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REVIEW

Pharmacogenetics of Breast Cancer Treatments: A Sub-Saharan Africa Perspective

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Abstract: Breast cancer is the most frequent cause of cancer death in low- and middle-income countries, in particular among sub-Saharan African women, where response to available anticancer treatment therapy is often limited by the recurrent breast tumours and metastasis, ultimately resulting in decreased overall survival rate. This can also be attributed to African genomes that contain more variation than those from other parts of the world. The purpose of this review is to summarize published evidence on pharmacogenetic and pharmacokinetic aspects related to specific available treatments and the known genetic variabilities associated with metabolism and/or transport of breast cancer drugs, and treatment outcomes when possible. The emphasis is on the African genetic variation and focuses on the genes with the highest strength of evidence, with a close look on *CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, CYP19A1, UGT1A4, UGT2B7, UGT2B15, SLC22A16, SLC38A7, FcγR, DPYD, ABCB1*, and *SULT1A1*, which are the genes known to play major roles in the metabolism and/or elimination of the respective anti-breast cancer drugs given to the patients. The genetic variability of their metabolism could be associated with different metabolic phenotypes that may cause reduced patients' adherence because of toxicity or sub-therapeutic doses. Finally, this knowledge enhances possible personalized treatment approaches, with the possibility of improving survival outcomes in patients with breast cancer.

Keywords: breast cancer, genetic variability, inter-ethnic differences, pharmacogenetics, sub-Saharan Africa, toxicity

Introduction

Pharmacogenetics evaluates the effect of inherited genomic variation on patient response (including resistance) to treatment. Genetic variability in germline DNA in the form of chromosomal alterations or DNA sequence variants can affect drug metabolism and/or toxicity, which can have important consequences on a patient's response to breast cancer treatment.[1] Conversely, genomic changes (DNA variants and gene expression profiles) in the breast tumour's somatic genome may influence rates of apoptosis, cell proliferation, and DNA damage repair, which may also have effects on response to treatment and survival.[2] This review will focus solely on human genetic variation in germline DNA underlying breast cancer drug metabolism and possible treatment outcomes, which may impact toxicity, recurrence, and survival. We will address, in particular, the drugs most widely used in Africa and the genetic variants identified in African individuals. Indeed, ethnic differences in anticancer drug disposition are important factors accounting for populations' variation in treatment response and tolerability.[3] It is also important to note that breast cancer incidence as well as cancer presentation in terms of age at onset and stage of cancer among African women tend to differ from that of more developed regions of the world. However, breast cancer types seem to show a similar pattern regardless of age, stage and ethnicities. Having said that, in the era of the development of personalized medicine few major problems arise for African populations: i) the socio-economic context may explain a particular epidemiology in terms of the age of onset and stage of cancer and access to treatment without excluding the genetic aspects predisposing to the disease and determining responses to treatments; ii) the great genetic diversity of African populations implies considering each one separately, taking the precaution of not generalizing data established for one ethnic group to all the others; iii) data on the frequencies of polymorphism in genes of

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interest in different populations are fragmentary; iv) the number of studies of association between the polymorphisms considered and the responses to breast cancer treatment is very limited.

Breast Cancer in Africa

Breast cancer is ranked as the most common cancer in women worldwide, increasing from 1.7 million incident cases in 2005 to 2.4 million cases in 2015.[4] In the more developed regions of the world (Europe/USA/Australia and New Zealand) the age-standardized incidence rates (per 100,000 women per year) ranged between 74.5 and 91.6, whereas recent estimates for sub-Saharan Africa (SSA) were as follows: 30.4 in East Africa; 26.8 in Central Africa; 38.6 in West Africa; and 38.9 in Southern Africa.[5] Although the incidence of breast cancer appears to be relatively low in SSA, survival from the disease is markedly poor in the region, with high mortality recorded in many settings.[5,6] Sub-Saharan Africa has the highest age-standardized breast cancer mortality rate globally.[5] Breast cancer is the most frequent cause of cancer death in less developed regions,[7] causing one in five deaths in African women, described as a new "shift" from the previous decade.[8] The poor survival of breast cancer patients in SSA has been attributed to several factors, inter alia: late presentation, poor healthcare infrastructure, reduced diagnostic capacity and delays, including substandard pathological data, together with lack of adequate funding, amidst other competing public health challenges.[9] In addition, the steadfast adherence to some negative socio-cultural beliefs that delay presentation to health services may contribute to the observed lower survival rates compared to high-income countries. Breast tumours are diagnosed ten or twenty years earlier among Africans compared to developed countries and are at advanced stages at presentation. One possible explanation for this could be that breast cancer among young women in any population tends to be clinically and pathologically aggressive,[10] which is also attributed to a consequence of the demographic structure of the population.[11] Nevertheless, studies showed a comparable receptor status prevalence in SSA with that of the West.[12,13] Further possible explanations for such high rate of aggressive phenotypes could be socio-economic aspects as well as susceptibility factors.

Given that African genomes contain more variation than those from any other continent,[14,15] it is therefore of paramount importance to measure the extent of African pharmacogenetics in the context of disease treatment response, including breast cancer. In fact, African genetic variability, which has been well linked to disease resistance and susceptibility, also accounts for the variability in detoxifying pathways that are responsible for eliminating modern drugs.[16] During evolution, different populations' practices exposed individuals to xenobiotics that sometimes-imposed serious health and environmental risks, leading to the selection of specific adaptations linked to an efficient detoxification pathway. For example, significant differences in prevalence of acetylation phenotypes are found between hunter-gatherer and food-producing populations, both in SSA and worldwide, and between agriculturalists and pastoralists in Central Asia.[17] This is likely an explanation for such large genetic variation in detoxifying pathways observed among African ethnic groups.

In view of all these factors, it is important to evaluate and discuss the specific pharmacogenetic landscape relevant to breast cancer treatments used in the SSA context, to enhance possible personalized treatment approaches, ultimately improving outcomes in patients with cancer.

Types of Breast Cancer

Breast cancer has a complex aetiology where susceptibility is influenced by both environmental and genetic factors, including increased estrogen exposure throughout a woman's lifetime, age, family history, as well as modifiable risk factors, such as nutrition, exercise, and alcohol/tobacco use.[18,19] Breast cancer may be more appropriately defined as a myriad of diseases characterized by variability in developmental pathways, propensity to metastasize, and response to treatment that can benefit from precision regimens targeted at individual patients.

Breast cancer types are either hormone receptor-positive (HR+) or hormone receptor-negative (HR-), based on tumour cells' expression of the estrogen receptors (ER) and/or progesterone receptors (PR). ER+ breast cancer types are prognostic for improved survival outcomes and predict responsiveness to endocrine treatment (such as tamoxifen). By binding to ER (either ER-alpha or -beta), estrogen regulates a wide variety of cellular effects and physiological conditions including breast cancer cell proliferation and growth. Nearly two thirds of breast cancers are classified as ER+, and this is broadly true also for Africa, with regional variations.[12,13] For example, HR+ breast cancer subtypes have an estimated prevalence of 80% in Nigeria.[20] Other studies show a prevalence of ER+ breast cancer between 58% and 64% in South Africa.[21] These subtypes have been associated with different prognoses, with patients with luminal A tumours having the best prognosis, and patients

with triple negative subtype (ER-/PR-/HER2-) having the worst prognosis[22] (Table 1). However, a significant minority of patients relapse despite adjuvant anti-estrogen therapy, with most patients with metastatic disease ultimately developing resistance to anti-estrogen therapies.

Table 1 Classification of Breast Cancer Subtypes Based on the Hormone Receptor (HR) Status, Treatment of Choice, and the Related Metabolizing Genes

Breast Cancer Markers[¥]	Proliferation Rate	Treatment	Drugs	Gene	Known African Variants
ER+ PR+ HER2- (*Luminal A*)	Ki-67 <14%	Hormonal Therapy	Tamoxifen	*CYP2D6*	**2, *3, *4,* 5, *10, *17, *41*, copy number variation
				CYP2C9	**2, *3, *5, *6, *8, *9, *11*
				CYP2C19	**2, *3, *9, *13, *15, *17, *22*
				CYP3A4/5	**1B, *1G, *12, *15, *23, *24*
					**3, *6, *7*
				CYP2B6	**4, *6, *9, *16, *17, *18*
				UGT1A4	**2, *3B, *4*
				UGT2B7	**2*
				UGT2B15	**2, *4*
				SULT1A1/2	**2, *3*, [rs1042157]
					N/A
ER± PR± HER2- (at least one ER or PR is +) (*Luminal B*)	Ki-67 >14%		Aromatase Inhibitors (anastrozole, letrozole and exemestane)	*UGT1A4*	**2, *3B, *4*
				SLC38A7	[rs11648166]
				CYP2A6	**2, *4, *9, *12, *17, *20*
				CYP3A4	**1B, *1G, *12, *15, *23, *24*
ER+ PR+ HER2+ (*Luminal B*)	Any Ki-67	Targeted Therapy	Trastuzumab	FcγR	*2A* and *3A*
ER- PR- HER2- (*Triple negative*)	N/A	Cytotoxic Chemotherapy	Paclitaxel	*CYP2C8*	**2, *3, *4*
				CYP3A4/5	**1B, *1G, *12, *15, *23, *24*
			Doxetaxel		**3, *6, *7*
			Capecitabine	*DPYD*	Y186C [rs115232898], **2A*, D949V [rs72975710]
			Doxorubicin	*SLC22A16*	[rs12210538]
				ABCB1	[rs3842], [rs1045642]
			Cyclophosphamide	*CYP2B6*	**4, *6, *9, *16, *17, *18*
				CYP2C9	**2, *3, *5, *6, *8, *9, *11*
				CYP3A4	**1B, *1G, *12, *15, *23, *24*
ER- PR- HER2+ (*HER2 enriched*)	N/A	Targeted Therapy	Trastuzumab	*FcγR*	*2A* and *3A*

Note: [¥]In italic is represented the breast cancer *Molecular Subtype*.

Abbreviations: ER, Estrogen Receptor (positive or negative); PR, Progesterone Receptor (positive or negative); HER2, Human Epidermal Growth Factor Receptor 2 (positive or negative); Ki-67, Proliferation rate.

Breast cancer cells with higher than normal levels of the HER2 receptor protein are defined as HER2+. These cancers tend to grow and spread faster than other breast cancers but are much more likely to respond to treatment with HER2 targeting drugs (Table 1), such as monoclonal antibodies.

This narrative review aims to provide an overview of pharmacogenetic variation relevant to the treatment options for women with breast cancer in SSA. The focus will be on pharmacogenetic variants found in populations in SSA, where information is available. We will review the African genetic variation and focus on the genes with the highest strength of evidence. After identifying the most likely relevant pharmacogenes, a comment specifically on the patterns and frequencies of genetic variants in SSA populations will be given. The information will be used to comment on which drugs may be effective in Africans as compared to Caucasians and Asians, where most clinical trials and pharmacogenetic studies are conducted. For allelic frequency look-up and comparison several options, including Ensembl (http://useast.ensembl.org/index.html) and gnomAD (https://gnomad.broadinstitute.org/) are publicly available. Finally, helpful figures of the metabolism and pharmacology for each of the drugs described in the present work can be accessed via PharmGKB (https://www.pharmgkb.org).

Pharmacogenetics of Breast Cancer in Sub-Saharan Africa

Hormonal Therapy

Several hormonal agents have been approved for the prevention or treatment of breast cancer and prevention of recurrence, including the selective estrogen receptor modulator (SERM) tamoxifen, as well as the third-generation aromatase inhibitors (AIs) anastrozole, letrozole and exemestane. Hormonal therapy for breast cancer is one of the most available treatment options even in poorer countries. For example, many companies supply generic tamoxifen at a very low cost making it readily available and, in some countries it is available free of charge.[8] Unlike tamoxifen, the access and availability of AIs are restricted in most of Africa.[8] For example, recent data from Ghana, Nigeria and Kenya indicate that only 21–29% of eligible patients receive AI treatment.[23]

Tamoxifen

Tamoxifen is a potent antagonist of the ER with inhibitory effects on tumour growth that has become the gold standard for endocrine treatment of HR+ breast cancer in premenopausal and is also used in postmenopausal women when AIs are intolerable or unavailable.[24] Nevertheless, its clinical effectiveness varies among individuals. Tamoxifen is a prodrug that undergoes considerable first-pass oxidative metabolism into more potent active metabolites, such as 4-hydroxytamoxifen (4-OH-tamoxifen) and 4-hydroxy-N-desmethyl-tamoxifen (endoxifen). These metabolites have a 30- to 100-fold higher affinity to ERs compared to tamoxifen. Because endoxifen reaches a steady-state plasma concentration 6- to 10-fold higher than 4-OH-tamoxifen, it is considered the most relevant metabolite in determining the parent drug's clinical efficacy.[25] CYP2D6 is the primary enzyme responsible for the activation of tamoxifen. However, other metabolic enzymes and transporters[26] have been identified as possible contributors to tamoxifen plasma concentration variations.[27]

CYP2D6

Over the last few decades, a huge body of research first discovered and then elaborated on tamoxifen metabolism, identifying CYP2D6 as the main enzyme responsible for tamoxifen activation to endoxifen, the most potent antiestrogenic metabolite.[28–30] *CYP2D6* interindividual gene variation is the predominant predictor of plasma endoxifen level in a gene-dose dependent manner. In fact, *CYP2D6* explains ~40–50% of endoxifen plasma concentration, while all the other known genes and clinical variables combined explain <10%.[27] Globally, it has been challenging to demonstrate that endoxifen plasma concentration determines treatment efficacy, and a direct genotype–phenotype association has not yet been confirmed. Some studies have found that patients who carry reduced-function or non-functional *CYP2D6* alleles derive inferior therapeutic benefits from tamoxifen,[25] or have significantly shorter disease-free survival than non-carriers,[31] while other studies did not find any association, or an inverse association.[32–34] The clinical validity of this association has not been demonstrated, hence providing insufficient data for the clinical utility of *CYP2D6* genotyping to guide tamoxifen treatment.[34] It should be stressed that most of the studies to date have been conducted among

Caucasians and/or Asians, and limited research has been conducted among Africans. From the few papers published on SSA breast cancer pharmacogenetics, a study conducted in Ethiopia[26] found that an increase in *CYP2D6* activity was associated with increased endoxifen concentration, confirming the notion of a linear relation between *CYP2D6* and endoxifen plasma concentration. The authors also showed that all null or low activity genotypes (poor and intermediate metabolizers) in this Ethiopian cohort were associated with low endoxifen levels.[26] In addition, other factors, such as environmental/dietary and regulatory mechanisms including other genetic polymorphisms, have been suggested as contributors to the generally low endoxifen concentration described in the study.[26,35]

Given the evolving data regarding the role of CYP2D6 for tamoxifen bioactivation and efficacy, it is critical to consider which *CYP2D6* functional alleles may be found in African individuals. In general, more than 70 alleles of *CYP2D6* have been identified with large interindividual and interethnic differences, and this is also true within SSA. For example, Africans have the second highest observed frequency of *CYP2D6* poor metabolizer phenotypes globally (about 3%) after Caucasians (about 5%),[36,37] and this reflects specific ethnic characteristics among different African populations. Importantly, the rate of *CYP2D6* ultra-rapid metaboliser phenotypes among Africans is believed to be the highest worldwide.[37] It should be noted that a huge range of variations could also be found among African ethnic groups concerning Single Nucleotide Polymorphisms (SNPs).

Alleles known to be unique to SSA populations include the reduced function *CYP2D6*17* and *CYP2D6*29* alleles[38] (Table 2). However, other *CYP2D6* low activity variants show a marked difference in distribution among African populations compared with other global populations: *CYP2D6*3, CYP2D6*4, CYP2D6*9, CYP2D6*10* and *CYP2D6*41*, having higher (**10*) or lower (**3, *4, *9* and **41*) frequencies.[39] Interestingly, the South African Cape Coloured population, which is a unique and genetically complex admixed group, shows distinctive allele frequencies for most of the genes analysed. For example, *CYP2D6*5* (*CYP2D6* gene deletion, that is a no activity variation) occurs more frequently in the South African Cape Coloured population[40,41] than among other sympatric South African ethnic groups (Table 2).

In the last few years to simplify genotype interpretation and improve phenotype prediction, the utility of an "activity score" (AS) system was evaluated[42] and subsequently improved.[43] It spans from values 0 to 2, and >2, where AS is calculated based on an additive model counting individual alleles and haplotypes, similarly developed also for *CYP2A6*,[44] *CYP2B6*[45,46] and for *CYP2C19*.[47] The *CYP2D6* AS distribution in world populations shows that Africans (in general) do not express particularly outlying metabolic phenotypes.[48]

Other Tamoxifen-Related Pharmacogenes

Tamoxifen is N-dealkylated and 4-hydroxylated to endoxifen by CYP2D6 but also by several other CYP enzymes that combined together may explain only a fraction (<10%) of tamoxifen metabolism.[27] Among them, CYP2C9 and CYP2C19 play a major role, and CYP3A4, CYP3A5, and CYP2B6 a minor role.[49] That could be due to the observation that *CYP2C9/19* genes are more polymorphic than *CYP3A4/5* genes. Furthermore, tamoxifen metabolites are inactivated prior to elimination by other non-CYP450 enzymes, through conjugation with a glucuronide or sulphate group (UGTs and SULT enzymes, respectively), specifically UGT1A4, UGT2B7, UGT2B15, and SULT1A1, SULT1A2 and UGT1A4.[27]

There is evidence that variation in *CYP2C9* gene (together with *CYP2D6*) may also predict active metabolite concentrations and therefore may be useful to guide tamoxifen dosing.[50–52] Lower concentrations of endoxifen and endoxifen/4-hydroxytamoxifen ratios were seen with impaired CYP2C9 activity if patients had the same CYP2D6 phenotype and were not taking CYP2D6 inhibitors.[50] However, the only report from Africa (Ethiopia) concerning the possible effect of *CYP2C9* polymorphisms (namely **2* and **3* alleles) did not show any association with tamoxifen and metabolite concentrations.[26] Known *CYP2C9* variants among Africans are as follows: **2, *3, *5, *6, *8, *9, *11, *31* and **32* (Table 3). There is no substantial difference in *CYP2C9* frequencies between Africans and other world populations. In line with these observations, it is important to highlight that the influence of *CYP2C9* genetic variants on the metabolism of the CYP2C9 probe drug warfarin has been shown to differ by "race".[53]

CYP2C19 catalyzes the formation of several tamoxifen metabolites, including the conversion of 4-OH-tamoxifen to endoxifen. Some studies have detected an association between *CYP2C19* status and clinical outcomes, while others have not. For example, Damkier et al[49] and Sanchez-Spitman et al[54] found no evidence to support the clinical role of *CYP2C19* polymorphisms and response to tamoxifen in breast cancer patients. Conversely, one study found that

Table 2 *CYP2D6* Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Group	Type of Subjects[§], n	*2 [rs16947; rs1135840] 2850C>T; 4180G>C (R296C; S486T)	*3 [rs35742686] 2549delA (Frameshift Variant)	*4 [rs3892097] 1846 G>A, Also Known as 1934 G>A (Splicing Defect/ Null)	*5 13 kb Deletion	*10 [rs1065852] 100C>T (P34S)	*17 [rs28371706] 1023 C>T, Also Known as 1111 C>T (T107I)	*29 Reduced Functioning Haplotype: 1660G>A; 2851C>T; 3184G>A; 4181G>C (V136I; R296C; V338M; S486T)	*41 [rs28371725] 2988G>A (Splicing Defect)	*1xN, *2xN and *4xN (Gene Duplication)	Reference
		Suspected Activity									
		Depending on the Substrate	No Detectable Levels of Enzyme	No Detectable Levels of Enzyme	No Detectable Levels of Enzyme	↓	↓	↓	↓	↑ (*1xN and *2xN) No Detectable Levels of Enzyme (*4xN)	
West-Central Africa											
Gabon	48	0.115 (0.025–0.205)	-	0.073 (−0.001–0.147)	-	0.021 (−0.02, 0.062)	0.104 (0.018–0.190)	0.094 (0.011–0.177)	-	-	[181]
Ghana	193	0.106 (0.063–0.149)	0.000 (0.000–0.000)	0.070 (0.034–0.106)	0.060 (0.026–0.094)	0.031 (0.007–0.055)	0.277 (0.214–0.340)	-	-	0.016 (−0.002–0.034) (*2x2)	[182]
Cameroon/ Bakola Pygmies	16	0.281 (0.061–0.501)	-	0.031 (−0.054–0.116)	0.156 (−0.022–0.334)	-	-	0.063 (−0.056–0.182)	-	0.031 (−0.054–0.116) (*2x2)	[183]
CAR/ Baka Pygmies	36	0.500 (0.337–0.663)	-	0.014 (−0.024–0.052)	0.014 (−0.024–0.052)	0.083 (−0.007–0.173)	0.125 (0.017–0.233)	0.028 (−0.026–0.082)	0.014 (−0.024–0.052)	-	[184]
CAR/ Baka	30	0.367 (0.195–0.539)	-	-	-	-	0.100 (−0.007–0.207)	0.100 (−0.007–0.207)	0.067 (−0.022–0.156)	0.033 (−0.031, 0–097) (*1x2 and *2x2)	[183]
DRC/ Mbuti Pygmies	15	0.600 (0.352–0.848)	-	-	0.100 (−0.052–0.252)	-	0.033 (−0.057–0.123)	0.033 (−0.057–0.123)	-	0.133 (−0.039–0.305) (*1x2)	[184]
West Africa/ Mandinka	24	0.125 (−0.007–0.257)	-	0.125 (−0.007–0.257)	0.063 (−0.034–0.160)	0.063 (−0.034–0.160)	0.188 (0.032–0.344)	0.063 (−0.034–0.160)	0.104 (−0.018–0.226)	-	[184]
Nigeria/ Yoruba	25	0.120 (−0.007–0.247)	-	-	0.040 (−0.037–0.117)	0.040 (−0.037–0.117)	0.060 (−0.033–0.153)	0.120 (−0.007–0.247)	0.020 (−0.035–0.075)	-	[184]

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East Africa											
Ethiopia	122	-	0.000 (0.000–0.000)	0.012 (−0.007–0.031)	0.033 (0.001–0.065)	0.086[¥] (0.036–0.136)	0.090 (0.039–0.141)	-	0.216 (0.143–0.289)	-	[185]
Ethiopia	Breast cancer patients receiving tamoxifen, 81	0.333 (0.230–0.436)	-	0.049 (0.002–0.096)	0.043 (−0.001–0.087)	0.019 (−0.011–0.049)	0.105 (0.038–0.172)	-	-	0.148 (0.071–0.225) (*1x2 and *2x2)	[26]
Tanzania	106	0.184 (0.110–0.258)	0.005 (−0.008–0.018)	0.014 (−0.008–0.036)	0.033 (−0.001–0.067)	-	0.203 (0.126–0.280)	-	-	-	[186]
Tanzania	106	0.400 (0.307–0.493)	0.000 (0.000–0.000)	0.009 (−0.009–0.027)	0.063 (0.017–0.109)	0.038 (0.002–0.074)	0.170 (0.098, 0.242)	0.198 (0.147–0.258)	-	0.034 (−0.001–0.069) (*1x2 and *2x2)	[187,188]
Southern Africa											
Madagascar	Malaria exposed subjects, 211	0.064 (0.031–0.097)	-	0.021 (0.002–0.040)	0.017 (−0.000–0.034)	0.171 (0.120–0.222)	0.109 (0.067–0.151)	0.066 (0.032–0.100)	0.035 (0.010–0.060)	-	[189]
South Africa/ Venda	76	0.178 (0.092–0.264)	0.000 (0.000–0.000)	0.033 (−0.007–0.073)	0.046 (−0.001–0.093)	-	0.240 (0.144–0.336)	-	-	-	[186]
South Africa/ San	7	0.643 (0.288–0.998)	-	-	0.143 (−0.116–0.402)	-	0.071 (−0.119–0.261)	-	-	-	[184]
South Africa/ Coloured	200	0.268 (0.207–0.329)	-	-	0.172 (0.120–0.224)	-	-	-	-	-	[42]
South Africa/ Mixed ancestry	99	-	-	-	-	-	-	-	0.035 (−0.001–0.071)	-	[40]
South Africa/ Xhosa	109	-	-	-	-	-	-	-	0.019 (−0.007–0.045)	-	[190]

(*Continued*)

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Table 2 (Continued).

Geographic Region/ Ethnic Group	Type of Subjects[§], n	*2 [rs16947; rs1135840] 2850C>T; 4180G>C (R296C; S486T)	*3 [rs35742686] 2549delA (Frameshift Variant)	*4 [rs3892097] 1846 G>A, Also Known as 1934 G>A (Splicing Defect/ Null)	*5 13 kb Deletion	*10 [rs1065852] 100C>T (P34S)	*17 [rs28371706] 1023 C>T, Also Known as 1111 C>T (T107I)	*29 Reduced Functioning Haplotype: 1660G>A; 2851C>T; 3184G>A; 4181G>C (V136I; R296C; V338M; S486T)	*41 [rs28371725] 2988G>A (Splicing Defect)	*1xN, *2xN and *4xN (Gene Duplication)	Reference
		Suspected Activity									
		Depending on the Substrate	No Detectable Levels of Enzyme	No Detectable Levels of Enzyme	No Detectable Levels of Enzyme	↓	↓	↓	↓	↑ (*1xN and *2xN) No Detectable Levels of Enzyme (*4xN)	
South Africa/ Mixed populations	200	0.138 (0.090–0.186)	-	0.031 (0.007–0.055)	0.087 (0.048–0.126)	-	0.194 (0.139–0.249)	-	-	0.005 (−0.0050.015) and 0.02 (0.001–0.039) (*2xN and *4xN)	[41]
Zimbabwe/ Shona	114	-	-	-	-	0.056 (0.014–0.098)	-	-	-	-	[191]
Zimbabwe	228	0.130 (0.086–0.174)	0.000 (0.000–0.000)	0.020 (0.002–0.038)	0.040 (0.015–0.065)	-	0.340 (0.279–0.401)	-	-	-	[186]
Zimbabwe/ San	64	-	-	0.009 (−0.014–0.032)	-	-	-	-	-	-	[192]
African Americans											
-	720	-	0.002–0.006	-	-	-	-	-	-	-	[193–196]
-	246	-	-	-	-	0.050 (0.023–0.077)	-	-	-	-	[194]
-	308	0.269 (0.219–0.319)	0.003 (−0.003–0.009)	0.078 (0.048–0.108)	0.062 (0.035–0.089)	0.075 (0.046–0.104)	0.146 (0.107–0.185)	-	-	-	[195]

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-	502	-	-	0.054 (0.034–0.074)	0.066 (0.044–0.088)	0.036 (0.020–0.052)	0.213 (0.177–0.249)	0.072 (0.049–0.095)	-	0.014 (0.004–0.024) (*1x2, *2x2, and *4x2 gene duplications, combined frequency)	[196]
	272	0.140 (0.099–0.181)	0.002 (−0.003–0.007)	0.039 (0.016–0.062)	0.064 (0.035–0.093)	0.029 (0.009–0.049)	0.191 (0.144–0.238)	0.075 (0.044–0.106)	0.018 (0.002–0.034)	-	[42]
-	Psychiatric patients, 222	0.045 (0.018–0.072)	0.005 (−0.004–0.014)	-	-	-	-	0.052 (0.023–0.081)	-	-	[197]
-	Psychiatric patients, 452	-	-	-	-	0.038 (0.020–0.056)	-	-	-	-	[198]
-	5674	-	-	-	-	-	0.027 (0.023–0.031)	-	-	-	[199]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity; ↑ increased enzyme activity. [§]When available.

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Table 3 *CYP2C9* Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Group	Type of Subjects[§], n	*2 [rs1799853] 430 C>T (R144C)	*3 [rs1057910] 1075 A>C (I359L)	*5 [rs28371686] 42619 G>C (D360E)	*6 [rs9332131] 818delA (Frameshift Variant)	*8 [rs7900194] 449 G>A (R150H)	*9 [rs2256871] 752 A>G (H251R)	*11 [rs2837168] 1003 C>T (R335W)	*31 [Novel, No *rs* Number] 42519T>C (I327T)	*32 [Novel, No *rs* Number] 50341G>T (V490F)	Reference
		Suspected Activity									
		↓[a]	↓[a]	↓	No Detectable Levels of Enzyme	↓	↔	↓	↓	↓	
West-Central Africa											
Benin	111	-	-	0.018 (−0.007–0.043)	-	-	-	0.027 (−0.003–0.057)	-	-	[200]
Benin	109	-	-	-	0.027 (−0.003–0.057)	0.086 (0.033–0.139)	0.157 (0.08– 0.225)	-	-	-	[201]
Gambia	Malaria patients, 128	0.010 (−0.007–0.027)	-	-	-	0.020 (−0.004–0.044)	0.060 (0.019–0.101)	0.030 (0.000–0.060)		-	[202]
Ghana	195	-	-	-	-	-	-	0.020 (0.00–0.040)	-	-	[203]
Nigeria/Hausa	13	-	-	-	0.040 (−0.067–0.147)	-	-	-	0.04 (−0.067,0.147)	-	[204]
Nigeria/Yoruba	24	-	-	0.042 (−0.038–0.122)	-	-	-	-	-	-	[204]
East Africa											
Ethiopia	150	0.077 (0.034–0.120)	0.060 (0.022–0.098)	-	-	-	-	-	-	-	[205]
Ethiopia	Breast cancer patients receiving tamoxifen, 81	0.043 (−0.001–0.087)	0.074 (0.017–0.131)	-	-	-	-	-	-	-	[26]
Ethiopia	Breast cancer patients receiving cyclophosphamide, 267	0.067 (0.037–0.097)	0.011 (−0.002–0.024)	-	-	-	-	-	-	-	[179]
Tanzania	131	-	-	0.008 (−0.007–0.023)	-	-	-	-	-	-	[206]
Tanzania/Bantu	12	-	-	-	-	-	-	-	-	0.05 (−0.073,0.173)	[204]

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Southern Africa											
Mozambique	106	-	0.022 (−0.006–0.05)	-	-	-	-	-	-	-	[207]
South Africa	200	-	0.005 (−0.005–0.015)	-	-	0.080 (0.042–0.118)	-	0.045 (0.016–0.074)	-	-	[208]
Cumulative data											
Mixed African Ancestry	93	-	-	-	-	-	0.000–0.180 (0.102–0.258)	-	-	-	[204]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity; ↔ no measurable difference in enzyme activity. [§]When available. a: according to Ahmed et al[179] increased cyclophosphamide clearance was significantly higher in carriers of *CYP2C9*2* or **3* alleles who also carry *POR*28* allele, therefore an expected fast metabolic phenotype has been measured in association to the two alleles.

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*CYP2C19*17* allele is linked to improved benefits with respect to lower breast cancer recurrence and relapse-free survival.[55] This is also supported by another report which found that low activation of tamoxifen in patients with poor *CYP2D6* activity and fast *CYP2C19* (**17* allele) metabolism represents the fraction of patients that have the worst clinical outcome.[56] The only report from Africa (Ethiopia) concerning the possible effect of *CYP2C19* polymorphisms (namely **2* and **3* alleles) did not show any association with tamoxifen and metabolite concentrations,[26] supporting the non-association relationship. Known *CYP2C19* variants among Africans are as follows: **2, *3, *9, *13, *15, *17, *22* (Table 4). Global data comparison suggests that Africans have a high rate of fast metabolizers predicted phenotypes (around 20%, similar to Caucasians) and a relatively lower frequency of poor metabolizer phenotypes.[37]

As for the other contributors to tamoxifen metabolism, available data indicate the existence of a *CYP3A4* main "African" polymorphism, *CYP3A4*1B*, with functional importance as to enzyme expression.[16,57] The *CYP3A4*1B* slow metaboliser allele (rs2740574) is associated with a significantly reduced oxidation capacity compared to the *CYP3A4*1* wild-type allele for several drugs.[16,58] Importantly, there is a strong linkage disequilibrium (LD) between *CYP3A4*1B* and *CYP3A5*3*, which may also be responsible for the reported findings.[59] In fact, high LD between haplotypes spanning *CYP3A4* and *CYP3A5* confounds the interpretation of the effects of polymorphisms in either gene on drug metabolism. However, despite *CYP3A4*1B* having been associated with a poor metabolizer phenotype and showing high to very high frequencies in African populations (Table 5), no data on *CYP3A4*1B* and tamoxifen metabolism has been reported to date. In addition, there is evidence that *CYP3A4* is a very conserved gene with <10% of alleles harbouring identified variant haplotypes, and there is no substantial phenotype difference among global populations based on available studies.[60]

Another important pharmacogene is *CYP3A5*. To our knowledge, the only report from Africa (Ethiopia) concerning the possible effect of CYP3A5 (but also CYP2C9 and CYP2C19) on altered tamoxifen metabolism and altered exposure to its metabolites, is that of Ahmed et al,[26] where no evidence of association was observed. This confirms previous findings where *CYP3A5*3* allele did not significantly contribute to explaining the inter-variability among patients treated with tamoxifen.[61] *CYP3A5*3* hampers enzyme expression and is dominant in Asian/Caucasian populations, whereas most Africans are *CYP3A5*1* (so-called wild-type allele, associated with full enzyme expression). Conversely, a study from 2007 showed that the *CYP3A5*3* allele was associated to higher 5-year recurrence-free survival (RFS) rate (but not 2-year RFS) in breast cancer patients from Sweden.[62] Nevertheless, the association reported has not been validated, and it should be stressed that CYP3A5, which explains <2% of tamoxifen metabolism, would be extremely unlikely to be responsible for meaningful associations with tamoxifen efficacy and/or survival. Furthermore, although *CYP3A5*3* shows its highest frequencies among Asians and Europeans (69–74% and 93–96%, respectively),[63] the variant spectrum of *CYP3A5* in Africans is distinctly different, with higher frequencies in *CYP3A5*6* and **7* alleles, conferring a substantial homogeneity among world populations.[64] The known *CYP3A5* variants among Africans are **3, *6, and *7* (Table 6).

The *SULT1A1* and *SULT1A2* are polymorphic genes that may affect endoxifen level. SULT1A1/2 catalyse the sulfation of endogenous and exogenous molecules, including endoxifen, thus contributing to their excretion.[27,65] Two SNPs in the *SULT1A1* gene, namely rs6839 (902 A>G) and rs1042157 (973 C>T), have been associated with decreased enzyme activity, and when carried together, showed higher levels of endoxifen plasma concentration.[27] Conversely, a study made in Spain assessed that subjects who are wild-type for *CYP2D6* and carry *SULT1A2*2* or *SULT1A2*3* showed significantly higher plasma levels of 4-OH-tamoxifen and endoxifen, than wild type.[66] Similar to the inconsistent effects on endoxifen exposure, studies in tamoxifen treated women have reported that patients who carry *SULT1A1*2* had better[67] or poorer[65,68] survival than non-carriers. These associations have not been validated, and no data are currently available from Africa in the context of breast cancer treatment. Known *SULT1A1* variants assuming relevant frequencies in Africans are as follows: *SULT1A1*2, SULT1A1*3* and rs1042157 (Table 7).

Another route to tamoxifen metabolite elimination is via glucuronidation by UGT enzymes. These UGTs (1A4, 2B7, 2B15) have an almost negligible effect on inactive secondary metabolites. However, in a study conducted in Ethiopia, breast cancer patients carrying the *UGT2B15*4* allele showed a lower plasma concentration of tamoxifen compared to those with wild-type genotype.[26] Another set of data also suggests that in Caucasians, the co-presence of *UGT1A4*2* and *UGT1A4*3B* may be associated with reduced concentrations of glucuronidated metabolites.[69] Concerning *UGT2B7*, the *UGT2B7*2* allele has been associated with decreasing activity against tamoxifen metabolites in vitro.[70] No data are

Table 4 *CYP2C19* Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Group	Type of Subjects[§], n	*2 [rs4244285] 681 G>A (P227P, Frameshift Variant)	*3 [rs4986893] 636 G>A (W212X)	*9 [rs17884712] 12784 G>A (R144H)	*13 [rs17879685] 87290 C>T (R410C)	*15 [rs17882687] 55 A>C (I19L)	*17 [rs12248560] −806 C>T (Promoter Polymorphism)	*22 [Novel, No *rs* Number] 17869 G>C (R186P)	Reference
		Suspected Activity							
		↓	↓	↔	↔	↔	↑	↓	
West-Central Africa									
Benin	111	0.130 (0.067–0.193)	-	-	-	-	-	-	[200]
Gabon	Malaria infected children, 48	0.146 (0.046–0.246)	-	0.042 (−0.015–0.099)	0.031 (−0.018–0.08)	-	-	-	[181]
Ghana	169	0.060 (0.024–0.096)	-	-	-	-	-	-	[203]
Ghana	828	0.170 (0.144–0.196)	-	-	-	-	-	-	[209]
East Africa									
Ethiopia	126	-	-	-	-	-	0.180 (0.113–0.247)	-	[210]
Ethiopia	Breast cancer patients receiving tamoxifen, 81	0.117 (0.047–0.187)	0.012 (−0.012–0.036)	-	-	-	-	-	[26]
Kenya/Luo	30	-	-	-	0.030 (−0.031–0.091)	0.050 (−0.028–0.128)	-	-	[204]
Tanzania	106	0.174 (0.102–0.246)	0.000 (0.000–0.000)	-	-	-	-	-	[186]

(*Continued*)

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Table 4 (Continued).

Geographic Region/ Ethnic Group	Type of Subjects[§], n	*2 [rs4244285] 681 G>A (P227P, Frameshift Variant)	*3 [rs4986893] 636 G>A (W212X)	*9 [rs17884712] 12784 G>A (R144H)	*13 [rs17879685] 87290 C>T (R410C)	*15 [rs17882687] 55 A>C (I19L)	*17 [rs12248560] −806 C>T (Promoter Polymorphism)	*22 [Novel, No *rs* Number] 17869 G>C (R186P)	Reference
		Suspected Activity							
		↓	↓	↔	↔	↔	↑	↓	
Tanzania/Bantu	10	-	-	-	-	-	0.050 (−0.085–0.185)	0.060 (−0.087–0.207)	[204]
Southern Africa									
South Africa	200	0.200 (0.145–0.255)	-	0.025 (0.003–0.047)	-	0.050 (0.020–0.080)	0.155 (0.105–0.205)	-	[47]
South Africa/ Venda	76	0.217 (0.124–0.310)	0.000 (0.000–0.000)	-	-	-	-	-	[186]
South Africa/ Venda	9	-	-	0.060 (−0.095–0.215)	-	-	-	-	[204]
Zimbabwe	84	0.131 (0.059–0.203)	0.000 (0.000–0.000)	-	-	-	-	-	[186]
Cumulative data									
Mixed African Ancestry	137	0.070–0.330 (0.251–0.409)	-	-	-	-		-	[204]
African Americans									
-	Psychiatric patients, 956	0.183 (0.158–0.208)	0.010 (0.004–0.016)	-	-	-	-	-	[198]
-	5477	0.230 (0.219–0.241)	-	-	-	-	0.220 (0.209–0.231)	-	[37]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity; ↑ increased enzyme activity; ↔ no measurable difference in enzyme activity. [§]When available.

Table 5 *CYP3A4* Allele Frequency in Sub-Saharan Africa

Geographic Region/Ethnic Group	Type of Subjects[§], n	*1B [rs2740574] −392 A>G (Promoter Variant)	*1G [rs2242480] −392 A>G and 20230 G>A (Intronic Variant)	*12 [rs12721629] 1117 C>T (L373F)	*15 [rs4986907] 14269 G>A (R162Q)	*23 [rs57409622] 14268 C>T (R162W)	*24 [rs113667357] 15649 A>T (Q200H)	Reference
		Suspected Activity						
		↓	↓	↓	↓	↑	↓	
West-Central Africa								
Burkina Faso	Malaria infected subjects, 41	0.793 (0.669–0.917)	-	-	-	-	-	[140]
Gabon	Malaria infected subjects, 48	-	-	0.010 (−0.018–0.038)	0.021 (−0.020–0.062)	-	-	[181]
Ghana	100	0.690 (0.599–0.781)	-	-	-	-	-	[211]
Ghana	129	0.810 (0.742–0.878)	-	-	-	-	-	[212]
Ghana	95	0.820 (0.743–0.897)	-	-	-	-	-	[213]
Ghana	203	0.720 (0.658–0.782)	-	-	-	-	-	[203]
Ghana	787	0.780 (0.751–0.809)	-	-	-	-	-	[209]
East Africa								
Tanzania	103	0.692 (0.603–0.781)	-	-	-	-	-	[214]
Tanzania	Pregnant women with malaria, 92	0.761 (0.674–0.848)	-	-	-	-	-	[215]
Uganda	23	0.674 (0.482–0.866)	-	-	-	-	-	[216]
Southern Africa								
South Africa/ Bantu	983	0.660 (0.630–0.690)	-	-	-	-	-	[217]

(*Continued*)

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Table 5 (Continued).

Geographic Region/Ethnic Group	Type of Subjects[§], n	*1B [rs2740574] −392 A>G (Promoter Variant)	*1G [rs2242480] −392 A>G and 20230 G>A (Intronic Variant)	*12 [rs12721629] 1117 C>T (L373F)	*15 [rs4986907] 14269 G>A (R162Q)	*23 [rs57409622] 14268 C>T (R162W)	*24 [rs113667357] 15649 A>T (Q200H)	Reference
		Suspected Activity						
		↓	↓	↓	↓	↑	↓	
South Africa/Khoisan	29	0.768 (0.614–0.922)	0.914 (0.812–1.016)	-	-	0.036 (−0.032–0.104)	0.103 (−0.008–0.214)	[16]
South Africa/ Mixed Ancestry	65	0.459 (0.338–0.580)	0.600 (0.481–0.719)	-	-	-	0.032 (−0.011–0.075)	[16]
South Africa/Xhosa	65	0.730 (0.622–0.838)	0.939 (0.881–0.997)	0.023 (−0.013–0.059)	0.024 (−0.013–0.061)	0.008 (−0.014–0.030)	0.031 (−0.011–0.073)	[16]
African Americans								
-	95	0.824 (0.747–0.901)	-	-	-	-	-	[213]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity; ↑ increased enzyme activity. [§]When available.

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Table 6 *CYP3A5* Allele Frequency in Sub-Saharan Africa

Geographic Region/Ethnic Group	Type of Subjects[§], n	*3 [rs776746] 6986 A>G (Splicing Defect)	*6 [rs10264272] 14690 G>A (Splicing Defect)	*7 [rs41303343] 27131_27132insT (Frameshift Variant)	Reference
		Suspected Activity			
		No Activity	↓	↓	
West-Central Africa					
Angola	102	0.152 (0.082–0.222)	-	-	[207]
Cameroon	72	0.170 (0.083–0.257)	0.160 (0.075–0.245)	-	[217]
Gambia	288	0.208 (0.161–0.255)	0.205 (0.158–0.252)	0.122 (0.084–0.160)	[218]
Ghana	864	0.140 (0.117–0.163)	-	-	[209]
Ghana	194	0.150 (0.100–0.200)	0.140 (0.091–0.189)	-	[219]
Ghana	95	-	0.160 (0.086–0.234)	-	[220]
East Africa					
Ethiopia	Breast cancer patients receiving tamoxifen, 81	0.670 (0.568–0.772)	-	-	[26]
Tanzania	Pregnant women with malaria, 92	0.228 (0.142–0.314)	0.206 (0.123–0.289)	0.122 (0.055–0.189)	[215]
Tanzania	103	0.153 (0.083–0.223)	0.181 (0.107–0.255)	0.016 (−0.008–0.040)	[214]
Southern Africa					
South Africa/ Bantu	163	0.220 (0.156–0.284)	0.170 (0.112–0.228)	-	[217]
South Africa/ Xhosa	320	0.147 (0.108–0.186)	0.200 (0.156–0.244)	0.020 (0.005–0.035)	[221]
Zimbabwe	200	0.776 (0.718–0.834)	0.220 (0.163–0.277)	0.100 (0.058–0.142)	[222]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity. [§]When available.

currently available from Africa in the context of breast cancer treatment. The African *UGT* frequencies are shown in Table 8.

Aromatase Inhibitors

In contrast to tamoxifen, the third-generation aromatase inhibitors (AIs), anastrozole, letrozole and exemestane, are considered active in the parent form, and metabolism serves as a means of inactivation. Several large, randomized trials comparing AIs with tamoxifen as adjuvant hormonal therapy have demonstrated significant improvement in disease-free survival and reduction in breast cancer events.[71] In general, AIs have demonstrated better efficacy than tamoxifen, but they are not easily available and are often too expensive for patients in developing countries.[72] However, some studies have been conducted in South Africa where AIs are used as an alternative to tamoxifen.[73,74]

These drugs function by inhibiting the enzyme aromatase, which is encoded by the *CYP19A1* gene. The aromatase enzyme is responsible for the conversion of androgens to estrogens that ultimately fuel ER+ breast cancer cells.

Table 7 *SULT1A1* Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Populations	Type of Subjects[§], n	*2 [rs9282861] 638 G>A (R213H)	*3 [rs1801030] 667A>G (M223V)	N/A [rs1042157] 973 C>T (Non Coding Transcript Variant)	Reference
		Suspected Activity			
		↓	↓	↓	
West-Central Africa					
Nigeria	52	0.269 (0.148–0.390)	-	-	[223]
Nigeria/Yoruba	180	-	-	0.122 (0.074–0.170)	[92]
Southern Africa					
South Africa/Tswana	2010	0.320 (0.300–0.340)	-	-	[224]
African American					
-	70	0.294 (0.187–0.401)	0.229 (0.131, 0.327)	-	[225]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval. [§]When available. Arrows reflect the metabolic activity: ↓ decreased enzyme activity.

Therefore, AI pharmacogenetics involves several genes encoding enzymes and transporters, while genetic variability of the *CYP19A1* target enzyme may affect cancer susceptibility and/or AI treatment efficacy.[75]

Pharmacogenetics of AI Systemic Concentrations

Current knowledge of AI pharmacogenetics suggests that variability in anastrozole, letrozole and exemestane-metabolizing genes contributes to drug plasma concentrations, but there is much weaker evidence that drug concentrations have any meaningful effect on treatment toxicity[76] or efficacy, including systemic estrogenic response.[77] Anastrozole metabolism in vitro (using human liver microsomes and Baculovirus-insect cells expressing human P450s) is mediated by CYP3A4 and CYP3A5, with minor contribution by CYP2C8, CYP2D6 and CYP2B6.[78] However, a recent genome-wide association study (GWAS) identified a polymorphism in the *SLC38A7* gene (rs11648166) that was associated with higher systemic anastrozole concentration.[79] This SNP may affect the expression of a glutamine plasma membrane influx transporter not previously known to transport drugs (including anastrozole). In vitro studies also implicate UGT1A4 in anastrozole metabolism and suggest that three promoter SNPs, rs3732219 (−219C>T), **1G* allele (no *rs* number assigned, −217T>G) and rs3732218 (−163G>A), increase anastrozole glucuronidation.[80] There are no known reports on the frequencies of these SNPs among Africans; however, three other low-activity *UGT1A4* variants have been reported in a non-cancer context[81] (Table 8).

Letrozole is pharmacologically similar to anastrozole, however its metabolism is dependent on CYP2A6, with a minor contribution by CYP3A4 and CYP3A5.[82,83] A study by Borrie et al[84] showed that the *CYP2A6* reduced-function genotypes were significantly associated with increased plasma letrozole levels in Canadian patients. The relevance of *CYP2A6* pharmacogenetics to letrozole pharmacokinetics was recently confirmed by GWAS.[85] African frequencies for *CYP2A6* alleles are shown in Table 9.

Exemestane undergoes metabolism primarily through CYP3A4 with minor contribution from CYP1A1 and CYP4A11. The loss of function *CYP3A4*22* allele is associated with a higher exemestane plasma concentration.[86] *CYP3A4*22* has an allelic frequency of 6–8% in Caucasians, whereas it has not been reported in African subjects.[87] Nevertheless, it is well known that among Africans the *CYP3A4*1B* allele has a very high frequency (Table 5), but its possible contribution to exemestane metabolism has not yet been established.

Table 8 *UGTs* Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Group	Type of Subjects[§], n	*UGT1A4**2* [rs6755571] 70 C>A (P24T)	*UGT1A4**3B* [rs2011425] 142 T>G (L48V)	*UGT1A4**4* [rs3892221] 31 C>T (R11W)	*UGT2B7**2* [rs7439366] 802 C>T (H268Y)	*UGT2B15**2* [rs1902023] 253 G>T (D85Y)	*UGT2B15**4* [rs4148269] 1568 C>A (T523K)	Reference
		Suspected Activity						
		↓	↓	N/A	↓	↓	↑	
West-Central Africa								
West Africa[¶]	133	-	-	-	0.210 (0.141–0.279)	-	-	[226]
Nigeria/Yoruba	180	-	-	-	0.016 (−0.002–0.034)	-	-	[92]
East Africa								
Ethiopia	Breast cancer patients receiving tamoxifen, 81	-	-	-	-	0.202 (0.115–0.289)	0.403 (0.296–0.510)	[26]
Southern Africa								
South Africa	Healthy HIV uninfected subjects, 48	0.010 (−0.018–0.038)	0.042 (−0.015–0.099)	0.042 (−0.015–0.099)	-	-	-	[81]
Zimbabwe	Healthy HIV uninfected subjects, 51	0.010 (−0.017–0.037)	0.069 (−0.001–0.139)	0.010 (−0.017–0.037)	-	-	-	[81]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity; ↑ increased enzyme activity. [§]When available. [¶]Ghana (n=23), Guinea (n=22), Ivory Coast (n=36), Sierra Leone (n=43), Senegal (n=9).

Pharmacogenetics of AI Toxicity

Up to one quarter of patients discontinue AI therapy due to intolerable toxicities.[88] The most common signs of toxicity are musculoskeletal, such as arthralgias, myalgias and tendinopathies, which can also be severe.[76] One initial study assessed that a variant of *estrogen receptor 1 signaling* gene (*ESR1*), rs9322336 (151879295T>C), was associated with an increased risk of musculoskeletal toxicity during exemestane administration.[88] A later GWAS implicated genetic variability in *T-cell leukaemia protein 1* gene (*TCL1A*) that may increase AI-induced musculoskeletal toxicity, though other studies have been unable to replicate this finding.[88–90] Recent work by Hertz et al[91] suggests that carriers of *osteoprotegerin* gene (*OPG*) rs2073618 may be at increased risk of musculoskeletal adverse events. However, further validation of the role of *ESR1, TCL1A* and *OPG* genes awaits further research. *ESR1* rs9322336 frequency in African Americans is 4.33%.[92]

Pharmacogenetics of Aromatase (CYP19A1)

CYP19A1 encodes for the aromatase enzyme that catalyses the conversion of androgens to estrogens. AIs target aromatase to reduce estrogen production, ultimately blocking replication of ER+ breast cancer cells. *CYP19A1* polymorphisms therefore may impact estrogen production (that is a susceptibility factor for breast cancer) and also respond to AI treatment.

Sequencing of *CYP19A1* reveals many variants, some of which have been shown to decrease aromatase activity in vitro.[93] Alterations in aromatase expression have been implicated in the pathogenesis of estrogen-dependent diseases including breast cancer. For example, the data on *CYP19A1* support an association between the number of (TTTA)n repeats in intron 4 and breast cancer risk, but the biological mechanism for this relationship is unknown.[94] The same

Table 9 *CYP2A6* Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Group	Type of Subjects[§], n	*2 [rs1801272] 1799 T>A (L160H)	*4 (Gene Deletion)	*9 [rs28399433] −48 T>G (Promoter Polymorphism)	*12 [esv2663194] (Exons 1–2 from *CYP2A7*, Exons 3–9 from *CYP2A6*, 10 Amino Acid Substitutions)	*17 [rs28399454] 1093 G>A (V365M)	*20 [rs568811809] 2141_2142delAA (Frameshift Variant)	Reference
		Suspected Activity						
		↓	No Activity	↓	↓	↓	No Activity	
West-Central Africa								
Gabon	Malaria infected children, 48	-	-	-	0.042 (−0.015–0.099)	0.073 (−0.001–0.147)	0.042 (−0.015–0.099)	[209]
Ghana	105	-	-	0.057 (0.013–0.101)	-	0.120 (0.058–0.182)	-	[227]
Nigeria	180	-	-	0.110 (0.064–0.156)	-	0.125 (0.077–0.173)	-	[228]
Southern Africa								
South Africa/ Xhosa	HIV positive adults, 47	-	-	0.090 (0.008–0.172)	-	-	-	[229]
Cumulative Data								
Africans[¶]	N/A	0.000–0.011	0.005–0.027	0.057–0.096	0.000–0.004	0.071–0.110	0.011–0.017	[230]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity. [§]When available. [¶]Confidence Intervals could not been calculated for lack of sample size.

polymorphism has been associated with bone homeostasis in response to hormone replacement therapy.[73] Studies of the putative association of *CYP19A1* genetics and AI treatment outcomes have reported inconsistent results. For example, the SNP rs4646, in the context of letrozole treatment efficacy, was found to be associated with longer disease-free survival in metastatic breast cancer patients from Spain.[95] Similarly, a study from China detected superior tumour response, clinical benefit, time to progression and overall survival in carriers of rs4646 receiving anastrozole treatment.[96] Conversely, another study reported that patients rs4646 carriers were more likely to be non-responders to letrozole.[97] Conflicting results for these and other *CYP19A1* polymorphisms suggest null or negligible effects on AIs treatment outcomes.[76] A recent report on *CYP19A1* and bone loss with anastrozole in South Africa[74] showed that genotyping for rs10046 (1531 G>A) is an additional tool for risk stratification in AI-related bone outcomes. Women with AA genotype were found to be about 10 times more likely to have an increased percentage of bone loss.[74] Table 10 reports allele frequencies for relevant polymorphisms in African populations.

Targeted Biological Therapy

Trastuzumab is a humanized monoclonal antibody that binds specifically to the HER2 receptor and suppresses cell proliferation that is driven by over-expression of the HER2 protein. The monoclonal antibody also binds Fc gamma (Fcγ) receptor on an effector cell, such as a natural killer cell, monocyte, or macrophage. The combination of trastuzumab with chemotherapy has led to a significant reduction in breast cancer recurrence and mortality in HER2 overexpressing or amplified tumours (HER2+) when used in the adjuvant setting.[98–100] Despite substantial improvements in outcomes with the use of trastuzumab, with disease-free survival of more than 10 years in high-income countries, there are variations in

Table 10 *CYP19A1* Allele Frequency in Sub–Saharan Africa

Geographic Region/ Ethnic Group	Type of Subjects[§], n	[rs700518] 240 A>G (V80V)	[rs700519] 1123 C>T (R264C)	[rs10046] 1531 G>A (3'-UTR variant)	[rs4646] 51,210,647 A>C (3'-UTR Variant)	Reference
		Suspected Activity				
		Homozygous (AA and GG) Patients had Superior Clinical Benefit Than Heterozygous (AG)	***Enhanced Aromatase Enzymatic Activity***	***Increased risk of Bone Loss for GA and AA Genotypes***	***Superior Tumour Response, Clinical Benefit, Time to Progression and Overall Survival in Carriers of the C Allele***	
Southern Africa						
South Africa	Breast cancer subjects, 72	-	-	0.306 (0.200–0.412)	-	[74]
African Americans						
-	Postmenopausal women with ER + breast cancer, 17	0.294 (0.077–0.511)	-	-	-	[232]
-	341	-	0.172 (0.132–0.212)	-	-	[233]
-	11,33	-	-	-	0.692 (0.683,0.701)	[92]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. [§]When available.

response to adjuvant trastuzumab. Furthermore, in Africa, trastuzumab is increasingly used, but it is not widely available due to high drug pricing in many countries.[101]

Studies on the pharmacogenomics of trastuzumab have been mostly focused on polymorphisms of the Fcγ receptors 2a and 3a genes (*FCGR2A* and *FCGR3A*). There are two main candidate SNPs in the two genes thought to possibly influence trastuzumab treatment outcomes, namely *FCGR2A* H131R (rs1801274) and *FCGR3A* F158V (rs396991) (Table 11). These variations are also associated with auto-immune, auto-inflammatory and infectious diseases' susceptibility,[102] and with the efficacy of immunotherapy in cancer patients. However, genetic analysis of the variants at the locus is hampered by the genetic complexity deriving from a segmental duplication, inconsistent nomenclature, and a high degree of linkage disequilibrium.[103] Nevertheless, the combination of the two wild-type genotypes (H/H and/or F/F, which are in linkage disequilibrium) has been associated with better response rate and progression-free survival compared with variant genotypes,[104–106] According to the higher *FCGR2A* H131R and *FCGR3A* F158V frequencies among Africans (Table 11) than Caucasians,[107] it can be hypothesized that African patients may not respond as well to trastuzumab treatment as non-African, though this has not been demonstrated and/or confirmed.

Another possible source of variation concerning trastuzumab and its targets, is the genetic variation at *HER2* gene. Indeed, an association of rs1136201 (I655V, 1963 A>G) of *HER2* with trastuzumab cardiotoxicity has been described[108] where the allele G has been associated with response to trastuzumab. But in another study it has been found that there was no association between the aforementioned rs1136201 and toxicity; however, another polymorphism, rs1058808 (P1170A, 3418 C>G), was more likely to be found in cases with trastuzumab cardiotoxicity.[109] In spite of this, the correlation between variations at the *HER2* gene and cardiotoxicity risk have not been validated.[110] Finally, no specific studies have been performed on SSA.

Table 11 FCG RECEPTORS Allele Frequency for Sub-Saharan Africa

Geographic Region/ Ethnic Group	Type of Subjects[§], n	*FCGR2A* [rs1801274] 519 A>C (H131R)	*FCGR3A* [rs396991] 559 T>G (F158V)	Reference
		Suspected Activity		
		Wild Type Allele (131H) Has Higher Affinity for Human IgG	Variant Allele (158V) Has Higher Affinity for Human IgG	
West-Central Africa				
Mali	242	0.769 (0.716–0.822)	-	[102]
Nigeria/Yoruba	88	0.530 (0.426–0.634)	0.750 (0.660–0.840)	[107]
East Africa				
Kenya/Luhya	97	0.459 (0.360–0.558)	0.861 (0.792–0.930)	[107]
Rwanda	HIV infected subjects, 110	0.519 (0.426–0.612)	0.650 (0.561–0.739)	[233]
Southern Africa				
South Africa	131	0.557 (0.472–0.642)	0.633 (0.55–0.716)	[107]
Zambia	HIV infected subjects, 89	0.573 (0.470–0.676)	0.781 (0.695–0.867)	[233]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. [§]When available.

Cytotoxic Chemotherapy

HR+ tumours are not responsive to endocrine treatment and are therefore treated with chemotherapy. Cytotoxic drugs have a narrow therapeutic index, and there is substantial inter-patient variability in reaction to the administration of standard doses. As with the use of hormonal agents and other targeted therapies, pharmacogenetics may partly explain differences in the safety and efficacy of cytotoxic agents.

Antimetabolites

Capecitabine, an orally administered prodrug of the pyrimidine analog 5-fluorouracil (5-FU), is used frequently in the treatment of metastatic breast cancer.[111] The rate of systemic 5-FU catabolism is the main determinant of capecitabine side effects, and it is dictated by the enzyme dihydropyrimidine-dehydrogenase (DPD), which is implicated in about 50% of cases of severe toxicity.[112,113] Although capecitabine is not widely used in the African public health sector, reports show that it is being used in Nigeria and South Africa, at least.[8,114,115]

DPYD

DPD, encoded by *DPYD* gene, is the rate-limiting step in pyrimidine catabolism and deactivation of 5-FU.[116] DPD is responsible for the degradation and removal of >80% of 5-FU administered to patients. Up to 7% of the overall populations carry a *DPYD* variant that reduces DPD enzyme activity, which causes excess drug accumulation and toxicity.[116,117] Fluorouracil toxicity has a wide range of symptoms that include vomiting, nausea, kidney failure, and even death.[118] Unlike the vast majority of other pharmacogenes described in this review, this association has been adequately confirmed, and there are prospective studies demonstrating improved clinical outcomes (decreased toxicity) in patients following a *DPYD* genotype-guided dose individualisation for fluoropyrimidine treatment.[119,120] It is worth noting that DPD deficiency is a very rare condition (~1/200–1/1000) in which one has no DPD activity; however, a much larger percentage of patients carry a *DPYD* variant that reduces DPD activity (~7%). In fact, multiple *DPYD* variants have been

identified, including well-known non-synonymous and splice site variations within the coding regions of the gene, and more novel variations within non-coding regions.[121] Furthermore, reduced DPD activity may be partially due to epigenetic factors including gene promoter methylation.[122] Among the variants associated with reduced DPD activity, *DPYD*2A* (rs3918290, intron mutation) displays similar allele frequencies across all ethnic groups tested, including Africans.[123] *DPYD*13* (rs55886062, 1679A>C) and 2846A>T are present in less than 2% of Caucasians.[124] Importantly, in this review paper, a study[125] searching for deleterious mutations in subjects of different ethnicities identified a non-synonymous variant, Y186C (rs115232898), that was found in heterozygosity in 6.4% of African Americans. The variant has been previously described among deficient African Americans[122] and correlates with 5-FU toxicity.[126,127] In vitro experiments demonstrated a 15–29% relative decrease in the activity of *DYPD* Y186C compared with wild-type *DPYD*.[128] The *DYPD* Y186C appears to be nearly exclusive to African individuals,[129] with an average frequency of 3% (Table 12).

In summary, it is important to consider the pharmacogenomic risk of using fluoropyrimidine-based treatments in Africans. Variants with high predictive value for the onset of toxicity in Europeans were not observed in the African populations studied.[130] African *DPYD* variants with predicted functional impacts, such as Y186C, should be validated and considered for inclusion in guidelines or testing strategies for African populations. Finally, additional research is needed to identify more variants that reduce DPD activity in Africans.

Antimicrotubules

The taxanes, paclitaxel and docetaxel, are some of the most effective chemotherapeutic agents against breast cancer and are indicated in both metastatic and adjuvant diseases. Taxanes disrupt microtubule depolymerization and spindle formation during cell replication, thereby causing cell death. Both paclitaxel and docetaxel are hydroxylated in the liver by CYP3A4/5, though paclitaxel is primarily metabolized by CYP2C8.[131]

Paclitaxel

Paclitaxel is a widely used drug for breast cancer treatment with an overall response rate of about 25%.[132] The advanced paclitaxel formulation as albumin-embedded nanoparticles (nab paclitaxel) increased the initial response rate to 42%.[132]

Table 12 DPYD Allele Frequency for Sub-Saharan Africa

Geographic Region/ Ethnic Populations	Type of Subjects[§], n	N/A [rs115232898] 557 A>G (Y186C)	*2A [rs3918290] IVS14+1G>A	N/A [rs67376798] 846 A>T (D949V)	Reference
		Suspected Activity			
		↓	Full DPYD Deficiency	↓	
West-Central Africa					
West African ancestry	12,481	0.022 (0.019–0.024)	-	0.001 (0.000–0.002)	[92]
East Africa					
Somalia	588	-	0.001 (−0.002–0.004)	0.001 (−0.002–0.004)	[234]
African Americans					
-	94	0.032 (−0.004–0.068)	0.001 (−0.004–0.068)	-	[125]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity. [§]When available.

However, resistance occurs frequently, and the evasion mechanisms remain unclear. Tumour recurrence occurs in 30% of node-negative, and up to 70% in node-positive breast cancer patients. Only 23% of relapsed patients survive 5 years after diagnosis, mainly due to metastasis to lymph nodes and distant organs.[133] Paclitaxel is dosed according to body surface area and in most regimens infused for 3 hours. The dose limiting toxicities are neutropenia and neuropathy. However, there is a large interindividual variability in toxicity and therapeutic effects of paclitaxel, which remains a clinically relevant problem with implications on survival and quality of life of the patients. All this has a practical effect regarding the handling of dose delay, dose reduction or cessation of the treatment. Several possible causes of this variability have been suggested, including the possibility that SNPs in genes responsible for paclitaxel metabolism (ie, *CYP2C8* and *CYP3A4*) could affect systemic exposure and toxicity.[134] *CYP2C8* is a polymorphic gene with several variant genotypes that may affect paclitaxel clearance.[135] CYP2C8 comprises 7% of the total hepatic CYP450 content and plays an important role in the metabolism of a limited number of exogenous compounds. A clinical pharmacokinetic study demonstrated a reduction in paclitaxel metabolism associated with the *CYP2C8*3* allele among Caucasians, and a modest reduction in paclitaxel metabolism with the *CYP2C8*4* allele.[136] Alternatively, another study reported that *CYP2C8*3* may increase metabolic elimination of paclitaxel,[137] as it does with most other substrates. Both of these alleles are found at lower frequencies in African populations, whereas *CYP2C8*2* is found at higher frequencies.[138–143] There is relatively little knowledge about the impact of *CYP2C8*2* on paclitaxel metabolism. Some in vitro studies have found that *CYP2C8*2* has a two-fold lower intrinsic clearance for paclitaxel than the wild-type,[144–146] however, this has not been confirmed in a clinical pharmacokinetics study. Another study involving an African American breast cancer cohort found that the risk of paclitaxel-induced peripheral neuropathy was significantly greater in the *CYP2C8* low-metabolizer group, which included all carriers of *CYP2C8*2, CYP2C8*3*, or *CYP2C8*4*.[147] However, the influence of the *CYP2C8*2* and *CYP2C8*4* SNPs were not independently significant.[147] Table 13 shows African frequency for *CYP2C8* alleles, which does not suggest substantial high differences in metabolic activity phenotypes between Africans and non-Africans.

CYP3A4 and CYP3A5 were previously discussed in the tamoxifen section. *CYP3A4* alleles that affect enzyme activity, such as *CYP3A4*22*, may be associated with an increased risk of developing paclitaxel-induced peripheral neuropathy.[148,149] However, no studies have been performed on African patient cohorts. Other non-pharmacogenes that have been reported to be associated with peripheral neuropathy have not been validated.[150–152]

Docetaxel

Genetics have not been demonstrated to have a meaningful effect docetaxel on pharmacokinetics or peripheral neuropathy.[134] A GWAS reported a candidate polymorphism in *VAC14* (rs875858),[153] which is yet to be validated. To our knowledge, this SNP has not been described in African populations.

In the past decade, important new insights have also been obtained on polymorphic transporters involved in docetaxel elimination. Specifically, there is compelling evidence suggesting that hepatocellular uptake of taxanes from sinusoidal blood is regulated, at least in part, by the solute carrier OATP1B3 (encoded by *SLCO1B3* gene) but without evidence of the impact of its genetic variation on docetaxel elimination.[154,155] The secretion of taxanes from the liver into the bile, instead, depends on the ATP-binding cassette (ABC) transporters ABCB1 (P-glycoprotein) and ABCC2 (also called MRP2). There is some evidence of a possible effect of *ABCB1* rs1045642 (3435C>T) on docetaxel plasma levels[156] and toxicity,[157,158] and of rs1202179 (287-4740G>A) on chemotherapy-induced alopecia.[159] Although there are no association studies conducted in African cohorts, some of the variants of interest are found in African populations (Table 14).

Anthracyclines

The anthracyclines doxorubicin and epirubicin have been widely used in breast cancer treatment for several decades, including within Africa.[160–162] These drugs inhibit topoisomerase II and thereby induce cellular apoptosis. Pharmacogenetic variants have been observed in anthracycline-metabolizing enzymes, as well as transporters and proteins involved in oxidative stress and apoptosis.[163–165]

Approximately 50% of doxorubicin is eliminated from the body in its intact form, and the remainder through aldoketoreductase (AKR1A1) and carbonyl reductase (CBR1 and CBR3),[166] with a minor contribution from NADH dehydrogenase (NQO1) and nitric oxide synthases (NOS1, NOS2 and NOS3).[166] Variants in *CBR1* and *CBR3* have been

Table 13 CYP2C8 Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Populations	Type of Subjects[§], n	*2 [rs11572103] 805 A>T (I269F)	*3 [rs10509681, rs11572080] 2130 G>A and 30411 A>G (R139K, K399R)	*4 [rs1058930] 792 C>G (I264M)	Reference
		Suspected Activity			
		↓	↓[¥]	↓	
West-Central Africa					
Burkina Faso	275	-	0.040 (0.017–0.063)	-	[235]
Burkina Faso/Fulani	Malaria exposed subjects, 71	0.099 (0.030–0.168)	-	-	[140]
Burkina Faso/Mossi and Rimaibe'	Malaria exposed subjects, 435	0.237 (0.197–0.277)	-	-	[140]
Gabon	48	0.170 (0.064–0.276)	-	-	[209]
Ghana	200	0.167 (0.116–0.218)	-	-	[139]
Ghana	203	0.170 (0.134–0.207)	-	-	[203]
Nigeria/Hausa	Malaria exposed subjects, 40	0.133 (0.028–0.238)	-	-	[143]
Nigeria/Igbo	Malaria exposed subjects, 45	0.067 (−0.006–0.140)	-	-	[143]
Nigeria/Yoruba	Malaria exposed subjects, 195	0.600 (0.531, 0.669)	-	-	[143]
Republic of Congo	Symptomatic malaria children, 285	0.368 (0.31–0.424)	-	-	[142]
Senegal	88	0.222 (0.135–0.309)	-	-	[141]
East Africa					
Uganda	262	0.105 (0.068–0.142)	-	-	[141]
Tanzania/Zanzibar	Children with uncomplicated malaria, 165	0.139 (0.086–0.192)	0.021 (−0.001–0.043)	0.060 (0.024–0.096)	[138]
Southern Africa					
Botswana/San	160	0.175 (0.116–0.234)	-	-	[236]
Botswana/Tswana	384	0.085 (0.057–0.113)	-	-	[236]
African Americans					
-	82	0.180 (0.097–0.263)	0.020 (−0.010–0.050)	-	[144]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity. [§]When available. [¥]According to Marcath et al[180] *CYP2C8*3* has a ultra-rapid phenotype with paclitaxel.

Table 14 *ABCB1* Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Populations	Type of Subjects[§], n	[rs3842] 4036 A>G (*UTR* Variant)	[rs1045642] 3435 C>T (Synonymous Sequence Variant)	Reference
		Suspected Activity		
		↓	↓	
East Africa				
Ethiopia	HIV-infected subjects, 264	0.220 (0.170–0.270)	0.145 (0.103–0.187)	[237]
Ethiopia	Breast cancer patients, 81	0.148 (0.071–0.225)	0.169 (0.087–0.251)	[26]
Ethiopia	Breast cancer patients, 267	0.119 (0.080–0.158)	-	[179]
Tanzania	HIV-infected subjects, 183	0.155 (0.103–0.207)	0.220 (0.160–0.280)	[237]
Tanzania	Pregnant women with malaria, 92	0.272 (0.181–0.363)	-	[215]
Southern Africa				
Angola	98	-	0.134 (0.067–0.201)	[238]
Malawi	HIV-infected subjects, 30	-	0.210 (0.064–0.356)	[239]
South Africa	HIV-infected subjects, 979	0.202 (0.177–0.227)	0.120 (0.100–0.140)	[174]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity. [§]When available.

associated with doxorubicin pharmacokinetics and clinical outcomes in paediatric cancer survivors, but these associations were not found in patients with breast cancer.[167,168] Recent data suggest that *CBR1* rs20572 and *AKR1A1* rs2088102 might be protective factors for the hematologic toxicity during anthracycline-based chemotherapy in breast cancer patients.[169] Unfortunately, rs20572 has a very low frequency among Africans, suggesting a possible, though not yet studied, explanation for the increased risk of hematologic toxicity in African patients.[169] Data on *AKR1A1* rs2088102 among Africans have been reported to be 0.514.[92]

SLC22A16

SLC22A16 encodes an organic zwitterion transporter protein that transports carnitine and some anticancer drugs, including anthracyclines.[170] Carriers of the *SLC22A16* rs12210538 (1226 T>C) allele have been reported to have a higher incidence of leucopenia and dose delay but have no difference in survival.[171] *SLC22A16* expression in cancer cells is associated with increased sensitivity to the cytotoxic effects of doxorubicin.[163] Patients with the variant genotype may have greater uptake of doxorubicin into normal and tumour cells, leading to greater incidence of toxicity. Twenty–twenty five percent (20–25%) of Caucasians carry the variant,[172] while allele frequency in Africans has been measured as 0.038.[92]

ABCB1

ABCB1 is a drug transporter that effluxes drugs from malignant cells. In a study investigating 68 white European women with locally advanced breast cancer, there was a greater likelihood of clinically complete response to neoadjuvant chemotherapy in patients carrying *ABCB1* 3435C>T.[173] No data were retrieved concerning African patients using anthracyclines. See Table 14 for African *ABCB1* allele frequencies. Importantly, *ABCB1* 3435C>T is higher in Caucasians and Asians (50–60%) than Africans.[174] *ABCB1* 4036A>G frequencies seem to be comparable in Africans to Caucasians, which are somewhat lower than the frequency in Asians.[174]

Cyclophosphamide

Cyclophosphamide remains a stable component in many of the chemotherapy combinations used in breast cancer patients in SSA. Cyclophosphamide is a prodrug that undergoes metabolic activation, in the liver, which is primarily mediated by CYP2B6 and CYP2C9/CYP2C19, with a minor contribution from CYP3A4/5.[175] The active metabolite aldophosphamide is subsequently inactivated by glutathione-s-transferases (GSTs).[165]

Table 15 *CYP2B6* Allele Frequency in Sub-Saharan Africa

Geographic Region/ Ethnic Populations	Type of Subjects[§], (n)	*22 [rs34223104] −82 T>C (3'-UTR Variant)	*9 and *6 [rs3745274] 516 G>T (Q172H)	*4, *6 and *16 [rs2279343] 785 A>G (K262R)	*18 and *17 [rs28399499] 983 T>C (I328T)	Reference
		Suspected Activity				
		↑	↓	↑	↓	
West-Central Africa						
Cameroon	HIV-infected subject, 69	-	0.369 (0.255–0.483)	0.326 (0.215–0.437)	-	[217]
Cameroon/Bamileke'	168	-	0.443 (0.368–0.518)	-	0.128 (0.077–0.179)	[240]
Cameroon	HIV-infected subject, 122	-	0.594 (0.507–0.681)	-	0.086 (0.036–0.136)	[241]
Ghana	40	0.012 (−0.022–0.046)	0.488 (0.333–0.643)	0.475 (0.320–0.630)	0.060 (−0.014–0.134)	[242]
Ghana	42	-	0.540 (0.389–0.691)	0.460 (0.309–0.611)	0.076 (−0.004–0.156)	[243,244]
Ghana	HIV-infected subject, 74	-	0.446 (0.333–0.559)	-	0.460 (0.346–0.574)	[245]
Ghana	HIV-infected subject, 94	-	-	-	0.042 (0.001–0.083)	[246]
Ghana	HIV-infected subject, 705	-	0.480 (0.443–0.517)	-	0.040 (0.026–0.054)	[247]
Guinea	21	-	0.500 (0.286–0.714)	0.480 (0.266–0.694)	0.016 (−0.038–0.070)	[243,244]
Ivory Coast	41	-	0.400 (0.250–0.550)	0.380 (0.231–0.529)	0.055 (−0.015–0.125)	[243,244]
Nigeria	300	-	0.365 (0.311–0.419)	-	-	[248]
Nigeria	HIV-infected pregnant women, 77	-	0.437 (0.326–0.548)	-	0.132 (0.056–0.208)	[249]
Republic of Congo	HIV-infected subject, 288	-	0.550 (0.493–0.607)	-	-	[250]

(*Continued*)

Table 15 (Continued).

Geographic Region/ Ethnic Populations	Type of Subjects[§], (n)	*22 [rs34223104] −82 T>C (3'-UTR Variant)	*9 and *6 [rs3745274] 516 G>T (Q172H)	*4, *6 and *16 [rs2279343] 785 A>G (K262R)	*18 and *17 [rs28399499] 983 T>C (I328T)	Reference
		Suspected Activity				
		↑	↓	↑	↓	
Sierra Leone	52	-	0.470 (0.334–0.606)	0.360 (0.230–0.490)	0.038 (−0.014–0.090)	[243,244]
East Africa						
Burundi	HIV-infected subject, 204	-	0.316 (0.252–0.380)	-	0.069 (0.034–0.104)	[251]
Ethiopia	HIV-infected subject, 163	-	0.297 (0.227–0.367)	-	-	[252]
Ethiopia	HIV-infected subject, 245	-	0.314 (0.256–0.372)	-	-	[253]
Ethiopia	HIV-infected subject, 264	-	0.314 (0.258–0.370)	-	-	[237]
Ethiopia	HIV-infected subject, 298	-	0.292 (0.240–0.344)	-	-	[254]
Kenya	HIV-infected women, 66	-	0.326 (0.213–0.439)	-	0.098 (0.026–0.170)	[255]
Rwanda	HIV-infected subject, 80	-	0.319 (0.217–0.421)	0.325 (0.222–0.428)	0.092 (0.029–0.155)	[256]
Rwanda	HIV-infected subjects, 90	-	0.328 (0.231–0.425)	-	0.080 (0.024–0.136)	[257]
Rwanda	HIV-infected subjects, 39	0.064 (−0.013–0.141)	-	-	-	[258]
Tanzania	HIV-infected subjects, 183	-	0.418 (0.347–0.489)	-	-	[237]
Tanzania	242	-	0.360 (0.300–0.420)	-	-	[259]
Tanzania	HIV- and malaria-infected subjects, 251	-	0.356 (0.297–0.415)	-	0.198 (0.149–0.247)	[260]
Tanzania	Pregnant women with uncomplicated malaria, 91	-	0.335 (0.238–0.432)	-	0.093 (0.033–0.153)	[215]
Tanzania	HIV-infected subject, 37	-	0.338 (0.186–0.490)	-	-	[261]
Uganda	HIV-infected subject, 23	-	0.304 (0.116–0.492)	-	-	[216]

(*Continued*)

Table 15 (Continued).

Geographic Region/ Ethnic Populations	Type of Subjects[§], (n)	*22 [rs34223104] −82 T>C (3'-UTR Variant)	*9 and *6 [rs3745274] 516 G>T (Q172H)	*4, *6 and *16 [rs2279343] 785 A>G (K262R)	*18 and *17 [rs28399499] 983 T>C (I328T)	Reference
		Suspected Activity				
		↑	↓	↑	↓	
Uganda	187	-	0.318 (0.251–0.385)	-	-	[262]
Uganda	HIV-infected subject, 74	-	0.291 (0.188–0.394)	0.324 (0.217–0.431)	0.054 (0.003–0.105)	[263]
Uganda	TB/HIV-coinfected subjects, 166	-	0.394 (0.320–0.468)	-	-	[264]
Southern Africa						
Botswana	HIV-infected subjects, 101	-	0.366 (0.272–0.460)	-	-	[265]
Botswana	HIV-infected subjects, 1101	-	0.376 (0.347–0.405)	-	-	[266]
Botswana	HIV-infected subjects, 731	-	-	0.060 (0.043–0.077)	0.110 (0.087–0.133)	[267]
Botswana	570	-	0.381 (0.341–0.421)	0.330 (0.291–0.369)	0.135 (0.107–0.163)	[45]
Botswana	HIV-infected subjects, 227	0.033 (0.010–0.056)	0.432 (0.368–0.496)	0.326 (0.265–0.387)	0.172 (0.123–0.221)	[46]
Malawi	HIV-infected subjects, 150	-	0.405 (0.326–0.484)	0.371 (0.294–0.448)	0.086 (0.041–0.131)	[268]
Mozambique	HIV-infected subjects, 105	-	0.347 (0.256–0.438)	0.442 (0.347–0.537)	0.086 (0.032–0.140)	[269]
Mozambique	360	-	0.426 (0.375–0.477)	0.409 (0.358–0.460)	-	[270]
South Africa	HIV-infected subjects, 122	-	0.320 (0.237–0.403)	-	-	[271]
South Africa	HIV-infected subjects, 80	-	0.431 (0.322–0.540)	-	-	[272]
South Africa	HIV-infected subjects, 160	-	0.362 (0.288–0.436)	0.362 (0.288–0.436)	0.025 (0.001–0.049)	[217,273]
South Africa	HIV-infected subjects, 295	-	0.411 (0.355–0.467)	0.411 (0.355–0.467)	0.071 (0.042–0.100)	[273]
South Africa	HIV-infected subjects, 113	-	0.360 (0.271–0.449)	-	0.070 (0.023–0.117)	[274]

(*Continued*)

Table 15 (Continued).

Geographic Region/ Ethnic Populations	Type of Subjects[§], (n)	*22 [rs34223104] −82 T>C (3'-UTR Variant)	*9 and *6 [rs3745274] 516 G>T (Q172H)	*4, *6 and *16 [rs2279343] 785 A>G (K262R)	*18 and *17 [rs28399499] 983 T>C (I328T)	Reference
		Suspected Activity				
		↑	↓	↑	↓	
South Africa	HIV-infected subjects, 81	-	0.352 (0.248–0.456)	0.352 (0.248–0.456)	0.037 (−0.004–0.078)	[275]
South Africa	HIV-infected subjects, 60	-	0.410 (0.286–0.534).	0.408 (0.284–0.532)	0.110 (0.031–0.189)	[276]
Zimbabwe	HIV-infected subjects, 71	-	0.486 (0.370–0.602)	-	-	[277]
Zimbabwe	HIV-infected subjects, 36	-	0.514 (0.351–0.677)	0.528 (0.365–0.691)	0.111 (0.008–0.214)	[263]
Zimbabwe	HIV-infected subjects, 49	-	0.418 (0.280–0.556)	0.418 (0.280–0.556)	0.091 (0.010–0.172)	[278]
Zimbabwe	TB/HIV-coinfected subjects, 185	-	0.438 (0.367–0.509)	-	0.159 (0.106–0.212)	[279]

Notes: Allele frequencies are indicated as proportion ± 95% confidence interval (95% C.I.). Confidence Intervals have been calculated by the present manuscript authors. Arrows reflect the metabolic activity: ↓ decreased enzyme activity; ↑ increased enzyme activity. [§]When available.

Xie et al[176] showed that *CYP2B6* 516G>T has two-fold higher cyclophosphamide clearance in vitro compared to wild-type enzyme. *CYP2B6* 516G>T is a poor metabolizer polymorphism for the antiretroviral drugs efavirenz and nevirapine, with very high frequency in Africa,[46] however showing a higher cyclophosphamide clearance rate than wild-type *CYP2B6*.[176] However, several other studies have not found the effects of polymorphisms in *CYP2B6* and *CYP2C19* on cyclophosphamide pharmacokinetics.[177,178] Data concerning African frequencies for *CYP2B6* variants are shown in Table 15. In Ethiopia, it has been reported that carriers of *CYP3A5*3* and *CYP3A5*6* had lower cyclophosphamide elimination rate and longer half-life than subjects carrying the wild-type allele.[179] Additionally, increased drug clearance has been reported in carriers of *CYP2C9**2 and *CYP2C9*3*,[179] similar to the increased activity for other substrates.[180] Allele frequencies for these genes were previously reported in other sections.

Conclusion

This review paper summarized the findings with reference to the African variability of genes encoding for enzymes and transporters involved in the metabolism of drugs available to treat breast cancer in Africa. The high extent of diversification shown by African populations and ethnic groups is an example of adaptation and co-evolution between genetic loci deputed to the detoxification of exogenous molecules from the body, linked to different lifestyles in humans. This existing system is exploited by modern drugs, resulting in different pathways and rates of drug metabolism consistent with the extent of African genetic variability.

Most of the reported data for African alleles and/or SNP frequencies come from studies concerning malaria and HIV, the two main infectious diseases affecting the continent. This limits the availability of data for non-malaria and non-HIV treatment pharmacogenetics. Moreover, despite a growing interest and concern for non-communicable diseases, pharmacogenetics, and in particular breast cancer pharmacogenetics, is still a developing field in Africa. Indeed, some of the data reported in this paper are derived from studies conducted on African American subjects or patients, used as a proxy for Africans.

Only a small number of published studies have investigated the pharmacogenetics but also the pharmacokinetic/pharmacodynamic profile of drugs used to treat breast cancer in SSA. In particular, two studies, one on tamoxifen and another on cyclophosphamide among breast cancer patients, have been performed in Ethiopia.[26,179] Another study was focused on AIs in South African women with breast cancer.[74] We would like to stress that Ethiopia has a complex admixture component with a dynamic history of several Eurasian ancestries and some Nilotic and Semitic-Cushitic components. Similarly, South African ethnic diversity and admixture may hamper the transfer of these outputs to other African populations with different genetic backgrounds.

The data shown in this paper can be used to establish priorities in investigations but in no case be considered in the management of patients until pharmacogenetic studies have been carried out in the considered population. In fact, it is important to establish priority research in genetics of drug metabolism and transport because of the extent of breast cancer in all SSA. For example, because tamoxifen is used extensively in all settings, more research on this drug should be conducted in order to fill the gap in information about possible clinical outcomes among Africans, not yet demonstrated in other world populations. Additionally, *DPYD* genotyping for capecitabine may be clinically useful. More studies are needed to identify other low-activity alleles in African populations and to demonstrate the clinical benefit of pre-treatment *DPYD* genotyping to inform capecitabine treatment.

Several pharmacogenes (including transporters) show a non-negligible frequency for several African alleles, mostly poor metaboliser alleles. Among them, the *CYP2/3* families show alleles with high to very high frequencies. There is a clear need for more studies to ascertain the possible risk and/or benefit of a specific treatment in that particular ethnic population, in an effort to maximise therapeutic output and survival rate for the women affected by breast cancer.

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