Heber D (2004) *Ganoderma lucidum* spore extract inhibits endothelial and breast cancer cells in vitro. Oncol Rep 12:659–662
129. Martinez-Montemayor MM, Acevedo RR, Otero-Franqui E, Cubano LA, Dharmawardhane SF (2011) *Ganoderma lucidum* (Reishi) inhibits cancer cell growth and expression of key molecules in inflammatory breast cancer. Nutr Cancer 63:1085–1094
130. Shang D, Li Y, Wang C, Wang X, Yu Z, Fu X (2011) A novel polysaccharide from Se-enriched *Ganoderma lucidum* induces apoptosis of human breast cancer cells. Oncol Rep 25:267–272
131. Sliva D, Labarrere C, Slivova V, Sedlak M, Lloyd FP Jr, Ho NW (2002) *Ganoderma lucidum* suppresses motility of highly invasive breast and prostate cancer cells. Biochem Biophys Res Commun 298:603–612
132. Sliva D, Sedlak M, Slivova V, Valachovicova T, Lloyd FP Jr, Ho NW (2003) Biologic activity of spores and dried powder from *Ganoderma lucidum* for the inhibition of highly invasive human breast and prostate cancer cells. J Altern Complement Med 9:491–497
133. Zhang M, Huang J, Xie X, Holman CDJ (2009) Dietary intakes of mushrooms and green tea combine to reduce the risk of breast cancer in Chinese women. Int J Cancer 124:1404–1408
134. Chen Z, Gu K, Zheng Y, Zheng W, Lu W, Shu XO (2008) The use of complementary and alternative medicine among Chinese women with breast cancer. J Altern Complement Med 14:1049–1055
135. Tian HQ, Wang YJ, Wang B, Huang YL, Li HL, Huang XQ, Zhang XC, Yang YL (2013) Effect of ruji recipe on the post-surgical survival of female breast cancer patients. Zhongguo Zhong Xi Yi Jie He Za Zhi 33:1336–1340
136. Akarolo-Anthony SN, Ogundiran TO, Adebamowo CA (2010) Emerging breast cancer epidemic: evidence from Africa. Breast Cancer Res. doi:10.1186/bcr2737
137. Sylla BS, Wild CP (2012) A million Africans a year dying from cancer by 2030: what can cancer research and control offer to the continent? Int J Cancer 130:245–250
138. Siegel R, Ward E, Brawley O, Jemal A (2011) Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 61:212–236
139. Phillips C, Jeffree R, Khasraw M (2017) Management of breast cancer brain metastases: a practical review. Breast 31:90–98