

MINI-REVIEW

Breast Cancer in Morocco: A Literature Review

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Abstract

In Morocco, breast cancer is the most prevalent cancer in women and a major public health problem. Several Moroccan studies have focused on studying this disease, but more are needed, especially at the genetic and molecular levels. It is therefore interesting to establish the genetic and molecular profile of Moroccan patients with breast cancer. In this paper, we will highlight some pertinent hypotheses that may enhance breast cancer care in Moroccan patients. This review will give a precise description of breast cancer in Morocco and propose some new markers for detection and prediction of breast cancer prognosis.

Keywords: Breast cancer - epidemiology - genetic -molecular-treatment - Morocco

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Introduction

Worldwide breast cancer is the most common malignancy in women with nearly a half million deaths each year (IARC Globocan, 2008). In Morocco, breast cancer represents a serious public health problem. It's the first cancer among women and the third one of all registered cancer cases.

In Morocco, the interest of studying breast cancer has clearly increased during the last decade, and different studies were conducted to characterize breast cancer at epidemiological, molecular and genetic levels. Since 2005, date of creation of Lalla Salma Foundation (ALSC), Cancer care in Morocco has improved and became a public health priority.

The aim of this review is to summarize all Moroccan studies done in the field and highlight the most relevant findings that should be more investigated to improve the prognosis and the treatment of the Moroccan patients.

Epidemiological Studies on The Moroccan Population

It's widely accepted that establishment of the epidemiological profile of breast cancer is essential to provide hypothesis for understanding the etiology of the disease.

Moroccan patients are diagnosed at early age

In Morocco, two cancer registries have been implemented in the greater areas of Rabat and Casablanca. Overall, the incidence of breast cancer have clearly

increased during the last decade, the 2012 updated versions of the RCRC (Registre des Cancers de la Region du grand Casablanca) and RCR (Registre des Cancers de Rabat) have reported a standardized incidence of 39, 9 and 49, 2 per 100.000 women respectively (RCRC, 2012; RCR, 2012).

According to RCRC and RCR, women diagnosed with breast cancer are aged between 18 and 80 years old, and the mean age at diagnosis is 49.5 and 50 years respectively (RCRC, 2012; RCR, 2012). On the other side, Abbas et al. showed in a cohort of 265 women with breast cancer in the Fez region, that the median age is 45 years (Abbass et al., 2011). Overall, the mean age at diagnosis in Morocco is less than in western countries where the average age of onset of breast cancer is 55 years old (Blamey et al., 2010).

In a recent study conducted by Tazi et al., 39,9% of cancer cases are breast cancer patients, this study included all new cases of cancer diagnosed in the resident population of the Rabat area between 2005 until 2008 (Tazi et al., 2013).

In a comparative clinical study, Chalabi et al. have clearly demonstrated that South Mediterranean breast cancer patients are younger than French patients. In this study, including Moroccan, Tunisian and Lebanese patients, authors found that South Mediterranean patients were 10 years younger than French breast cancer patients ($p < 0.001$), with more aggressive parameters; more SBRIII grade (Scarff Bloom and Richardson histological grade) and positive lymph node invasion (Chalabi et al., 2008). Interestingly, large tumor size and high histological grade were found in a Moroccan series, which was explained

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by the lack of awareness of breast cancer risks (Abbass et al., 2011).

As the average age of onset of breast cancer in Morocco is young, many authors were interested to investigate the epidemiological, clinical and treatment characteristics in patients under 35 years old. In Morocco, reported data showed that 8 to 25.4% of women with breast cancer are young (Boufettal et al., 2010; Abahssain et al., 2010; Znati et al., 2012) (Table 1). While worldwide studies have reported that approximately 2-24% of patients with breast carcinoma are under 35 years old at the time of diagnosis (Merill et al., 2000; Agarwal et al., 2007). These results obtained by Boufettal et al., are the highest level published so far (Boufettal et al., 2010).

The family history of breast cancer seems to affect young women as it was described by Tazzite et al., the findings of this study that was conducted on 570 cases of breast cancer were significant. 18,4% of the cases had a family history of Breast Cancer and presented high SBR grade tumors, positive lymph node status and absence of progesterone receptors (Tazzite et al., 2013). These results must be more investigated to be used as predictor markers in this subtype group.

Triple negative breast cancer incidence in Morocco

Triple Negative Breast Cancer (TNBC) is defined as a tumor that does not express estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2). In Morocco two studies (Table 1) have explored the prevalence of Triple Negative Breast Cancer cases. In these studies, TNBC represent 17.5% and 16.5% of total breast cancer cases (Akasbi et al., 2011; Rais et al., 2012). These frequencies are in agreement with published data around the world with TNBC accounting for some 10-17% of all breast cancers (Foulkes et al., 2010).

Inflammatory breast cancer in Morocco

Inflammatory Breast Cancer (IBC) is the most aggressive subtype of breast cancer. It was reported that IBC is more common in North Africa than Europe and North America (Sutherland et al., 2010). In Morocco, only one study was published on IBC (Table 1) and showed that IBC cases represent 6.3% of total breast cancer cases (Errihani et al., 2008). However, this study was based on data from 2003 and has to be updated to evaluate the evolution of IBC cases in Morocco. Similarly, IBC cases represent 5.7% of total breast cancer in Tunisia (Boussen et al., 2010), whereas, in Europe and North America, IBC represents 2-5% of breast cancer cases (Nokes et al., 2013; Sutherland et al., 2010). No explanations could be given for these high frequencies in North Africa; further investigations are needed to identify the probable impact of genetical, virological and immunological factors in IBC development in this area.

Lipid profile among breast cancer patients

400 overweight Breast Cancer patients were compared to a group of 400 healthy controls at the National Institute of Oncology of Rabat. This 2-years case control study shows very interesting and significant results.

Hypertriglyceridemia and obesity are connected to breast cancer risk while physical activity have protective role on breast cancer risk (Laamiri et al., 2013).

By using the findings of this study, overweight women in Morocco should be alarmed about this situation through public awareness campaigns encouraging them to adopt a healthy lifestyle and frequent sports activity.

Men breast cancer in Morocco

Worldwide men breast cancer is uncommon and represents less than 1% of all cancers registered (Cutuli et al., 2010). In Morocco, two studies have focused on Men Breast Cancer as shown in Table 1. In the first study, El Omari-Alaoui et al., identified 71 Moroccan male with breast cancer between 1985 and 1998 which represents 0.94% of all breast cancers cases (El Omari-Alaoui et al., 2002).

In the second study, Bourhafour et al., identified 171 men diagnosed with breast cancer between 1985 and 2007 at the National Institute of Oncology (INO) in Rabat (Bourhafour et al., 2011). Clinical and treatment characteristics of male breast cancer seems to have many similarities with women breast cancer but still have more aggressive behavior. As suggested by El Youbi et al. (2013) no study to date has concerned the assessment of the psycho-social impact of this disease on the Moroccan patient and his family.

Molecular and Biological Characterization of Breast Cancer in Morocco

Breast cancer is a complicated disease characterized by the accumulation of multiple molecular alterations that give each tumor a specific phenotype that can be used as a molecular signature to reach a personalized therapy.

Molecular classification of breast cancer in Morocco

Two recent studies were done on the Moroccan patients; the findings are giving the same results and both studies were conducted in the same institution (Table 2).

The first one was conducted by Bennis et al. and has reported a molecular classification of breast cancer on a Moroccan series of 366 patients (Bennis et al., 2012). In this study, the expression of 7 markers was investigated: ER, PR, Her-2 (Human Epidermal growth factor Receptor 2), Her-1 (Human Epidermal growth factor Receptor 1), CK8/18 (cytokeratins 8/18), CK5/6 (cytokeratins 5/6), and CK14 (cytokeratin 14) [22]. The subtype luminal A (ER+and/or PR+, HER2- CK8/18+) was predominant with a prevalence of 53,6%. Subtypes Luminal B (ER+and/or PR+, HER2+, CK8/18+), Her2+ (ER-, PR-, HER2+), Basal-like (ER-, PR-, HER2- and CK 5/6+, HER1+ and/or CK14+) represented respectively 16,4%, 12,6%, and 12,6%; while the percentage of unclassified subtype (ER, PR-, HER2-, CK 5/6-, HER1- and CK14-) was 4,9% (Table 2). Luminal A subtype seems to be associated with favorable prognosis, a better overall survival (OS) and the highest disease free survival (DFS) unlike basal-like subgroup that was associated with a poor prognosis and the lowest OS/DFS. Interestingly, Znati et al. (2012) have reported the similar results on young women with breast

Table 1. Epidemiological Studies Conducted in Morocco

Topic of the study	Reference of the study	Institution where patients were recruited	No.of patients	Period of study
All breast cancer subtypes	Abbass et al., 2011	CHU Hassan II FEZ	265	January 2007-September 2009
	Bennis et al., 2012	CHU Hassan II FEZ	366	January 2007-June 2010
	Abbass et al., 2012	CHU Hassan II FEZ	335	January 2007-Septembre 2011
	Tazzite et al., 2013	CHU Ibn Rochd CASABLANCA	570	2009
Breast cancer in young women	Abhssain et al., 2010	INO RABAT	409	2003-2007
	Boufettal et al., 2010	CHU Ibn Rochd CASABLANCA	165 vs 286*	January 2000-July 2009
	Znati et al., 2012	CHU Hassan II FEZ	74	September 2004-December 2009
Triple negative breast cancer	Akasbi et al., 2011	CHU Hassan II FEZ	64	January 2007-June 2010
	Rais et al., 2012	INO RABAT	152	January 2007-December 2008
	Errihani et al., 2008	INO RABAT	51	2003
Inflammatory Breast Cancer	El Omari-Alaoui et al., 2002	INO RABAT	71	1985-1998
Breast cancer in Men	Bourhafour et al., 2011	INO RABAT	127	1985-2007

*cases vs controls

Table 2. Comparison between two Moroccan Studies Concerning Molecular Classification of Breast Cancer Subtypes

Bennis et al. 2012 Molecular subtype	Percentage	Abbass et al. 2012 Molecular subtype	Percentage
Luminal A (ER+and/or PR+, HER2- CK8/18+)	53.60	luminal A (ER+et/ou PR+, Her2-, CK8/18+et Ki-67>14%)	54.30
Luminal B (ER+and/or PR+, HER2+, CK8/18+)	16.40	Luminal B (ER+et/ou PR+, Her2+, CK8/18+et Ki-67 >14%)	16
HER2+(ER-, PR-, HER2+)	12.60	Her2+ (ER-, PR-, Her2+)	11.30
basal-like (ER-, PR-, HER2- and CK 5/6+, HER1+and/or CK14+)	12.60	Basal-like (ER-, PR-, Her2-, CK 5/6+ et/ou EGFR+)	11.30
Unclassified (ER-, PR-, HER2-, CK 5/6-, HER1-and CK14-)	4.90	Unclassified (negative for all markers)	7

cancer.

On the other hand, Abbass et al., conducted a study on 335 women diagnosed with breast cancer, and investigated 7 markers also: ER, PR, Her2, Her1, CK8/18, basal CK5/6 and KI67 (Antigen KI67). In this series, and as shown in Table 2, Luminal A subtype was more predominant followed by Luminal B, Her2, Basal-like and the unclassified variants [(Abbass et al., 2012) (Table 2).

Her2 is a key molecular marker in the classification of breast cancer types. In these studies, Her2 profile was routinely determined by immunohistochemistry. However, Elghissassi et al., have found that the Her2 status in a breast cancer patients changed from positive (score 3+) to negative (score 1+) after a single treatment with herceptin, suggesting that the Her2 status should always be confirmed by FISH for adequate results (Elghissassi et al., 2009).

Biological markers on Moroccan patients

In this paragraph we will be reviewing the case of three biological markers.

Cancer antigen 15-3: Serum tumor marker CA15-3 is commonly used in follow-up for evaluation of breast cancer prognosis. Bensouda et al. suggested that ER/PR positivity seems to be highly correlated with CA15-3 (Cancer Antigen 15-3) level at the time of metastatic relapse. CA15-3 is elevated in 69% of the cases of HR+/Her2- primary tumors (Bensouda et al., 2009). This correlation was also confirmed by Atoum et al., where CA15-3 was elevated in 54.2% of ER+/PR+ breast tumors (Atoum et al., 2012). This serum marker may be useful in therapeutic decisions when more correlation is established between CA15-3 and ER/ PR/Her2 status.

CD44: For more than three decades, the monoclonal antibody CD44 has been extensively studied in breast cancer because of its implication in lymph node invasion (Louderbough et al., 2011).

This marker was evaluated in the Moroccan patients and results showed a statistically significant difference between the group of patients with lymph node invasion (N+) and those without lymph node invasion (N-). These Moroccan results indicated that the use of this molecule and its variants as a diagnostic tool or as a prognostic marker of malignancy in breast cancer seems interesting and may also be a potential therapeutic target (Yahyaoui et al., 2001).

RhoC: RhoC (Ras homolog gene family, member C) is a small signaling G protein which the overexpression is associated with tumor cell invasion and metastasis (Hakem et al., 2005). It's also been characterized as a transforming oncogene for human mammary epithelial cells. It's widely accepted that overexpression of RhoC is involved in IBC metastasis and associated with poor clinical outcome. Some authors suggest that RhoC overexpression may contribute in the development of IBC and it confers its aggressiveness (Kleer et al., 2004). In a recent study, Soliman et al. conducted a comparative study between patients from Egypt, Tunisia and Morocco, and showed that the overexpression of RhoC is detected in 87%, 50%, 38,1% of IBC cases, respectively which was correlated with tumor emboli status (Soliman et al., 2012).

Genetic aspect of Breast Cancer in Morocco

During the last decade, molecular genetics have known a great evolution at both conceptual and methodological levels and has made an outstanding contribution to our understanding of genetic disease etiology. Molecular genetics highlighted the partly involvement of predisposition and genetic mutations in breast carcinogenesis.

BRCA1/2 mutations found in Moroccan patients are

frequent in Mediterranean population

Worldwide, genetic predisposition is observed in about 5 to 10% of cancers (Yoshida et al., 2004). Two genes with high penetrance susceptibility to breast cancer have been identified, BRCA1 (Breast Cancer 1) in 1994 and BRCA2 (Breast Cancer 2) in 1995 (Miki et al., 1994; Wooster et al., 2005). Germline mutations in BRCA1 and BRCA2 have been shown to play an important role in genetic predisposition to breast/ovarian cancer, and are responsible for 3 to 5% of breast cancers (Risch et al., 2006).

In Morocco, three studies have focused on the study of BRCA1 / 2 mutations. The first study was conducted by Laarabi et al., and was interested in the study of BRCA1 / 2 mutations in 5 healthy women belonging to 3 families with an elevated risk of breast cancer. As results of this study, 3 asymptomatic women were carriers of BRCA1/2 mutations (Laarabi et al., 2011).

The second study is a Moroccan cohort with 40 women diagnosed with Breast Cancer with a familial history of breast/ovarian cancer or aged less than 40 years old. Tazzite et al. showed that 25.64% of patients carried BRCA1/2 mutations (Tazzite et al., 2012). This prevalence is higher compared to Tunisia and Algeria with respectively 19.4% and 11.4% of breast cancer patients carrying BRCA1/2 mutations (Troudi et al., 2007; Cherbal et al., 2010).

The last study was conducted by Laraqui et al., on 121 Moroccan women diagnosed with breast cancer, only BRCA1 status was investigated. BRCA1 mutations were found in 36.1% of familial cases and 1 % (1/102) of early-onset sporadic (Laraqui et al., 2013).

Overall, 14 BRCA1/2 point mutations have been reported; 9 in BRCA1 and 5 in BRCA2 (Laarabi et al., 2011; Tazzite et al., 2012; Laraqui et al., 2013) and are summarized in Table 3.

BRCA1-185delAG

Mutation was first described in the Ashkenazi Jewish population (Roa et al., 1996). In Morocco, it was detected in two unrelated families (Laarabi et al., 2011). The confirmation of occurrence of this mutation in the Moroccan population will be of great benefit to simplify genetic testing and may have a major impact on public health in Morocco.

c.798_799delTT

Mutation (917delTT) was first described in two unrelated French families (Muller et al., 2004), then it was reported in Spain (John et al., 2007) and in Italy (Palomba et al., 2005). This mutation was also found in four Algerian families (Uhrhammer et al., 2008; Cherbal et al., 2010), three unrelated Tunisian families (Mahfoudh et al., 2011) and recently in a Moroccan patients (Tazzite et al., 2012; Laraqui et al., 2013). These findings suggest the presence of a founder effect mutation in the Mediterranean population.

Mutation c.181T>G (300T>G), was recently found in a 38 years old Moroccan patient diagnosed with breast cancer with a family history of breast / ovarian cancer (Tazzite et al., 2012). It is described as a founder mutation in the population of Central Europe (Ramunas et al., 2010)

Table 3. BRCA1/2 Mutations Found in the Moroccan Population

Gene	Exon	Systematic Nomenclature	Reference
BRCA1	exon 2	c.68_69delAG	Laarabi et al., 2011
	exon 5	c.181T>G	Tazzite et al., 2012
	exon 11	c.798_799delTT	Tazzite et al., 2012; Laraqui et al., 2013
	exon 11	c.3279delC	
	exon 11	c.2805delA	Tazzite et al., 2012
	exon 11	c.1016dupA	Laraqui et al., 2013
	exon 16	c.4942A>T	Laraqui et al., 2013
BRCA2	exon 17	c.5062-5064delGTT	Tazzite et al., 2012
	exon 18	c.5095C>T	Laraqui et al., 2013
	intron 6	c.517-1G>A	Tazzite et al., 2012
	exon 11	c.3381delT	Tazzite et al., 2012
	exon 11	c.5073dupA	Laarabi et al., 2011
	exon 14	c.7110delA	Tazzite et al., 2012
	exon 14	c.7235insG	Tazzite et al., 2012

and was also observed in an Algerian study (Cherbal et al., 2010).

Methylenetetrahydrofolate reductase gene in the Moroccan population

Methylenetetrahydrofolate reductase (MTHFR) is one of the main regulatory enzymes in the metabolism of homocysteine that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (Forges et al., 2007). MTHFR gene plays an important role in the genomic integrity and DNA biosynthesis leading to genetic instability and increasing the risk of several cancers including breast cancer (Ergul et al., 2003).

Many authors have studied the association between MTHFR C677T polymorphism and the risk of developing breast cancer. Qi et al. reported that the MTHFR C677T polymorphism may play a low penetrance role in the development of breast cancer and therefore could be involved in breast cancer susceptibility (Qi et al., 2010). Whereas Maruti et al. concluded that women with a higher number of variant T alleles had higher risk of breast cancer (Maruti et al., 2009). However, the meta-analysis conducted by Zhang et al. suggested that women with at least one T allele have a lower risk of developing breast cancer (Zhang et al., 2010).

In Morocco, the study of Diakite et al. revealed a positive correlation between the T allele of MTHFR C677T variant and risk of breast cancer among Moroccan women with an odds ratio of 1.59. They also found a significant difference between patients with breast cancer and controls regarding the frequency of C677T genotypes in the additive and dominant models, suggesting that the T allele may influence the risk of breast cancer. On the other hand, the correlation between MTHFR C677T polymorphism and PR hormonal status has been documented and showed a positive association (p= 0.04) (Diakite et al., 2012).

MTHFR C677T polymorphism should be more investigated in order to elucidate its complete implication in breast cancer susceptibility.

Other markers

In 2008, the breast Mediterranean Consortium published data on the comparative transcriptomal profiles of breast cancer between French and south Mediterranean (Lebanon, Morocco and Tunisia) patients, giving the opportunity for further explorations to better understand the breast carcinogenesis and highlight potential molecular biomarkers that might open the way for new prevention, diagnosis and therapeutic approaches (Chalabi et al., 2008).

Indeed, differentially expressed genes were reported. The most significant up-regulated genes in South Mediterranean patients were MMP9 (Matrix metalloproteinase 9), BRCA1, TFAP2C (Transcription factor AP-2 gamma), CDKN1 (Cyclin-dependent kinase inhibitor), CEACAM5 (Carcinoembryonic antigen-related cell adhesion molecule 5) while VEGF (Vascular endothelial growth factor), PHB1 (Prohibitin), TFF1 (Trefoil factor 1), GJA1 (Connexin 43) were down-regulated (Chalabi et al., 2008).

Treatment for Breast Cancer care in Morocco

Therapeutic protocol for treatment of breast cancer is based on radiological, clinical and pathological profiles. Thus radical surgery or conservative, neoadjuvant or adjuvant chemotherapy, radiotherapy, hormone therapy and targeted treatments are possible for better management of patients.

Chemotherapy and radiotherapy treatment

Anthracyclines chemotherapy is a major benefic protocol for breast cancer treatment either in adjuvant, neoadjuvant, or metastatic situations. In a series of 126 Moroccan patients treated with anthracyclines as neoadjuvant therapy according to AC60 protocol (doxorubicin+cyclophosphamide), two clinical predictive factors for complete response (CR) and pathological complete response (pCR) were identified: tumor size T2-T3 (T4b were less sensible and T4d did not have a CR), and clinical nodal status N0-N1 (Bensouda et al., 2011). Validating and standardizing these predictors should be valuable and helpful for clinicians. Anthracyclines combined with Vinorelbine as neoadjuvant chemotherapy for pregnant patients with locally advanced breast cancer seems to be benefic and non-harmful for fetus (Mrabti et al., 2010).

The concomitant use of adjuvant chemotherapy and radiotherapy is more valuable for Breast cancer treatment but remains controversial (Kao et al., 2005).. Ismaili.N et al., have conducted a retrospective cohort study in a single institution on 400 Moroccan patients divided into two groups. Group A received concurrent chemioradiotherapy with anthracyclin based regimen while group B received concurrent chemioradiotherapy with CMF (cyclophosphamide 500 mg/m², methotrexate 60 mg/m², and 5-fluorouracil 500 mg/m²) based regimen. Results showed similarity between both groups for DFS and 5years-OS; while a very good loco regional control was described in group A but with more hematologic and non hematologic toxicities. Concurrent chemoradiotherapy should not be used before further investigation (Ismaili

et al., 2010).

In metastatic breast cancer, Bevacizumab may be indicated as chemotherapy first line treatment and provides substantial benefit in terms of PFS (progression free survival) and objective response (OR) (O'shaughnessy et al., 2010). In a Moroccan study that included 19 patients with Her2 negative metastatic breast cancer, it has been demonstrated that Bevacizumab first line chemotherapy combined with taxanes extends PFS (Boulaamane et al., 2011).

Trastuzumab is used as adjuvant therapy for the treatment of localized breast cancer. However it has some side effects such as cardiotoxicity. In a recent Moroccan study, the cardiac safety of trastuzumab was evaluated by Aitelhaj et al., 38% of patients showed a cardiotoxicity which is comparable to the published data in this field (Aitelhaj et al., 2013).

Hormonotherapy treatment in Moroccan breast cancer patients

Tamoxifen is widely prescribed as hormonal therapy for ER+ breast cancer, its role in prolonging DFS and OS has been proven (Morgan et al., 2011). Beyond its beneficial role, it can cause endometrial cancer (Fornander et al., 1989). In Morocco, a rare case of granulosa cell tumor of the ovary was reported in a 47 year-old women ten months after stopping tamoxifen. This case appears to be rare since it is only the third one that was reported in literature. Comparing this result to worldwide use of Tamoxifen showed that Tamoxifen does not increase the risk of granulosa cell tumor of the ovary (Abahssain et al., 2010).

It has also been reported a rare case of Tamoxifen hepatotoxicity in a 46-year-old Moroccan woman, without medical history of hepatic disease four weeks after initiation of Tamoxifen (Ahbeddou et al., 2011).

Moroccan Traditional Medicine and Antiproliferative Effects on Breast Cancer Cell Lines

In Morocco, the use of traditional medicine is a widespread practice. The ethnobotanical and ethnopharmacological surveys conducted in different areas allowed the compilation of an inventory of 360 species and more than 500 prescriptions are recorded (Bellakhdar, 1997).

In the Moroccan traditional medicine, the use of plants in the form of infusions or decoctions is a common practice among people of rural communities, and their use is increasing in urban populations. Moroccan medicinal plants were already studied for their use in different human diseases (Bellakhdar, 1997).

In the course of screening strategy for the anticancer compounds from plants, Chaouki et al., have focused their interest on the evaluation of the anticancer activity of some medicinal plants used in Morocco, such as *Aristolochia baetica* L., *Origanum compactum* Benth, and *Daphne gnidium* L. (Chaouki et al., 2009; Chaouki et al., 2010). Reported results showed that various extracts from these plants have an antiproliferative effect on human

breast cancer cell line MCF7. Moreover, reported data showed that Daphne gnidium L. might be of potential chemopreventive interest with a pro-apoptotic effect (Chaouki et al., 2009).

These studies provide an important basis for further investigations into the isolation, characterization and molecular mechanism elucidation of natural active compounds with potential chemotherapeutic effect.

Conclusions

Development of national and significant studies to explain the very young epidemiological profile of breast cancer.

Develop a national study for molecular classification of Breast Cancer in Morocco.

Evaluation of the viral etiology of breast cancer in Moroccan population. This study has to include the most viruses susceptible to be associated with breast cancer development, especially HPV (Human Papillomavirus), MMTV-like (Mouse mammary tumor virus like), EBV (Epstein Barr Virus).

Molecular characterization of inflammatory breast cancer, which seems to be more frequent in North Africa. In this field, IBC related work like RhoC implication should be more investigated.

Evaluation of MUC1 (Mucin 1) gene expression in breast cancer cases. Indeed, MUC1 regulates positively CA15-3 which seems to be more elevated in metastatic phase when hormonal receptors are positive.

Evaluation of the use of the monoclonal antibody CD44 and its variants as a diagnostic tool and/or a prognostic marker of malignancy in breast cancer and as a potential therapeutic target.

Conduction of a large study on the implication of BRCA1 and 2 in breast cancer development in Morocco. This study must be extended to all breast cancer patients, including sporadic cases, and could be limited to the most relevant mutations that have already been found in Morocco and frequent in the Mediterranean region such as c.68_69delAG/185delAG, c.181T>G/300T>G and c.798_799delTT/917delTT.

Evaluation of the association of 677T polymorphism and the risk of development of breast cancer and assessment of the use of this polymorphism as a genetic factor for breast cancer predisposition.

On the other hand, large and extensive public awareness campaigns should be conducted for early diagnosis of breast cancer to avoid having patients with aggressive form and advanced tumors' stages.

Investigating these themes will allow a precise description of breast cancer in Morocco. The success of breast cancer national program to fight this disease will depend on the introduction of new molecular tools that will give a molecular signature to reach a personalized therapy. This approach will be of benefit for: *i*) The patient (earlier diagnosis, improved outcomes, reduced health-care costs); *ii*) The health care provider (definitive diagnosis earlier, focused diagnostic testing, optimum patient care); *iii*) The hospital (briefer period of hospitalization, reduction of hospital' costs, optimization of hospital resources for

more patients); *iv*) The public health program.

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