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Afr. J. Biomed. Res. Vol. 21 (January, 2018); 7- 10

Mini Review

BRCA1 and BRCA2 Gene Mutations in Breast Cancer among West African Women

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ABSTRACT

There is an increase in the prevalence of cancer in Africa, while cancer was previously related to the industrialized countries. In fact, until today studies are scanty in all the African regions to find out more about the reality of the disease. However, in West Africa, there are few reports on the genetic factors of breast cancer. Our review was able to establish that very few studies have described the mutations of the BRCA1 / 2 genes in Africa. The dearth of scientific data in West Africa has impacted negatively on prevention, sensitization and management of breast cancer. We strongly suggest studies in general cancer registries of these countries and particularly on the genetic etiology of breast cancer

Keywords: Breast cancer- Genetic risks- BRCA1/2- West Africa

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Received: May, 2017; Accepted: November, 2017

Abstracted by:

Bioline International, African Journals online (AJOL), Index Copernicus, African Index Medicus (WHO), Excerpta medica (EMBASE), CAB Abstracts, SCOPUS, Global Health Abstracts, Asian Science Index, Index Veterinarius

INTRODUCTION

Practically everywhere in the world, each year, 1.7 million women are diagnosed with breast cancer. In 2012, 6.3 million women were living with breast cancer diagnosed in the previous five years. Since the latest estimates for 2008, the incidence has increased to more than 20% and mortality to 14% (Ferlay *et al*, 2015). Breast cancer is the most common cancer diagnosed in Africa and Sub-Saharan Africa, and the first leading cause of death from cancer (63,100 deaths in 2012) (IARC-WHO, 2012). Most of the cases are sporadic, whereas 5 to 10% are due to an inherited predisposition to breast and ovarian cancers, transmitted as an autosomal dominant form with incomplete penetrance (Guaoua, 2014). The genes BRCA1, BRCA2 and TP53, LKB1/STK11 and CDH1, have been identified as high-risk genes conferring 40–85% lifetime risk. The other genes TGFβ1, CASP8, PALB1, BRIP, ATM and CHEK2 have a moderate risk gene (20–40% risk) (Zhang *et al*, 2009; Lalloo and Evans, 2012). BRCA1 or BRCA2 mutations are responsible for 10% of ovarian cancer cases and 3–5% of breast cancer cases. In the presence of a BRCA1 mutation, women have around 70-80% lifetime risk of developing breast cancer and 50% risk of developing ovarian cancer. Women carrying a BRCA2 mutation have 50-60% lifetime risk of developing breast cancer and a 30% risk of developing ovarian cancer (Clark *et al*, 2012). In USA, most studies of BRCA1 and BRCA2 related to breast cancers have focused on white populations. However, several observations suggest that there might be a genetic component to breast cancer susceptibility in families of African ancestry. When breast cancer occurs, it is characterized by an early age of onset and a higher mortality (Fackenthal, 2005).

In West Africa, research on breast cancer as clinical data, medical treatments, risk factors, is not fully elucidated (Zouré *et al*, 2016). For West African patients, it is important to identify and characterize recurrent mutations that are associated with an increased risk of cancer in women. The identification of all mutations and founder mutations is important for designing genetic testing strategies. The Ashkenazi Jewish founder mutations BRCA1 185delAG, 5382insC and BRCA2 6174delT, are very useful in screening this population. Also, BRCA1 and BRCA2 founder mutations

have been identified in different European populations. Several studies have also reported the presence of BRCA1 and BRCA2 founder mutations in Asian populations. However, only one mutation (BRCA1 943ins10) has been identified as a potential founder mutation in patients of West African ancestry (Mefford *et al*, 1999; Zhang *et al*, 2009). African Americans and Africans may have a mutation spectrum in the BRCA1 and BRCA2 genes, which must be identified in these populations (Broome, 2002).

Mutations in BRCA1 and BRCA2 have been reported in African-American women, but the extent of their contributions to breast cancer burden in Africa is not totally known (Elnour *et al*, 2012). This review focuses on BRCA1 and BRCA2 in breast cancer incidence among West Africans.

MATERIALS AND METHODS

The key words used were "Breast Cancer", "Africa" "Genes", "BRCA Genes", "BRCA1" and "BRCA2" in different combinations with each name of all West African countries (Benin, Burkina Faso, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone, Togo, Cape Verde) to identify data on breast cancer genetics. The databases used were PubMed, African Journals Online (AJOL) and Google Scholar. Studies combining and/or comparing Africans with other ethnic groups were included.

RESULTS

In our bibliographic search, we found very few articles on the mutations BRCA1 and BRCA2, conducted in West African countries (Table 1). However, a few studies have been conducted in Nigeria, Côte d'Ivoire and Senegal. On the other hand, in general, we were able to record many studies in African Americans.

In a Breast Ovarian Cancer family from Côte d'Ivoire, Stoppa-Lyonnet *et al* (1997) evaluated the whole of the BRCA 1 gene and reported a frame shift case truncating BRCA1 mutation (926ins10) (Oluwagbemiga *et al, 2012*). In a study conducted in Nigeria, two mutation carriers of 943ins10 were found in African American cohort and no mutation carriers were identified in the Barbadian cohort (Zhang *et al*, 2012).

Table 1
Studies Conducted on the BRCA1 and BRCA2 mutations in West Africa

Title of study	Reference	No. of patients	Countries/comment
BRCA1 Sequence Variations in 160 Individuals Referred to a Breast/Ovarian Family Cancer Clinic	Dominique Stoppa-Lyonnet *et al,* 1997	249	**Ivory Cost** BRCA1 926ins10 mutation was detected
Evidence for a BRCA1 Founder Mutation in Families of West African Ancestry	Mefford *et al*, 1999	263	**African American from West Africa** BRCA1 mutation 943ins10 was founder
Complete allelic analysis of BRCA1 and BRCA2 variants in young Nigerian breast cancer patients	Fackenthal *et al*,2005	39	Nigeria 29 of 39 (74%) mutation of BRCA1 and BRCA2
Evidence for an ancient BRCA1 mutation in breast cancer patients of Yoruba ancestry	Bifeng Zhang *et al*, 2009	365	**Nigeria** BRCA1 Y101X(422 T[G) mutation was detected in four Yoruba patients of 365
Novel BRCA1 deleterious mutation (c.1949_1950delTA) in a woman of Senegalese descent with triple-negative early-onset breast cancer	Orland Diez *et al*, 2011	10	**Senegal descent** Novel exon 11 *BRCA1* c.1949_1950delTA mutation
Recurrent BRCA1 and BRCA2 mutations in breast cancer patients of African ancestry	Jing Zhang *et al*, 2012	434	**Nigeria** BRCA1 943ins10 mutation not detected. BRCA1/2 Y101X , M1775R ,1742insG, 4241delTG, Q1090X and 1623delTTAAA, were detected
Searching for large genomic rearrangements of the BRCA1 gene in a Nigerian population	Jing Zhang *et al*, 2010	352	**Nigeria** A novel deletion BRCA1 exon 21 (c.5277+480_5332 +672del) was detected in 1 out of 352 (0.3%). one AluSg in intron 20 and AluY in intron 21 BRCA1
BRCA1c.68_69delAG(exon2), c.181T>G(exon5),c.798_799delTT and 943ins10 (exon11)	Zouré *et al*, 2017	15	**Burkina Faso** No detection

Orland Diez *et al*, reported a novel mutation involving a deletion of 2 bp (c.1949_1950delTA) (p.Ile650LysfsX22) (HGVS nomenclature) or 2068delTA (BIC database nomenclature) in the exon 11 of the BRCA1 gene. It was present in Senegalese women with a triple-negative breast tumor and a family history of breast cancer. This is a frameshift responsible for a premature stop codon downstream in the BRCA1 protein (Diez, 2017) (Table 1).

Unlike other countries of western Africa, studies have been carried out in Nigeria in this field hence, availability of scientific data. So, Nigerian breast cancer patients have an exceptionally high frequency of BRCA1 and BRCA2 mutations (7.1 and 3.9 %, respectively). Among these mutations, eight BRCA1 mutations (Y101X, 1742insG, 4241delTG, M1775R, 4359insC, C64Y, 1623delTTAAA, and Q1090X) and three BRCA2 mutations (1538delAAGA, 2630del11, and 9045delGAAA) are recurrent (Diez 2017). Twenty-four non-truncating mutations (4 BRCA1 and 20 BRCA2) were detected in the screening of all regions of the BRCA1 and BRCA2 genes about 70 young African breast cancer patients. Fackenthal *et al*. (2005) studied 39 early onset breast cancer patients (< 40 years) in Nigeria. Twenty-nine (74%) patients carried a genetic variation in BRCA1 (4 variants), BRCA2 (30 variants) or both genes. A truncating mutation in BRCA1 (Y101X (422 T > G), exon 7) previously identified in Nigerian Yoruba ethnic group Breast Cancer patients led by Zhang *et al*. (2009) to screen 365 Nigerian women with Breast cancer and 177 controls for this mutation (Oluwagbemiga *et al*, 2012). Fackenthal *et al* reported that 29 of 39 (74%) women carried at least one genetic variation in BRCA1, BRCA2, or both, in cohort of early onset Nigerian breast cancer cases. BRCA2 variations were found in a surprising 27 cases (69%). Thirty-four different variants were detected and only one (2.5%) is a known deleterious truncating mutation (BRCA2 3034del4). Of the 21 previously reported non-truncating exotic variants, 15 were described as 'unclassified variants'' and only six were described as polymorphisms (Zhang *et al*, 2009).

Large genomic rearrangements (LGRs) of BRCA1 detected a novel deletion of BRCA1 exon 21 (c.5277; 480_5332; 672del) in 1 out of 352 Nigerian breast cancer patients (0.3% occurrence frequency). Further analysis of breakpoints revealed that the deletion involves two Alu-elements: one AluSg in intron 20 and the AluY in intron 21. These data suggest that while BRCA1 genomic rearrangement exists, they do not contribute significantly to BRCA1-associated risk in the Nigerian population (Zhang *et al*, 2010).

In addition, studies of mutations of the BRCA1 and BRCA2 genes have been carried out on black or African populations. In South Africa, Van der Merwe *et al*, found no Ashkenazi Jewish mutation with black (van der Merwe, 2012) and none of these mutations were found in any of the patients Studies of Yawitch *et al* (2000) who evaluated 206 black South African women for 185delAG in exon 2, 4184del4, 943ins10 and 1832deI5 in exon 11, and 5382insC in exon 20, and Met1775Arg in exon 21 mutations in BRCA1 (Oluwagbemiga *et al*, 2012). In African American women with breast cancer, a recurrent BRCA2 frameshift mutation, 2816insA, has been identified by several studies. So, three novel BRCA2 mutations (1536de14, 6696delTC and 7795delCT) were identified (Johnson, 1996). There were no significant differences in the frequency of deleterious BRCA2 mutations in African Americans compared with Caucasians (Kanaan *et al*, 2003) (Table 1).

In conclusion, since the discovery of BRCA1 and BRCA2, genetic testing for mutations is getting more and more common in clinical genetic practice. the study of the prevalence of mutations in the BRCA1 and BRCA2 genes associated with cancer is not yet fully elucidated in West African. Since data is scanty for most countries, the results from the few studies available makes it impossible to clearly draw scientific proofs mutations specific to each country. For a disease whose prevalence is increasing in the region, it will be necessary to conduct studies in the 15 countries. These types of mutations must be investigated in each population and not extrapolated to studies carried out elsewhere in the world.

Author Disclosure Statement

The authors declare that they have no conflicting interests

Acknowledgement

We thank all the authors who have already initiated work on BRCA1 / 2 of breast cancer in West Africa. This work is supported by ISESCO. Internet access for this work was supported by LABIOGENE.

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