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Hereditary Breast Cancer in Moroccan Populations: BRCA1 & BRCA2 at the Glance

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Abstract

Breast cancer (BC) is worldwide the most frequent cancer in women. It is the leading cause of female cancer mortality and hence constitutes a serious public health problem throughout the world. Extensive population awareness campaigns should be in place in Morocco in order to avoid having patients with metastatic and late stage tumors.

Keywords: Breast cancer; BRCA1 & BRCA2 genes; Moroccan incidence

Introduction

Breast cancer (BC) is worldwide the most frequent cancer in women [1]. It is the leading cause of female cancer mortality and hence constitutes a serious public health problem throughout the world. In Morocco and according to RCRC (Cancers Register of Grand Casablanca) [2] the incidence of breast cancer was continuously increasing in the last decade to reach 39.9 new cases per 100,000 women in 2007 (Table 1). While, in western countries the average age of onset of breast cancer is 55 years [3], most of breast cancer studies that have been performed in Morocco point out the young age of the diagnosed patients (<45 years) [4-7]. Unfortunately, the majority of these Moroccan patients come to hospitals at late stage of cancer. In Fez-Boulmane region, a recent study conducted on 265 relatively young patients (median age 45 years) with breast cancer over 3 years, showed that invasive tumors were found in 95.5% of the women with a large tumor size (3.6 cm) and only 14% were histological grade 1. The large tumor size and high histological grade in the Moroccan population was explained by a serious lack of early diagnosis and awareness about breast cancer risks [8]. In that sense and during the last decade more efforts have been mobilized to raise the public awareness toward that fatal disease. The Moroccan Lalla Salma Foundation Against Cancer has launched few years ago a periodical annual campaign for early breast cancer detection and eventually gives financially support for clinical and scientific studies aiming to contribute in establishing a national epidemiological database and in deciphering molecular and genetic pattern throughout the Moroccan populations.

	2005	2006	2007	Total
Number of case	666	690	763	2119
Crude incidence	35.9	36.6	39.9	37.5
Cumulative incidence 0-74 years (%)	3.76	3.7	4.17	3.88
Standarised incidence on the Moroccan population	30.4	31.5	34.6	32.2
Standarised incidence on the International population	35.1	35.4	38.6	36.4
Percentage based on total cancers	33.4	33	33.4	33.3
Percentage based on total cancers (Excluded Skin, Except Melanoma)	34.2	34.1	34.7	34.3

Table1: Breast cancer incidence in Moroccan women (2005-2007), RCRC

While the vast majority of breast cancer cases amongst Moroccan patients are sporadic, about 10% are of hereditary forms, especially BRCA1 and BRCA2 mutations, identifiable in some families with an excess of breast cancer and characterized usually by a young age at diagnosis (<45 years) [8]. Segregation analysis shows that, in these families, the susceptibility is inherited in adominant autosomal transmission mode with high penetrance [8].

The aim of the present communication is to discuss the established relationship between the mutations occurring both in BRCA1 & BRCA2 genes and the inherited breast cancer in female Moroccan patients and to summarize most of the relevant Moroccan studies that have been performed in this field.

BRCA1 and BRCA2 Mutations in Breast Cancer

During the four last decades, the identification and the localization of two genes predisposing to breast and ovarian cancer, BRCA1 and BRCA2, have been a major scientific breakthrough toward a clear understanding of family related breast cancer and has led to major changes in the treatment of women with inherited predisposition to breast and ovarian cancer. Indeed, having a clear understanding of the pathways in which BRCA1 and BRCA2 are involved and this in both normal and tumoral breast cells becomes fundamental for the non-invasive intervention in the case of women at high risk of developing hereditary breast cancer. Elucidating the normal functions and regulation of BRCA1 and BRCA2 may explain how direct or indirect functional inactivation of BRCA genes could lead to breast tumorigenesis. It is now well known that both BRCA1 and BRCA2 are essential genes for cellular development. BRCA1 and BRCA2 defective

cell lines and knockout mice exhibit similar sensitivities to DNA-damaging agents [9-12]. Genetic studies conducted in BRCA1- and BRCA2-defective cell lines [13,14] have also demonstrated that these tumor suppressor genes play key role in maintaining the genome integrity and for normal levels of resistance to DNA damage. Moreover, without functional BRCA genes, cells are inefficient in repairing DNA damage by homologous recombination [15-18] which can lead to apoptosis or cell transformation [19,20].

Even though BRCA1 and BRCA2 are able to interact with each other, however, only a minority of the BRCA1 was actually found in association with BRCA2 [21,22]. Moreover, the recent identification of proteins that associate with either BRCA1 or BRCA2 indicates that the two BRCA proteins each participate in different protein complexes, and that these complexes may play quite distinct roles in DSB repair.

BRCA1 (Breast Cancer 1)

Gene

The BRCA1 gene is located on the long arm of chromosome 17 in the q21 region [23]. This is a very large gene, covering more than 80 kb of genomic DNA [24]. The coding sequence is composed of 22 exons. The RNA messenger has a length of 7.8 kb. However, a large number of variants have been described (alternative splicing) and some messengers do not include exon II, corresponding to more than 50% of the coding sequence [24].

Protein

The BRCA1 gene is expressed as a 7.8 kb mRNA transcript in several organs, including breast and ovary. The BRCA1 gene encodes a nuclear phosphoprotein of 1863 amino acids with a predicted molecular weight of 220 kDa [24,25].

The analysis of the mitotic index (proliferation rate) of breast cancer related to BRCA1 gene has shown that mutations located in the conserved regions were associated with highly proliferative tumors, suggesting that these regions play an important role of cell proliferation of the mammary gland. On the other hand, the second region may correspond to a conserved tandem repeat pattern which interacts with p53. It is interesting to note that breast cancers associated with BRCA1 are more often associated with over expression of p53, the well-known tumor suppressor protein [26-28].

Mutations linked to BRCA1

More than 100 distinct germline mutations have been described in BRCA1. They are scattered throughout the coding sequence. An international database (Breast Cancer Information Core: BIC) is constituted and into which are listed the majority of constitutional mutations [29].

The most well-known founder mutation is BRCA12:185delAG which has been observed in 1% of the unselected Ashkenazi Jewish population and in 41% of high-risk families of that population [30]. This genetic alteration has been estimated to account for 20% of cases of breast cancer and 39% of ovarian cancer diagnosed in Jewish women before age 50. In addition, two other BRCA1 mutations, 188del11 and 5382insC, seem to be overrepresented in the Ashkenazi Jewish population.

To date, little is known about BRCA1 mutations in Moroccan breast cancer patients. Regarding the founder mutation 185delAG, populations other than the Ashkenazi Jewish population have been investigated, including the Moroccan Jewish population, which shows the same mutation rate, therefore opening the discussion about the origin of this particular mutation [31,32]. The relevance of this mutation in the non- Jewish Moroccan population remains unknown, although two such familial cases have already been described [5].

BRCA2 (Breast Cancer 2)

The gene

The BRCA2 is a very large gene, located on the long (q) arm of chromosome 13 at position 12.3 (13q12.3) [33]. The human reference BRCA2 gene contains 27 exons [34] and its sequence is distributed over about 70 kb of genomic DNA and gives rise to a transcript of 10.4 kb, coding for a protein of 3418 amino acids.

The protein

BRCA2 is a tumor suppressor deeply implicated in familial breast cancer. Genetic and biochemical characterization has shown that BRCA2 is involved in the maintenance of chromosomal stability and that it has an important role in recombination-mediated double-strand DNA break repair [35]. Two recent structures of BRCA2 domains have revealed that it may serve as a critical mediator of DNA repair through direct interactions with Rad51, the eukaryotic homolog of RecA, and with single-stranded DNA. Taken together, the structures provide striking insights into the role of BRCA2 in double-strand DNA break repair and suggest a direct role for BRCA2 in homologous recombination that was not evident from earlier studies [36].

BRCA2 bind the single strand DNA and directly interacts with the recombinase Rad51 to stimulate strand invasion which is a key step of homologous recombination. The localization of Rad51 to the DNA double-strand break requires the formation of BRCA1-PALB2-BRCA2 complex. PALB2 can function synergistically with a BRCA2 chimera. By repairing DNA, these proteins play a role in maintaining the stability of the human genome and prevent dangerous gene rearrangements that can lead to hematologic and other cancers. Similarly to BRCA1, BRCA2 probably regulates the activity of other genes and plays a critical role in embryo development [37].

Mutations linked to BRCA2

Given the complexity of mutation screening for BRCA2, these common mutations may simplify the methods required for mutation screening in certain populations. A striking example of a founder mutation is found in Iceland, where a single BRCA2 (999del5) mutation accounts for virtually all breast/ovarian cancer families. This frame-shift mutation leads to a highly truncated protein product. In a large study examining hundreds of cancer and control individuals, this 999del5 mutation was found in 0.6% of the general population. Of note, while 72% of patients who were found to be carriers had a moderate or strong family history of breast cancer, 28% had little or no family history of the disease. This strongly suggests the presence of modifying genes that affect the phenotypic expression of this mutation, or possibly the interaction of the BRCA2 mutation with environmental factors.

In Morocco, some recent studies have been interested on the investigation of BRCA1/2 mutations as summarized into the table below (Table 2). Laarabi and collaborators reported in a study conducted in 5 asymptomatic women belonging to 3 families with an elevated risk of breast cancer, that 3/5 women carried out BRCA1/2 mutations [5]. In another study including 40 Moroccan (<40 years) women diagnosed with breast cancer and with a familial history of breast/ovarian cancer, Tazzite and collaborators showed that 25.64% of patients carried BRCA1/2 mutations [4]. Nine pathogenic mutations were then detected in ten unrelated families, five deleterious mutations in BRCA1 gene and four mutations in BRCA2 gene. Four novel mutations were found: one in BRCA1 (c.2805delA/2924delA) and 3 in BRCA2 (c.3381delT/3609delT; c.7110delA/7338delA and c. 7235insG/7463insG) [4]. This prevalence is higher compared to Tunisia and Algeria with respectively 19.4% and 11.4% of breast cancer patients carrying BRCA1/2 mutations [38,39]. The third study was conducted by Laraqui and collaborators on 121 Moroccan women diagnosed with breast cancer. BRAC1 mutations were found in 36.1% of familial cases and 1% (1/102) of early-onset sporadic [6]. Overall, 14 BRCA1/2 point mutations have been reported; 9 in BRCA1 and 5 in BRCA2 [4-6].

BRCA1 & BRCA2 Mutations in Moroccan Breast Cancer Patients

Gene	Exon/Intron	Systematic Nomenclature	Amino Acid modification	References
BRCA1	exon 2	c.68_69delAG	Stop39	Laarabi et al.(2011) [5]
	exon 5	c.181T>G	C61G	Tazzite et al. (2012) [5]
	exon 11	c.798_799delTT	Stop285	Tazzite et al. (2012) [4]
	exon 11	c.2805delA	Stop999	Laraqui et al. (2013) [6]
	exon 11	c.3279delC	Stop1108	Tazzite et al. (2012) [4]
	exon 11	c.1016dupA	Stop345	Laraqui et al. (2013) [6]
	exon 16	c.4942A>T	Stop1648	Laraqui et al. (2013) [6]
	exon 11b	c.1186A>G	Q356R	Tazzite et al. (2014) [7]
	exon 11b	c. 1100A>G	T327T	Tazzite et al. (2014) [7]
	exon 17	c.5062-5064delGTT	V1688del	Tazzite et al. (2012) [4]
	exon 18	c.5095C>T	R1699W	Laraqui et al. (2013) [6]
BRCA2	exon 11	c.3381delT	Stop1150	Tazzite et al. (2012) [4]
	exon 11	c.5073dupA	W1692MfsX3	Laarabi et al. (2011) [5]
	exon 14	c.7110delA	Stop2376	Tazzite et al. (2012) [4]
	exon 14	c.7235insG	Stop2413	Tazzite et al. (2012) [4]
	intron 6	c.517-1G>A		Tazzite et al. (2012) [4]

Table2: *BRCA1* and *BRCA2* pathogenic germline mutations found in Moroccan population

Recently, a study aiming to decipher BRCA1 gene regions (exon 2 and exon 11a/b) for eventual mutations detection was conducted in our laboratory on 50 female Moroccan breast cancer patients with early disease onset (<40 years) or familial disease backgrounds [7]. The results showed that no mutation was found in exon 11a. However, in exon 11b, a mutation generated by a nucleotide exchange was detected in 8% of patients, most of whom were young women (≤ 40). This mutation leads to substitution of the amino acid glutamine by an arginine at position 356 of the polypeptide sequence (Q356R) [7]. In addition, a second mutation (T327T) was found in exon 11b of young patients too. Both Q356R and T327T mutations were detected for the first time in Morocco and this at high frequency (4-8% of patients) when compared to western European breast cancer patients (<1%).

Overall, relatively few studies targeting BRCA1 and BRCA2 mutations in breast cancer patients have been performed in Morocco. In these studies, several BRCA1 or BRCA2 mutations were described especially in relatively young patients (<40 years).Analysis of a larger population is required in order to highlight the relevance of these important mutations in young Moroccan breast cancer patients. Furthermore, extensive population awareness campaigns should be in place in Morocco in order to avoid having patients with metastatic and late stage tumors.

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