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THE IMPLICATION OF GENETIC MEDICINE IN BREAST CANCER THERAPY IN NIGERIA: CLINICAL PRACTICE AND RESEARCH

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ABSTRACT

In the preceding three decades, breast cancer occurrence and mortality rates have proliferated in Nigeria. Despite the considerable health, socioeconomic and developmental burdens breast cancer imposes on Nigeria, researchers have not extensively explored the use of genetic medicine in the management of this disease in Nigerian patients. This review's objectives were to compare the diagnosis, treatment, and research of breast cancer in Nigeria and other countries. In addition, it also highlighted the setbacks and difficulties in breast cancer management in Nigeria. This journal employs a literature review. Detailed relevant articles were researched in two main electronic databases - Google Scholar and PubMed. The databases were analysed for keywords including: "breast cancer," "breast cancer therapy," "breast cancer diagnosis," "breast cancer in Nigeria," and "genetic medicine in breast cancer." Only journals written in the English language between 1998 and 2022 were considered. 34 journals were identified, of which 22 were used for this review. Findings showed that genetics is not often considered for predicting and treating breast cancer. They also show that due to late presentation at the hospital, triple-negative breast cancer, usually at stage III or IV, is the most common breast cancer type in Nigeria. Genetic medicine should be integrated into the therapy and management of breast cancer in Nigeria. It will allow prediction of the disease, and timely diagnosis and ultimately possibly lead to a decline in breast cancer mortality and morbidity, just like in developed countries (high-income countries) such as The United States of America, Canada, and Sweden.

Keywords: *Biomarkers, Breast cancer, Developing countries, Medical genetics, Nigeria, Oncology.*

INTRODUCTION

Globally, of all the women who have cancer, at least 25% of women are diagnosed with breast cancer annually (Sun *et al*., 2017). It is the second most prevailing cancer, the most prevalent that affects women, and one of the top causes of death worldwide (Akram *et al*., 2017; Momenimovahed & Salehiniya, 2019). About 23% of women in Nigeria have been diagnosed with breast cancer, making it the most diagnosed type of cancer (Eheazu & Uzoagu, 2021). Approximately 13% of women worldwide are at risk of developing cancer during their lifetimes. Some risk factors are age, genetic factors, female gender, lifestyle factors such as alcohol consumption, unhealthy diet, etc.; family history; and reproductive factors such as late age of menopause, use of contraceptives, etc. (Akram *et al*., 2017; Momenimovahed & Salehiniya, 2019; Sun *et al*., 2017).

Although breast cancer is more prevalent in developed nations, the mortality rates in developing nations are higher (Momenimovahed & Salehiniya, 2019). According to Eheazu & Uzoagu (2021), a study showed that the death rate in America was 19%, while the death rate in Nigeria was 51%, about three times that of America.

There has been growing evidence that genetic factors influencing breast cancer differ from population to population. In Nigerian breast cancer patients, the prevalence of mutated BRCA1 and BRCA2 genes is remarkably high (~7% and ~4%, respectively). Medical genetics has increased global importance in cancer management, and high-throughput sequencing methods have transformed cancer screening, therapy, and survival, aiding the prediction of response to therapy. By testing for the BRCA1/2 mutation, risk estimations based on genetics are now available for women who, based on family history, are at a high risk of developing breast or ovarian cancer (Adejumo *et al*., 2018).

A broad range of clinical aspects of breast cancer management benefit from incorporating genetic medicine. There is no doubt that genetic medicine is an essential tool for personalised and developed medical care, and focus must be placed on genetic research and its inclusivity in Nigeria. Designing an effective breast cancer screening and care plan requires understanding genomic medicine's current applications and limitations. In high-income countries (HICs), women with breast cancer may undergo genetic testing to see if they carry breast cancer-associated mutated genes. These results guide screening decisions and may also influence medical and surgical treatment for prophylaxis. In addition, breast cancer tumours can be characterised and targeted treatment enabled with genetic markers, which can be identified with immunohistochemistry studies (Silverstein *et al*., 2016).

There should be progress in breast cancer management in Nigeria, including the use of genetic medicine in the prediction, prevention, diagnosis, and therapy of the disease. Unfortunately, breast cancer therapy in Nigeria is not optimal due to some of the following reasons: inaccessibility to and cost of breast cancer screening, late presentation in the hospital, poor treatment compliance, and inaccessibility to radiotherapy (Anele *et al*., 2014; Erhabor, 2016; Ogundiran *et al*., 2013). These factors are mainly a result of poverty in the country. Many patients have no access to health insurance and must therefore pay for consultations and treatments by themselves or with the help of their relatives (Anele *et al*., 2014; Foerster *et al*., 2019; Ogundiran *et al*., 2013). This also implies that most breast cancer patients in Nigeria can not afford advanced treatments such as targeted therapy (with possibly

better effectiveness, efficacy, and lesser side effects), which are often more expensive (Anele *et al*., 2014; Ogundiran *et al*., 2013). These challenges, therefore, limit the use of advanced therapies and make clinical research and trials quite difficult.

BREAST CANCER SCREENING AND DIAGNOSIS

There is a significant difference in the global survival rate of breast cancer - a projected 5-year survival rate of about 80% in HICs and a less than 40% survival rate in developing countries such as Nigeria (Akram *et al*., 2017; Sun *et al*., 2017). The American Cancer Society and American College of Radiology urge women above 40 years to undergo yearly mammography screening to improve survival. In the UK, women from 50 to 70 years are routinely invited to undergo an early breast cancer screening test triennially. The European Cancer Observatory and the Canadian Task Force on Preventive Health Care suggest mammography every 2–3 years for women between 50 - 69 years. In Canada and Sweden, there is a 30% decline in mortality due to screening of women 40 years and older. Unfortunately, a significant number of women who live in Nigeria or other developing countries (low-middle-income countries) are not as privileged as most women in the West. Accessibility and cost limit Nigerian women's breast cancer screening, resulting in advanced-stage diagnosis and significantly reduced survival. The primary aim of breast cancer screening is early detection; lower cost of effective radiation, chemotherapy, and surgery; to mitigate the risk of death, and improve the quality of life. Prevention and early detection are significant in the management of breast cancer in developing countries. Prevention mandates routine breast cancer screening and preventable mortality (Zheng *et a*l., 2018).

The Nigerian Integrative Epidemiology of Breast Cancer (NIBBLE) observed patients that presented with breast lumps (87%). Others include breast size or shape changes, armpit lumps, and nipple discharge. Patients undergo recommended tests such as mammography, abdominal ultrasonography, chest radiography, and bone scintigraphy (Zheng *et a*l., 2018).

Breast cancer diagnosis in Nigerian women is made at advanced stages with poor prognoses (Jedy-Agba *et al*., 2017). The initial step in diagnosing breast cancer requires a medical history with breast self-examination (BSE). Women in developing countries require BSE to determine the need for a clinical breast examination (CBE) (Zheng *et a*l., 2018). In Nigeria, BSE and CBE practice is relatively poor. A study undertaken by Olasehinde *et al.* (2017) in Ife Central local government, Osun state, showed that out of 1,169 women between 40 and 86 years, only 31.2 % practiced regular BSE, 23.5% checked inconsistently, while 45.3% did not carry out the BSE. Less than 20% of these women had CBE, of which 6% were examined in the previous year, 4.4% in the previous two years, and 9.2% in more than two years.

After the breast examinations, imaging tests, including mammography, ultrasonography, and magnetic resonance imaging (MRI), are carried out. While mammography is widely available to women in the developed world, its availability in Nigeria is low due to poor access and unaffordability (Jedy-Agba *et al*., 2017). In a survey by Olasehinde *et al*. (2019), although 94-97 % of people in two towns in Nigeria had heard about breast cancer, only about 11% knew about mammography, while the mammography uptake was about 1.8-2.8%, even though one of

the towns offered mammography services. Ultrasonography is usually used in conjunction with mammography to distinguish between cysts and solid masses; and between benign and cancerous tumours, especially when the mammography findings are equivocal. Breast MRIs are often used together with mammograms for screening high-risk women (Zheng *et a*l., 2018). In addition, it can accurately detect residual tumours after neoadjuvant chemotherapy (Sun *et al*., 2017; Zheng *et a*l., 2018). However, patients' accessibility to MRI services in Nigeria is significantly low and could be much higher. (Zheng *et al*., 2018).

After physical examinations have been carried out, it is vital to carry out histological pathological diagnosis and immunohistochemistry (IHC) to provide further information. The former gives information about the growth pattern of the tumours (Weigelt *et al*., 2010), while the latter is used for detecting hormone-receptors (HR) biomarkers, which are human epidermal growth factor receptor 2 (HER2), oestrogen receptor (ER) and progesterone receptor (PR) (Zaha, 2014). HER2-positive (HER2+) breast cancer makes up approximately 15% of all breast cancers. Compared to the more common HR-positive (HR+)/ HER-negative (HER2-), the probability of diagnosing advanced-stage HER2+ breast cancers is higher in younger patients (Jerusalem *et al*., 2019). Breast cancer is diagnosed at later stages among Nigerian women. It is usually of the triple-negative type (TN), which is deadlier than in Europe or the United States (Zheng *et a*l., 2018). Olasehinde *et al*. (2021) study demonstrates 40% that had IHC carried out, were ER-positive (ER+) breast cancer, 32.8% had HER2+ breast cancer, and 43.5% had TN breast cancer.

A breast cancer diagnosis has undergone remarkable evolution due to the introduction of genomic techniques, for example, whole-exome sequencing (WES), next-generation sequencing (NGS), microarrays, and real-time reverse transcriptase PCR (RT-PCR). In addition, with these techniques, it is now possible to identify the biomarkers involved in breast cancer development and pathology, thereby improving general clinical practice of predicting, preventing, and treating breast cancer (De Abreu *et al*., 2014).

For precise diagnosis, it is imperative to know and understand genes that are biomarkers of breast cancer. Below are some genes indicated in breast cancer:

- BRCA1 and BRCA2: the BRCA1 (situated on chr17q) and BRCA2 (situated on chr 13) genes are tumour suppressor genes (Mehrgou *et al*., 2016; Sun *et al*., 2017). They are generally the most susceptible genes to breast cancer. The mutated genes are unable to carry out their primary function – repair damaged DNA. Carriers of the BRCA1 and BRCA2 genes are more likely to develop breast, ovarian, and prostate cancer. The BRCA1 gene confers breast cancer risk between 60 and 80%, while the BRCA2 mutation is observed in about 35% of families where the women have early-onset breast cancer (Mehrgou *et al*., 2016).

- ATM: the ATM gene, localised at 11q22.3 (Erhabor, 2016; Sun *et al*., 2017), assists with the repair of damaged DNA. In some families, the inheritance of one mutated copy of the ATM gene has been connected to a higher breast cancer risk (Erhabor, 2016).

- TP53: the TP53 gene gives commands for making the p53 protein, whose function is stopping abnormal cell growth. Inheriting the mutated TP53 gene causes Li-Fraumeni syndrome (Erhabor, 2016; Petrucelli *et al*., 2022]. People with this syndrome are more likely to develop breast cancer. This gene is also an important marker for prognosis during breast cancer therapy (Erhabor, 2016).

- PALB2: The BRCA2 gene produces a protein that interacts with the protein produced by the PALB2 gene (Erhabor, 2016). Mutated PALB2 genes may lead to a breast cancer risk of $\leq 58\%$ (Petrucelli *et al*., 2022).

Some other genes indicated in breast cancer include BARD1, BRIP1, RAD51C, MLH1, MSH2, MSH6, PMS2, STK11 (Petrucelli *et al*., 2022).

In a research conducted by Zheng *et al*. (2018), there were cases of invasive breast cancer in 1,136 women, 167 (14.7%) of whom carried an amorphic mutation in expressed breast cancer genes: BRCA1 in ∼80 women, BRCA2 in ∼47 women, PALB2 in ∼12 women, TP53 in ∼5 women, and ten other genes in about 24 women. Among Nigerian women, 12.5% of invasive breast cancers are due to inherited mutated BRCA1, BRCA2, TP53, or PALB2 genes (Zheng *et a*l., 2018) and are thus important and critical biomarkers to look out for in diagnosing breast cancer.

THERAPEUTIC AND PROPHYLACTIC TREATMENTS OF BREAST CANCER

In the Olasehinde *et al*. (2021) study, about 80% of people were reported to have presented at the hospital with ≥ stage III breast cancer. The stage at which breast cancer is diagnosed significantly affects the choice of therapy, recovery, and survival. Early breast cancer detection and treatment can increase the patient's chances of survival. Breast cancer in Nigerian women is characterised by the late presentation of patients at advanced stages and poor prognoses (Olasehinde *et al*., 2021; Zheng *et a*l., 2018).

THERAPEUTIC TREATMENT

The breast cancer type determines the choice of therapy. Often, patients with breast cancer undergo at least two forms of treatment. There are five (5) available forms of treatment, including surgery, radiotherapy, chemotherapy, targeted biological therapy, and hormone therapy (Akram *et al*., 2018).

1. Surgery

The standard therapeutic surgery for breast cancer in most countries worldwide, including Nigeria, remains a modified radical mastectomy (MRM) (Anele *et al*., 2014; Ogundiran *et al*., 2013). Due to late hospital presentation by most patients, large tumour sizes at diagnosis, and disease aggressiveness in mainly young women, removing the entire breast with its lymphatic drainage surgically is the most preferred surgical choice across countries, particularly in developing countries. In Nigeria, only an insignificant number of breast cancer patients undergo breast-conserving surgery (BCS). BCS has gained popularity in some parts of the world due to the available and broad use of adjuvant therapies and early presentation. In HICs, evidence shows that in early breast cancer, BCS is as applicable as MRM (Ogundiran *et al*., 2013).

Surgical therapy for breast cancer has undergone different stages, from early conservative excision to radical mastectomy, the latter of which experienced various modifications (Erhabor, 2016). Over the years, mastectomies have been used lesser than in the past, as there was no increase in survival while using intensely mutilating procedures. These days, most women receive BCS, often with radiotherapy, rather than mastectomy to the residual breast. Breast reconstruction is a significant complement to mastectomy, as it has an optimistic psychological impact on the patient, facilitating the improvement of life quality (Akram *et al*., 2017; Zurrida *et al*., 2011).

Now, there are three surgical options that primary breast cancer patients may consider, which are: mastectomy (MT), mastectomy and contralateral prophylactic mastectomy (MT & CPM), and breast-conserving surgery (BCS). In each situation, sentinel lymph node biopsy and probably axillary lymph node dissection manage the ipsilateral axilla. BCS is contraindicated in first-trimester pregnancy, previous breast radiotherapy, multicentric breast cancer, large tumours, active collagen vascular disease, and the presence of mutated *BRCA*. Recently, a decline in the use of MT increased MT & CPM rates, and relatively constant BCS rates have been observed in primary breast cancer treatment in the US (Jatoi, 2012).

2. Radiotherapy

High-energy radiation is used to destroy or damage cancer cells. Radiotherapy is often combined with various forms of breast cancer therapy (Akram *et al.,* 2017). Some examples of treatment sequences involving radiation are

- surgery, radiotherapy, and probably hormonal therapy
- chemotherapy, targeted or hormone therapy, surgery, radiotherapy, and possibly hormonal therapy
- surgery, chemotherapy, radiotherapy, and possibly hormonal therapy (Erhabor, 2016)

3. Chemotherapy

Chemotherapeutic agents are generally used alone or in combination to manage breast cancer (Akram *et al.,* 2017) (especially ER- & PR- types). The most commonly used chemotherapeutic drugs in the developed world to manage early breast cancer include taxanes (e.g., paclitaxel & docetaxel), anthracyclines, 5-fluorouracil, carboplatin, and cyclophosphamide. Commonly used chemotherapeutic medications for advanced breast cancer patients include docetaxel, capecitabine, paclitaxel, liposomal doxorubicin, mitoxantrone, ixabepilone, platinum agents (e.g., cisplatin, carboplatin), vinorelbine, gemcitabine, albumin-bound paclitaxel and eribulin (Erhabor, 2016).

The aforementioned chemotherapeutic agents, which are potentially lifesaving, are available to most breast cancer patients in HICs. However, they are unfortunately often beyond the reach of the majority of people with breast cancer in Nigeria and other LMICs (Erhabor, 2016).

4. Targeted biological therapy (immunotherapy)

Targeted biological therapy is essential in managing HER2+ breast cancers (Akram *et al.,* 2017). Breast cancer patients that may profit from HER-2 targeted therapy with agents such as trastuzumab, trastuzumab emtansine (T-

DM1), pertuzumab (Akram *et al.,* 2017; De Abreu *et al*., 2014), and lapatinib (De Abreu *et al*., 2014), are identified using amplification of HER2 gene as a pharmacogenomics test. Pertuzumab can be used in various combinations, such as with trastuzumab and docetaxel for HER2-positive cancers (De Abreu *et al*., 2014; Erhabor, 2016) or with trastuzumab and neoadjuvant chemotherapy for locally advanced HER2+ breast cancer patients. Not all HER2-positive breast cancer patients are responsive to therapy with trastuzumab. Metastatic tumours that show an initial response to therapy often become resistant. When resistance to trastuzumab occurs in metastatic HER2-positive breast cancer, a joint HER2 target approach using trastuzumab and lapatinib is efficacious. T-DM1 is used for HER2+ metastatic breast cancer treatment in patients that are not responsive to taxanes or trastuzumab (De Abreu *et al*., 2014).

The drastic rise in the availability of therapeutic agents for HER2+ breast cancer has resulted in a spectacular increase in survival rates for patients undergoing adjuvant therapy for early-stage breast cancer and a longer lifespan for metastatic breast cancer patients (Jerusalem *et al*., 2019).

5. Hormone therapy

The two isoforms of oestrogen receptor (ER) - ER-α and ER-β, are both presented in typical mammary gland-loping breast cancer tissue, but only ER-α is involved in disease conditions, including breast cancer (De Abreu *et al*., 2014). There are two main classes of drugs in hormone therapy:

- Selective Oestrogen Receptor Modulators (SERMs): SERMs target the oestrogen receptor and repress the oestrogen signaling in breast cancer patients. Tamoxifen, raloxifene, and toremifene are the three (3) US Food and Drug Administration (FDA) approved SERMs for breast cancer treatment and prevention in high-risk patients. Tamoxifen has been consistently used to treat all breast cancer stages. Multiple studies have shown that the use of tamoxifen has led to a reduction in the occurrence of invasive and ER+ breast cancers, the recurrence of the disease, and the pathogenesis of new contralateral breast cancer in early breast cancer patients. More evidence shows tamoxifen activity in metastatic breast cancer and ductal carcinoma *in situ* (De Abreu *et al*., 2014).

- Aromatase Inhibitors (AIs): AIs are further subdivided into non-steroidal (such as letrozole and anastrozole) and steroidal (such as exemestane). In ER+ breast cancer post-menopausal women, AIs have more therapeutic effectiveness than tamoxifen (De Abreu *et al*., 2014).

There is HER2 amplification in about 10% of ER+ breast cancer cases. Compared to ER+/HER2- tumours, ER+/HER2+ are more likely to relapse on adjunct hormonal therapy. For these ER-positive/HER2+ patients, standard care is considered to be combining trastuzumab and hormone therapy (De Abreu *et al*., 2014).

PROPHYLACTIC TREATMENT

- Chemoprevention

Chemoprevention describes drugs that are used to decrease the risk of developing cancer. The recommendation of the National Institute for Health and Care Excellence (NICE) is the consideration of chemoprevention in high-risk familial women. Medications used for chemoprevention include (Akram *et al.,* 2017)

- Tamoxifen
- Anastrozole
- Raloxifene

Tamoxifen and raloxifene have anti-estrogen properties (Akram *et al.,* 2017). These two drugs have been indicated in the decreased risk of breast cancer in patients with a strong family history (De Abreu *et al*., 2014). High-risk familial women between ages 40–60 years (and have been offered yearly mammography) and women with a BRCA2 mutation may consider chemoprevention. Anastrozole and raloxifene are used in post-menopausal women, while in post-menopausal and pre-menopausal women, tamoxifen is used (De Abreu *et al*., 2014).

- Surgery

In some situations, high-risk breast cancer people (BRCA1 and BRCA2 genes carriers) can undergo local therapies such as mastectomy or lumpectomy as a prophylactic measure. Unlike systemic therapies such as chemotherapy, hormone therapy, and targeted biological therapy, mastectomy, and lumpectomy target the tumour area. Women in developing countries like Nigeria should be able to choose to lessen their risk of developing breast cancer by getting tested for BRCA mutations. If these women test positive for BRCA, they must be able to choose to undergo risk-reducing prophylactic surgery to remove their breasts, like their counterparts in the developed world. Currently, women in developing countries do not enjoy this privilege (Erhabor, 2016).

RESEARCH

Currently, the effects of poly-adenosine diphosphate-ribose polymerase inhibitors, histone deacetylases inhibitors, CDK4/6 inhibitors, and PI3K/AKT/mTOR inhibitors indicated in any of the following - angiogenesis, proliferation, motility, apoptosis, metabolism of cells or repair of DNA damage, are currently investigated in various ongoing clinical trials (De Abreu *et al*., 2014).

Most chemotherapeutic agents used in managing breast cancer in LMICs have undergone clinical trials and testing in HICs. Unfortunately, the results cannot be generalised as the patient and tumour characteristics differ. Therefore, developing countries need to perform more clinical research in order to provide evidence-based information that can improve breast cancer management in these countries. Several challenges are responsible for scarce research in Nigeria. Some of these challenges include a lack of accurate databases, scarce data, poor record keeping (Azubuike *et al*., 2018; Erhabor, 2016), poor laboratory capacity, follow-up challenges, insufficient awareness,

poorly structured ethics approval, inadequate specialised clinical trial personnel, patronage of herbalists and spiritualists, shame associated with breast cancer, and suboptimal health infrastructures (Erhabor, 2016).

SOCIOECONOMIC EFFECTS OF BREAST CANCER IN NIGERIA

The evidence reflects professional and wealthy women with higher levels of education have a higher breast cancer risk. This implies that delayed breast cancer combat could lead to further widening of the existing employment gender gap. An indirect adverse effect of breast cancer is that family members of breast cancer patients are distracted especially their spouses working in various sectors of the country's labour force, leading to increased workplace absenteeism. This could cause grave economic consequences, negatively affecting Nigeria's already struggling gross domestic product (Azubuike *et al*., 2018).

Furthermore, breast cancer could become another huge barrier to female education in Nigeria, as there may be increased absenteeism of young girls who would have to take up roles to replace their mothers or to care for them as a result of the illness or death. The impact of breast cancer on maternal health will additionally exacerbate the current problem of child and infant mortality in Nigeria (Azubuike *et al*., 2018).

CONCLUSION

The relevance of incorporating genetic medicine in the prediction, early diagnosis, and precise breast cancer therapy is immensely underestimated in Nigeria. Therefore, it is of utmost importance that focus is placed mainly on preventing breast cancer by investing in research aimed at the precise identification of risk factors and environmental, genetic, social, and biological circumstances responsible for the increased breast cancer occurrence in the country (Azubuike *et al*., 2018).

Other measures include the employment of more health professionals, the introduction of clinical geneticists into healthcare, and sensitisation and education of citizens with the correct information to reduce the stigmas and biases associated with breast cancer, which in turn will promote early hospital presentation. Nigerians should also be encouraged to do gene testing for genes involved in breast cancer. It is also crucial that the government equips hospitals and makes healthcare more affordable, primarily through a functioning health insurance scheme (Erhabor, 2016).

CONFLICT OF INTEREST

The authors declare no conflict of interest

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