Genetic Screening For Breast Cancer In Nigeria: Any Prospects?

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INTRODUCTION

Breast cancer is the most common form of cancer in women in the United States and the number two cause of cancer death for women in the United States [1]. Data presented at the 29th Annual San Antonio Breast Cancer Symposium in Texas, USA revealed a 7% drop in the incidence of breast cancer in American women from 2002 to 2003. This was attributed in part to reduction in use of hormone replacement therapy, and re-emphasized the effort to increase awareness [1-2]. In addition to this, an effort to increase early detection has been supported by the Surveillance, Epidemiology, and End Results (SEER) 9 registry data in the United States from 1988 through to 2002 that showed the 5-year relative survival rates at diagnosis, for all races in the United States to be 98% for early stage or localized disease, 81% for regional disease and 26% for distant or metastatic disease [2].

In Nigeria, the picture for breast cancer is less optimistic with statistics indicating the incidence of breast cancer in Nigerian women has doubled within the last 20 years. In addition to this, most affected women present late with advanced stage disease which invariably leads to poor outcomes due to complications and/or disease progression [3-7].

In the United States, several studies have affirmed the importance of prompt and accurate diagnosis in achieving favorable outcomes in breast cancer. With continued development of cancer therapeutics, focus on awareness and screening initiatives is being made in an effort to improve outcomes for patients with breast cancer [8].

One new screening initiative which has become available for clinical use following the completion of the human genome project and the identification of BRCA 1 and BRCA2 genes is genetic screening [9-10]. Approximately 10 – 15 % of all breast cancer cases in the United States are thought to be familial and about a third of these individuals have been shown to carry an inherited BRCA 1 or BRCA 2 mutation, which is thought to confer breast cancer susceptibility [11-12].

Genetic screening is defined as the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Currently in the United States, it is the recommendation of the American Society of Clinical Oncology and several other advisory groups that genetic screening is offered to individuals with significant personal or family histories of breast cancer or features suggestive of genetic predisposition to cancers. Several studies have now shown that this could potentially lead to earlier detection in at-risk individuals, provide greater information for women deciding on cancer prevention options as well as offer a cost-effective means of identifying at-risk individuals who require additional screening [13]. While this has been successfully carried out in the United States, this cost-effective and potentially life-saving screening option has yet to be developed in Nigeria.

The purpose of this review is to highlight the severity of the problem of breast cancer in Nigeria, discuss the known literature regarding BRCA1 and BRCA2 mutations and variants occurring within the Nigerian populace, which might provide a rationale for the role and potential benefit of genetic screening, as well as to discuss the potential pitfalls and roadblocks in developing genetic testing as a tool for cancer control in women with breast cancer in Nigeria.

EPIDEMIOLOGY AND CHALLENGES OF BREAST CANCER IN NIGERIA

Breast cancer accounts for 32 % of all cancers in American women. In the United States, a woman's lifetime risk of breast cancer is 8.0 %, while the lifetime risk of dying from breast cancer is 3.6 % [1-2]. Breast cancer comparatively occurs less commonly in African women than in other populations, but conversely occurs in African women at a younger age, with a higher mortality [3]. While epidemiologic data for Nigeria might vary, breast cancer is considered to be the most common cancer among Nigeria women today, as well as the leading cause of cancer death among Nigerian women. Recently conducted studies have shown the incidence of breast cancer in Nigeria has not only doubled from 15.3 per 100,000 in 1974 to 33.6 per 100,000 in 1993 [3-6], but also the peak age of breast cancer in Nigerian women is about 10 years younger than what is observed in Caucasian counterparts in developed countries [7].

Risk factors for breast cancer in Nigeria

A study of epidemiologic risk factors for breast cancer in Nigeria was recently conducted by Adebamowo et al [7]. In this case controlled study of 250 consecutive Nigerian women, the peak age of incidence was 43 years. Up to 73% of patients presented with Manchester stage III or IV disease, with 96% of diagnosed patients having axillary node involvement. Results of this study identified prolonged endogenous estrogen exposure (through early menarche, low parity, late first parity, and late menopause), maternal birth order, and family history as risk factors for breast cancer in Nigerian women [7]. While this study highlighted several pertinent issues regarding risk factors, the Nigerian populace has been identified to be extremely heterogenous with differences in cultural beliefs and practices stemming from one region to another.

Challenges of breast cancer in Nigeria

Late presentation leading to poor outcomes, add up to the majority of cases, and this has been associated with lack of awareness of the disease and the benefits of screening [14].
In one study of 1000 participants by Okobia et al [15], only 21% of the respondents were aware that a breast lump could be an early symptom of breast cancer and only 43% of respondents were aware of breast self examination (BSE) as a screening tool for breast [15] which bears contrast to the study conducted in women in the United Kingdom by Grunfeld et al, in which 70% of respondents had knowledge regarding the early symptoms of breast cancer, such as a breast lump [16].

Despite the identification of lack of knowledge and awareness playing a key role in late presentation leading to advanced disease, several socioeconomic and cultural factors also come into play regarding early detection and treatment. Several studies including one conducted by Schootman et al revealed poverty rate to be an independently associated factor with low cancer screening rates [17].
This issue becomes very relevant in developing countries such as Nigeria, where the national poverty rate exceeds 34% [18], and health care services (including screening and prevention) can be expensive and difficult to access. In societies such as Nigeria, the diagnosis of cancer can also result in stigmatization and exclusion, and affected individuals may not be so willing to come for treatment or provide information regarding themselves and their families.

SCREENING FOR BREAST CANCER

Breast cancer screening, especially with mammography and routine breast examinations, is the national recommendation in the United States for American women for the last few decades following studies which showed significant reduction in mortality and morbidity rates with early detection [19, 20, 21 22].

Cancer screening has become a powerful tool in public health through early detection leading to better outcomes. Great care however, must be exercised prior to acceptance of any modality for screening, given the inherent implications. In the United States, criteria for use of a modality for cancer screening include the concepts that the population screened must have a significant burden of suffering, there must be an asymptomatic period during which the disease can be detected in the clinical setting, the screening test must be accurate during the asymptomatic period, the screening test must be accessible and acceptable to the patient, and preventive intervention must be available and superior to conventional follow-up [23]. In Nigeria, there is a lack of accurate definition of the disease burden and tumor biology amongst Nigerian women with breast cancer, and this has led to problems in developing a national policy for cancer screening and underlines the urgency for more research within this regard.

Even with several technological advancements in early detection, including the use of ultrasonography and magnetic resonance imaging, mammography has remained the most widely used and cost-effective method of early cancer detection in the United States [8].
In spite of the widespread benefit which has been observed in several countries which offer routine mammography for breast cancer screening, routine screening for breast cancer with mammography is still not currently practiced in

infrastructure and lack of awareness, as well as socioeconomic and cultural factors, and inability or poor ability to access health care services. More information is also needed to accurately identify who to screen, when to screen, and at what intervals screening should be done, in order to avoid unsupported extrapolation of existing guidelines from other countries such as the United States.

GENETIC SCREENING

The BRCA1 and BRCA2 genes were identified in 1994 and 1995 respectively [24, 25]. Up to 7.2 % of women in the United States with a family history of breast cancer, who develop breast cancer before age 45, carry a BRCA1 mutation [11]. However family history remains a strong predictor of breast cancer risk and a family history of breast and ovarian cancer should be explored in every Nigerian woman who presents with breast cancer [11, 12].

BRCA1 and BRCA2 genes

The BRCA1 gene occurs on chromosome 17 and has shown to be involved in tumor suppression. Women with a deleterious mutation in BRCA1 have a lifetime risk of 56 to 85 % for breast cancer and an increased risk of ovarian cancer. The BRCA1 mutation has been found in 0.3 % (one of 333) of women with breast cancer as compared to the general population, where it occurs in about 0.12 % of women (one of 833). In Ashkenazi Jewish women (most Jewish people in the United States are of this Eastern European origin), BRCA1 mutations occur in up to 1%. Other groups with high frequencies of mutations include people of Polish, Iceland, and Dutch ancestry [12, 24, 25, 26].

BRCA2 is another susceptibility gene for breast cancer and is found on chromosome 13. Mutations in BRCA2 confer an elevated breast cancer risk similar to that occurring with BRCA1 mutations. BRCA2 is also found in about 1% of Ashkenazi Jewish individuals [12, 25, 26, 27].

Mutations in BRCA1 and BRCA2 are associated with early-onset breast cancer. Founder mutations are specific mutations which are inherited from a common ancestor and have become amplified through chance effects, usually geographic isolation. The phenomenon of a founder mutation occurs quite frequently within the Ashkenazi Jewish population, where three significant mutations have been identified, namely the 185delAG and 5382insC occurring in BRCA1 and the 6174delT occurring in BRCA2. These three mutations account for 70% mutations that occur within this ethnic population [24, 25, 26].

The science of genetic screening for cancer is premised on the identification of mutations which can confer cancer susceptibility. Mutations that result in a truncated protein are thought to be deleterious, however the role of other changes such as missense mutations, especially those that result in an amino acid change, are still yet to be defined.

A study by Fackenthal et al recently investigated BRCA1 and BRCA 2 germline mutations in Nigerian women [29]. In this study, cases were all Nigerian women with breast cancer diagnosed at the age of 40 years or younger with only 15% having a documented family history of breast cancer. A total of 39 cases were assessed with 74 control subjects. Results from the complete allelic analysis of these affected women revealed that 74% (29 out of 39) of the breast cancer cases carried at least one BRCA1 or BRCA2 genetic variation, with 69% having these variations with the BRCA2 domain. While only one truncating allele (3034del4 in the BRCA2 gene) was detected, this study identified 11 different BRCA1/2 alleles which were potentially deleterious [28, 29].

A second study on BRCA mutations in Nigerian women by Gao et al identified three novel protein truncating mutations, two involving BRCA1 (Q1090X and 1742insG) and one involving BRCA 2 (3034del4 or 3036del4) [30]. In this study, 70 cases were examined, from whom only one patient reported a family history of breast cancer, with early onset breast cancer in three first degree relatives. Data from this study supported hypothesis regarding the role of BRCA1 and BRCA2 mutations/sequence variations in cases of early onset breast cancer [30], as well as underscored the need for more research in this area.

Genetic testing in the United States

Over the course of the last few years genetic testing has moved out of the realm of research into the clinical service setting. While the BRCA1/2 genes continue to be the focus of much research into hereditary and familial cancer, including breast cancer, genetic testing is finding ground in the United States as a clinical service which can be offered to identified high-risk individuals, in order to provide definitive counseling regarding cancer risk, as well as to provide targeted and cost-effective services for primary and secondary prevention [8, 13].

Genetic testing for cancer susceptibility in breast cancer is a continually evolving field especially in the United States. Genetic testing is having an evolving and critical role in the management of identified BRCA1 and BRCA2 mutation carriers, as well as their families. Owing to the sensitivity and dynamic nature of genetic testing, this option is currently only recommended within the context of pre and post genetic counseling [8, 9].

Criteria for recommending genetic testing in the United States

Genetic experts recommend genetic testing if the chance of BRCA gene mutation is greater than 5 to 10%. Insurance companies in the United States often cover the costs of such screening for women and men with more than a 10% chance of having this gene mutation, based on their personal and family history[10].

Currently the criteria for recommended testing in women include those with breast cancer under age 45 and a relative with ovarian cancer, those with breast cancer in both breasts under age 50 with one relative having ovarian or breast cancer, those diagnosed with ovarian cancer under age 50, and women with Ashkenazi Jewish heritage with breast cancer under age 45. Other less identified criteria which can merit recommendation for screening would include two sisters, each with breast cancer under age 40 or one with ovarian cancer under age 50, women with a family history of two relatives with breast cancer and one with ovarian cancer, a family history of breast or ovarian cancer under age 30, a family history of three relatives with breast cancer under age 50, women with Ashkenazi Jewish heritage and ovarian cancer, or women with a family history of male breast cancer at any age[20].
Until the psychosocial and ethical implication of genetic testing in Nigeria is studied, it is difficult to propose any criteria for genetic testing. Nonetheless, work by Olopade et al, at the University of Ibadan has identified BRCA1 and BRCA2 mutations in about 10% of Nigerian breast cancer cases with implications for family members .

COUNSELING AND PREVENTION OPTIONS FOR HIGH-RISK INDIVIDUALS

Primary Prevention

This option includes the prevention of cancer through active intervention. This can be through lifestyle changes, chemoprevention, or prophylactic surgery. Bernstein et al[31] reported an inverse association between physical activity and breast cancer risk in women with a 20% reduction observed in 4538 case patients with increased lifetime exercise activity (P= .002)[31].

Selective estrogen receptor modifiers (SERMs) such as tamoxifen have recently been indicated as a chemoprevention option for high risk women including those with a strong family history and BRCA mutation. One study by Gronwald et al investigated 285 patients with bilateral breast cancer and a *BRCA1* or *BRCA2* mutation along with 751 control subjects. This study did not observe a protective effect of tamoxifen in the women who had undergone an oophorectomy (*OR* = 0.83; 95%CI, 0.24-2.89), but a significant protective effect of tamoxifen was seen in women who were premenopausal or who had undergone natural menopause (*OR* = 0.44; 95% CI, 0.27-0.65)[31].

Prophylactic surgery for BRCA1/2 cancer prevention has included prophylactic mastectomy and prophylactic oophorectomy. Several studies including those by Meijers-Heijboer et al, Rebbeck et al, and Metcalfe et al, have all reported statistically significant benefit with near 100% reduction risk in breast cancer for women who undergo prophylactic mastectomy [33, 34, 35]. Total mastectomy is generally recommended over subcutaneous or nipple-sparing procedures while prophylactic oophorectomy is offered to high-risk women with BRCA 1 or BRCA 2 mutations as an approach to reducing circulating estrogen, which is felt to be a risk factor for developing breast cancer. Cohort studies have shown up to 50% reduction in breast cancer risk in study individuals who underwent prophylactic oophorectomy[36, 37, 38].

Secondary Prevention

Various studies have confirmed a statistically significant survival benefit with early detection. Early detection is imperative in BRCA1-associated breast cancers which typically are high-grade, estrogen receptor negative and thus tend to carry a poorer prognosis[26, 28].

In the United States, several advisory groups have released recommendations for surveillance of women with a hereditary risk of breast cancer and ovarian cancer. A summary of these recommendations include annual mammography beginning at the age of 25 to 30 years, as well as monthly breast self-examinations (BSE) and clinical breast examination (CBE) one to two times per year[8, 10,20].

For patients at higher risk for false negative results with mammography screening, such as younger women with small or dense breast tissue, other imaging modalities such as ultrasonography and magnetic resonance imaging can be offered. Serial monitoring of CA-125 levels and abdominal ultrasound imaging has been recommended for ovarian cancer screening however these modalities and recommended intervals for screening are still yet to be validated[20].

PROSPECTS OF GENETIC TESTING IN NIGERIA

While the prospects and applications of genetic testing are finding use in developed countries in terms of early detection, targeted screening of high-risk individuals, and availability of cancer prevention options, the role of genetic testing in developing countries still has yet to be defined[39].

In the United States, certain problems and controversies al

exist in the use of genetic testing for counseling and cancer prevention. Obvious problems include difficulty on identifying at risk individuals who are currently unaffected by cancer, usually direct family members of patients with breast cancer. Many unaffected members do not want to be informed of their potential risk in part because of potential implications of testing positive as well as their personal beliefs about cancer [8, 10, 20]. The contrary is seen in affected individuals, especially those undergoing adjuvant therapy, who are interested in modifying cancer risk for themselves and their families. This paradigm is now changing as recent studies including those conducted in African American women [40] indicated greater awareness and acceptance of genetic testing.

Studies by Olopade et al have identified the high presence of genetic variation in addition to BRCA1/2 variants which may confer cancer susceptibility to Nigerian women, in addition to African Americans in the United States. The implication of these variants is yet to be fully understood, but raises the question of accuracy in the current standard of genetic testing towards capturing these existing variants, as well as possible roles these variants may have in women with breast cancer who present at an earlier age with a high mortality rate [29, 41].

More work needs to be done at the level of health care policymakers to generate resourceful and creative initiatives designed to increase breast cancer awareness and to dispel false beliefs and stigma which may lead to affected individuals to not seek medical attention for screening or treatment purposes. The Nigerian federal government also needs to provide better funding to hospitals and community health services to allow the development of strong cancer screening and prevention initiatives.

In a country such as Nigeria, it can not be understated that the most precious resource of the nation is its people, and more needs to be done at the federal, state and local government levels to actively protect the health and value of this precious resource.

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