ORIGINAL ARTICLE

RELATIONSHIP BETWEEN FAMILY HISTORY OF BREAST CANCER AND CLINICOPATHOLOGICAL FEATURES IN MOROCCAN PATIENTS

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ABSTRACT

BACKGROUND: Breast cancer is the most common cancer affecting women all over the world. In addition to hormonal and environmental causes, family history is emerging as an important risk factor in the etiology of this disease. The aim of the present study is thus to compare the clinico-pathological features of familial and sporadic breast cancer in Moroccan patients.
METHODS: A comparative retrospective cohort study was conducted on 570 women with familial and sporadic breast cancer who were diagnosed and treated in the Oncology Center of Ibn Rochd University Hospital in 2009. Data on breast cancer risk factors and clinico-pathological characteristics of the tumors were extracted from patients' medical records.
RESULTS: Familial cases represented 18.4% of breast cancer patients. The age of onset appears to be earlier in familial breast cancers (P=0.0024). There were no significant differences between familial and sporadic groups according to histological type, tumor size and estrogen receptor status. However, Scarff-Bloom-Richardson grade III was found in 43.8% of familial cases vs 26.7% of sporadic cases (P=0.0127) and the lymph node involvement was observed in 72.4% of familial cases vs 58.9% in sporadic cases (P=0.0213). Moreover, familial breast cancer patients present especially progesterone receptor-negative tumors (P=0.0380).
CONCLUSIONS: Our initial significant findings show that familial breast cancer seems to affect young women and tends to present high Scarff-Bloom-Richardson grade tumors with lymph node involvement and absence of progesterone receptors. These preliminary results may be useful as clinical marker to identify familial breast cancer allowing the development of careful follow-up for this patients subtype.
Key words: Breast neoplasm, family history, clinico-pathological characteristics, Morocco

INTRODUCTION

Breast cancer is the most common cancer affecting women all over the world. The World Health Organization estimated that 1.38 million breast cancers were diagnosed worldwide in 2008 (1). The epidemiology of this cancer has been extensively studied in the world especially in developed countries where the incidence is much higher (2). In Morocco, according to the Greater Casablanca Cancer Registry, breast cancer seems to be the first female cancer with a standardized incidence of 36.4 for an average age of 49.5 years (3).

Breast cancer is a heterogeneous disease with multiple morphological phenotypes, specific histopathological forms and distinct prognostic features (4-6). In fact, the prognosis and treatment options of breast cancer depends on a

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variety of characteristics which correlate with the outcome of the disease such as its histologic type, lymph node status, tumor size, histological grade, vascular and lymphovascular invasion, hormone receptors and human epidermal receptor 2 expression. Moreover, many risk factors have been identified to explain this type of cancer in some women, such as increase in age, early menarche, late childbearing, late menopause, nulliparity, absence of breastfeeding, benign breast disease, high density of breast tissue, obesity, exposure to radiation, alcohol consumption, sedentary lifestyle, oral contraceptives use and hormone replacement therapy (7). In addition to the environmental causes, the family history is also emerging as an important risk factor in the etiology of this disease.

Women with a strong family history of breast cancer could inherit genetic alterations that modify their risk of disease (8), as a result of which risk factors and clinicopathological features may differ among familial and sporadic forms of breast cancer. The characteristics of familial breast cancer remain a controversial issue as several studies have shown inconsistent results. A number of studies have revealed that familial breast cancer has some specific clinical features compared to sporadic cases. Indeed, some investigations have shown that women diagnosed with positive family history present an early age of onset, bilateral breast cancer, advanced stage, lymph node involvement and negative hormone receptors with a less favorable prognosis (9, 10), whereas others have found no significant differences in terms of distribution of age at diagnosis, histology, tumor stage, nodal involvement and hormone receptors status (11-13).

In Morocco, it is not yet clear whether breast cancers arising in women with positive family history are different from sporadic breast cancers. In this study, we investigated the clinical and pathological characteristics of breast cancer in two distinct patient populations, familial and sporadic breast cancer patients.

MATERIAL AND METHODS

In this comparative retrospective cohort study, we analyzed data of 570 patients with histologically proven breast cancer, diagnosed and treated in Oncology Center in Ibn Rochd University Hospital of Casablanca in 2009. We considered only patients who had complete records. The original cohort contained 629 patients but 59 medical records were incomplete, and as a result, the final group size was reduced to 570 patients.

We divided our sample into two groups: Familial Breast Cancer (FBC) group including patients with positive family history (n=105) and Sporadic Breast Cancer (SBC) group including sporadic patients without any family history of breast cancer (n=465). The family history was considered as positive when the patient had one or more relative with breast cancer within three generations.

Information on age of diagnosis, age at menarche, age at first delivery, parity, menopause status, tumor localization, histology type, Scarff-Bloom-Richardson (SBR) grade, lymph nodes status and hormone receptors status were obtained through a detailed medical record review. The study was approved by the local ethics committee of our institution.

Statistical analyses were conducted with EpiInfo version 3.5.1 for Windows. The Chi-squared test/ Fisher's exact test with the threshold 5% were used for the statistical analysis of categorical variables. The student's t-test was used for the comparison of continuous variables.

RESULTS

For the present study, the total number of breast cancer cases analyzed, 59 (9.4%) incomplete records omitted, was 570.

The results showed that the mean age of all patients was 47.07 years with a standard deviation of 10.73. A total of 105 patients (18.4%) reported having a family history of breast cancer in which 76.2% had one affected relative, 16.2% had two relatives affected, 5.7% had three relatives affected and only 1.9% had four relatives with breast cancer. Moreover, among patients with positive family history 51.4% had a second-degree relative affected with breast cancer, 39.0% had an affected first-degree relative and 9.5% had both first and second degree relatives affected by the disease (Table 1).

Table 1: Distribution of breast cancer patients according to family history. Ibn Rochd Oncology Center, Morocco, 2009.

Group	Family History	Nb	%
FBC	Yes	105	18.4
	1st degree	41	39.0
	2nd degree	54	51.4
	1st and 2nd degree	10	9.5
SBC	No	465	81.6

FBC: familial breast cancer; SBC: sporadic breast cancer; Nb: number; %: percentage

The age of onset appears to be earlier in patients of FBC group with a mean age of 44.2 years compared to 47.7 years in the SBC group (P = 0,0024). Also, FBCs were more likely to be premenopausal (RR = 1.62, 95% CI 1.14-2.31, P = 0.0064). The mean age at menarche was 13.35 years in FBC group vs 13.62 years in SBC group. Early puberty was observed in 33.9% of FBC group and 27.3% of SBC group, without significant statistical difference. Similarly, the mean age at first pregnancy was 23.70 years in FBC and 23.04 years in SBC cases. The first pregnancy was late in 19.3% of FBC patients and 20.05% of SBC patients; no significant difference between the two groups was observed. On the other hand, FBC and SBC were similar with regards to parity (27.6% of patients in the first group were nulliparous vs 26.1% in the second group) and oral contraceptive use (60.9% of FBC and 53.5% of SBC reported that they use oral contraceptives). Moreover, it was found out that of the 105 patients of FBC group, 4 (3.8%) had bilateral breast cancer and 101 (96.2%) had unilateral breast cancer. There was no significant difference with the SBC group where frequencies were respectively 3.7% and 96.3% for bilateral and unilateral breast cancer respectively (Table 2).

Table 2: Association between family history and clinical parameters of breast cancer in Ibn Rochd Oncology Center, Morocco, 2009.

Variable	FBC	SBC	RR (95%CI)	p value
Mean age at diagnosis (years)	44.2 (SD=9.4)	47.7 (SD=10.9)	-	**0.0024**
Mean age at menarche (years)	13.35 (SD=1.65)	13.62 (SD=1.59)	-	0.1192
Mean age at first delivery (years)	23.70 (SD=5.69)	23.04 (SD=5.88)	-	0.2965
Nulliparious	29 (27.6%)	121 (26.1%)	1	
Parious	76 (72.4%)	344 (73.9%)	0.93 (0.63-1.37)	0.7362
Menopausal status				
Postmenopause	44 (41.9%)	264 (56.8%)	1	
Premenopause	61 (58.1%)	201 (43.2%)	1.62 (1.14-2.31)	**0.0064**
Oral contraceptive use				
No	41 (39.04%)	216 (46.5%)	1	
Yes	64 (60.9%)	249 (53.5%)	1.28 (0.89-1.82)	0.1714
Tumor localization				
Unilateral	101 (96.2%)	448 (96.3%)	1	
Bilateral	4 (3.8%)	17 (3.7%)	1.03 (0.42-2.54)	0.9396

FBC: familial breast cancer; SBC: sporadic breast cancer; SD: standard deviation, RR: relative risk

On histological examination (Table 3), invasive ductal carcinoma was identified as the predominant histological type in both groups (93.3% and 90.9% respectively). Invasive lobular carcinoma represented 4.8% in FBC group and 4.3% in SBC group. The tumor sizes T2, T3 and T4 were observed in patients of FBC group with frequencies of 47.6%, 15.2% and 18.1% respectively. Tumors with SBR grade III were found in 43.8% of FBC patients and 26.7% of SBC cases: this observed difference is statistically significant (RR = 2.43, 95% CI 1.16-5.10, P = 0.0185). Similarly, the lymph node involvement was observed in 72.4% of FBC group vs 58.9% of SBC group, with a statistically significant difference (RR = 1.57, 95% CI 1.06-2.32, P = 0.0237).

The results pertaining to hormonal status (Table 3) showed that the expression of estrogen receptor (ER) revealed no significant difference between FBC and SBC. groups. However, the expression of progesterone receptors (PR) showed a significant difference. It was shown that FBC cases had more PR- tumors (53.3%) than SBC patients (42.2%) (RR = 1.44, 95% CI 1.02-2.03, P = 0.0380).

Table 3: Association between family history and pathological characteristics of breast cancer in Ibn Rochd Oncology Center, Morocco, 2009

VARIABLES	Family history		Total	RR (95%CI)	p value
	FBC	SBC			
Histological type					
InSitu	0 (0%)	3 (0.6%)	3 (0.5%)	1	
Invasive ductal carcinoma	98 (93.3%)	423 (90.9%)	521 (91.4%)	1.50 (0.11-20.30)	0.7561
Invasive lobular carcinoma	5 (4.8%)	20 (4.3%)	25 (4.4%)	1.69 (0.11-25.10)	0.7022
Others	2 (1.9%)	19 (4.1%)	21 (3.7%)	0.90 (0.05-15.61)	0.9476
Tumor size					
T1	20 (19.04%)	95 (20.4%)	115 (20.2%)	1	
T2	50 (47.6%)	219 (47.1%)	269 (47.2%)	1.06 (0.66-1.71)	0.7817
T3	16 (15.2%)	68 (14.6%)	84 (14.7%)	1.09 (0.60-1.98)	0.7641
T4	19 (18.1%)	83 (17.8%)	102 (17.9%)	1.07 (0.60-1.89)	0.8129
SBR grade					
I	7 (6.7%)	56 (12.04%)	63 (11.05%)	1	
II	52 (49.5%)	285 (39.8%)	337 (59.1%)	1.38 (0.66-2.91)	0.3856
III	46 (43.8%)	124 (26.7%)	170 (29.8%)	2.43 (1.16-5.10)	**0.0185**
Node involvement					
N-	29 (27.6%)	181 (38.9%)	210 (36.8%)	1	
N+	76 (72.4%)	274 (58.9%)	350 (61.4%)	1.57 (1.06-2.32)	**0.0237**
Estrogen recptors status					
ER+	62 (59.0%)	285 (61.3%)	347 (60.9%)	1	
ER-	43 (41.0%)	180 (38.7%)	223 (39.1%)	1.07 (0.76-1.53)	0.6701
Progesterone recptors status					
PR+	49 (46.7%)	269 (57.8%)	318 (55.8%)	1	
PR-	56 (53.3%)	196 (42.2%)	252 (44.2%)	1.44 (1.02-2.03)	**0.0380**

FBC: familial breast cancer; SBC: sporadic breast cancer, RR: relative risk

DISCUSSION

Family history is an important risk factor for breast cancer (14, 15) with a relative risk association with the number of affected individuals, their age at diagnosis and the degree of relationship. It is well known that 10-30% of women with breast cancer have a relative with the same disease (6). In our study, 18.4% of the patients had a positive family history of breast cancer.

The results of our study indicate that FBC women were diagnosed at an early age. This finding supports the results of previous research which found a younger mean age in patients with a family history of breast cancer (16-18).

Moreover, family history of breast cancer has been variously appreciated in a series of young Moroccan women with breast cancer. Among women less than 35 years of age, 20.6% patients reported a family history of breast cancer (19). We observed that premenopausal women are more present among familial cases. Similarly, other reports noted a significantly higher frequency of premenopausal women among the FBC patients (20, 21). For these reasons, FBC patients should benefit more often from earlier detection through screening and surveillance.

Breast cancer is a hormone-dependent cancer, and the influence of hormonal factors on the familial risk of this disease has been widely studied (22). Our study has showed no significant difference between familial and sporadic breast cancer cases in terms of age at menarche, age at first delivery, parity and oral contraceptive use. This finding is inconsistent with some previous studies (23-26) but not in accordance with others (27-29). Indeed, Olsson and Bladström (30) suggested that reproductive factors tend to operate differently in women with or without family history. They reported that first full-term pregnancy before the age of 20 appears to offer significant protection in the family history group. The Nurses' Health Study found a little protection of later age at menarche; however, no protection was observed concerning multiparity and early age at first birth among women with positive family history (29). Hirose et al. (31) observed little modification of the effects of reproductive factors among women with positive family history of breast cancer; they found that multiple births and earlier age of childbirth demonstrated protective effects in this group of women. In addition, Israeli et al. (32) observed that patients with family history had used more oral contraceptives. Accordingly, in a large cohort study, Silvera et al. (33) found out that a relatively long duration of oral contraceptive use may be inversely associated with the risk among women with a family history of breast cancer.

Regarding tumor localization, our results showned no significant difference between familial and sporadic groups although there are some studies stating that bilateral carcinoma was diagnosed more frequently in patients with family history (13, 32).

Moreover, our histologic findings do not vary according to family history of breast cancer. As expected, ductal carcinoma is the most common histological form in both groups. In previous publications, invasive lobular carcinoma was believed to be more associated with family history of breast cancer (34, 35). In our study, a slightly higher rate of this histological subtype was observed in patients with family history though not statistically significant.

In agreement with others (11,12,32,36), we did not find significant difference in relation to tumor size between FBC and SBC patients, while Colditz et al. (37) found a higher proportion of T1 tumors in patients with positive family history.

The SBR grade and the absence or presence of axillary lymph node involvement is also powerful prognostic factors in primary breast cancer. In our series, high grade tumors with lymph node involvement were predominant in women with family history, with a significant statistical difference. Similarly, some studies reported that familial cases were more likely to have tumors with lymph node metastasis (38), a higher rate of proliferation (17) and a high grade (38). This, however, is not consistent with other author's findings (11, 12).

Concerning the expression of hormone receptors, it is established that estrogen and progesterone play a role in the development of mammary tumors. The hormone receptor status is classified as a major prognostic factor of breast cancer where the negativity is associated with poor prognosis (390). In this study, we observed that the expression of ER was similar between FBC and SBC groups-a finding that is similar with some previous studies (40, 41). However, Molino et al. (18) reported that breast cancer patients with a positive family history were more likely to have ER+ tumors. On the other hand, our data indicated a positive association between PR- and family history of breast cancer. This result was consistent with those reported by Fukutomi and Akashi-Tanaka (41) who found that the expression of PR was significantly lower in cases of familial breast cancer compared to sporadic cases, especially among patients of over 60 years. Similarly, D'Eredita et al. (42) reported that the expression of PR is statistically lower

among familial cases especially in patients over 50 years, whereas the expression of ER was similar in both groups. Moreover, Govindan et al. (43) indicated that the PR gene polymorphism may be considered a risk marker for predisposition to breast cancer.

In this first approach, we attempted to estimate the effect of family history on clinicopathological characteristics of breast cancer in Morocco. However, we should note that our study had some limitations. The main limitation was reduced statistical power due to the sample size which was relatively small compared to the population size and to some existing data. The second limitation is lack of some clinical and pathological data leading to exclusion of some cases that fit our criteria. Another limitation of this study was the absence of certain information including the BReast CAncer susceptibility gene 1 (*BRCA1*) and BReast CAncer susceptibility gene 2 (*BRCA2*) status of familial cases. Therefore, the results should be interpreted cautiously and may not be generalized. Thus, a larger scale study utilizing more accurate data is needed to confirm our findings. Furthermore, molecular analyses involving *BRCA1* and *BRCA2* genes of these patients may be more informative.

In conclusion, very little information exists about clinicopathological features of familial breast cancer Ethiopia. Our initial findings support that familial breast cancer seems to affect young women and tends to present high grade tumors with lymph node involvement and absence of progesterone receptors. These preliminary results may be useful as clinical marker to identify familial breast cancer allowing the development of careful follow-up for this patients subtype. Moreover, our study has the potential to trigger further research into the area of hereditary breast cancer in Morocco and other African countries.

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