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Research Article

FAMILY HISTORY AND AGE OCCURRED OF BREAST CANCER IN THE TRIPLE NEGATIVE PATIENTS OR NON-TRIPLE NEGATIVE: EXPERIENCE CENTER MOHAMMED VI FOR THE TREATMENT OF CANCER CHU IBN ROCHD CASABLANCA

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ABSTRACT

Breast cancer is the most frequent women cancer and is their first cause of cancer death. . This cancer is mostly sporadic, but familial aggregation was found in about 20% of cases. It is a heterogeneous disease with several subtypes.

This is a cross-sectional study gathering 1277 breast cancer cases supported between 2013 and 2014 at the Mohammed VI Center for the treatment of cancers. The statistical analysis was made by the Epi Info software.

The average age of patients was 50.2 ± 11,34ans (17-93 years). The notion of family history of breast cancer was in 13.5% of cases. Triple negative molecular profile was in 16.4% of cases and 83.6% were non-triple negative. The age of breast cancer occurred was younger in cases with a family history of breast cancer (48.5 ± 10.5 years vs. 50.4 ± 11.4 years) than patients without family history ($p = 0.03$). TN patients showed a younger age (47.9 ± 11.7 years versus 50.0 ± 10.9 years) than non TN patients ($p = 0.03$).

A family history of breast cancer has been proposed as one of the most important predictor of hereditary breast cancer. The TN breast cancers are associated with a worse prognosis and represent 16.4% of cases in our center.

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INTRODUCTION

Breast cancer is the most common cancer in women and is the leading cause of cancer death in women (Isaac and al., 2006). It is a highly heterogeneous disease. These cancers are mostly sporadic, without other cases in the family, but a familial aggregation was found in about 20% of cases (Collaborative Group, 2001). A family history is one of the most important risk factors for breast cancer development. Women with breast cancer history of first degree are twice as likely to develop breast cancer compared to women without breast cancer history. The risk is higher when the antecedent has a younger age at diagnosis (Bevier and al., 2012; Pharoah and al., 1997). Contemporary management of breast cancer has evolved since the advances in molecular biology. This cancer has become a heterogeneous disease with several subtypes according to the presence or absence of hormone receptors, and amplification or not the HER2/neu gene, excluding growth factors.

Perou and al. (2000) were the first to propose a classification of breast cancer based on the gene expression profile. Tumors that do not express the hormone receptor and do not overexpress HER2 gene are called "triple negative" (TN) (Ko et al., 2010). Breast triple negative cancer accounts for around 12-17% of all breast cancers (Billarand al., 2010, Boisserie-Lacroix and al., 2013.). This is a very heterogeneous group of tumors both at the genomic, transcriptomic morphological, clinical and prognostic levels (Whitman and al., 2010, Hamilton and Kopin, 2013). TN tumors are generally characterized by a poor prognosis with a frequency of metastases and risk of regional or distant recurrence (Greenup and al., 2013). In clinical

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practice, TN phenotype of breast cancer should suggest the possibility of a particular genetic mutation of the BRCA1 gene, particularly since it is a young patient with or without a family history presence. The breast TN cancers are more common in younger women, premenopausal, age 40 (Broisserie-Lacroix and al., 2014). In an oncogenetics investigation, even in the absence of family history, a BRCA mutation research must be proposed in case of TN before age 50.

The objective of this study is to compare the age of occurred of cancer, clinical, pathological features and family history of breast cancer in the triple negative patients and non-triple negative treated at the Mohammed VI center for cancers treatment.

Patients and Methods

Type of study

This is a cross-sectional study conducted at the Mohammed VI center for the treatment of cancers IBN ROCHD Hospital (One of the two major centers for the care and treatment of cancers in Morocco).

Study Population

We reviewed retrospectively and descriptively all breast cancer cases supported the Centre from 01 January 2013 until 31 December 2014. Data collection was done retrospectively, from patient medical records.

The data collected focused on

- socio-demographic data: age at diagnosis, marital status, number of children, smoking, use of oral contraceptives, menopause and the notion of family history breast cancer.
- Clinical data: The stage at diagnosis, tumor size, lymph node involvement, remote metastasis, histological type, histological grade, laterality with quadrant or tumor region, the hormone receptor status, HER2 Receptor (Human Epidermal growth factor) and proliferation index Ki-67.
- Therapeutic Data: neoadjuvant chemotherapy, radiotherapy, adjuvant chemotherapy, hormone therapy and targeted therapy.

The immunohistochemical profile of the tumor was performed on the basis of anatomical and biological findings, based on the evaluation of estrogen and progesterone receptors, HER2 overexpression and proliferation index Ki-67. These receptors are considered positive when more than 10% of cells are labeled; the HER2 receptor has a score of 3+ and the proliferation index when more than 14% of cells are labeled.

According to the different phenotypes, obtained phenotypic, two groups were defined: The triple negative or basal like (ER, PR-, HER2-) and non-triple negative (luminal A (ER + and / or PR +, HER2 and Ki67 <14), luminal B (ER + and / or PR +, HER2 and Ki-67> 14 or ER + and / or PR +, HER2 +), HER2 Positive (ER-, PR-, HER2 +)).

Statistical Analyses

Data entry was conducted by Microsoft Office Excel (2007) and analysis of variables by the Epi Info software. The study association by crossing the variables between groups was evaluated by the test of chi-square. The test is considered significant when $p < 0.05$.

RESULTS

A total of 1 277 patients diagnosed with breast cancer have been taken care of in Mohamed VI Center for cancer treatment during the two years of the study. Almost all of the patients were females (99.5% of all cases with a average age of 50.2 ± 11,34 years with extremes of 17-93 years).

32.5% of patients were menopaused at the time of diagnosis. 28.6% used oral contraceptives. Parity averaged 2.66 ± 2.28 children. The concept of a family history breast cancer was observed in 13.5% of cases, 48.3% of cases of the first degree, 25.0% of the second degree and 26.7% of the third degree (Table 1).

Table 1 Socio demographic and clinic pathological characteristics of patients

Characteristics	Percentage (%)
Average Age	50,20 ±11,3 years (17-93)
Average age at first pregnancy	23,6±6,5 years
Average age of menopause	49,1±5,9 years
Oral contraceptives	
Yes	19,0
No	7,6
Menopause Status	
Yes	32,5
No	67,5
Family history of Breast cancer	13,5
1st degree	48,3
2nd degree	25,0
3rd degree	26,7
Size of Tumor	
T1	37,8
T2	37,6
T3	10,4
T4	12,8
Lymph node metastasis (N)	
N0	50,6
N1	24,7
N2	15,1
N3	9,6
Metastasis at distance (M)	
M0	92,6
M1	7,4
Histological Type	
Infiltrating ductal carcinoma	
Invasive carcinoma	80,3
Invasive lobular carcinoma	7,6
infiltrating	4,6
medullary carcinoma	1,1
Other	6,4
Œstrogens Receptors	
Positive	55,9
Negative	19,9
Progesterone Receptors	
Positive	49,6
Negative	26,4
HER2 Receptors	
Positive	24,1
Negative	75,9
Triple negative	
Yes	16,4
No	83,6

In our series, the hormone receptor positivity was 55.9% to oestrogen and 49.3% to progesterone. Her2 is over expressed in

24.1% of cases. Triple negative molecular profile was found in 16.4% of cases and 83.6% were non-triple negative.

In 13.5% of cases with a family history of breast cancer, 23.3% were triple negative, 76.7% of non-triple-negative cases versus 15.3% of triple-negative cases and 84.7% non-triple negative case in patients with no family history of breast cancer with p =0.02.

Stage at diagnosis was earlier (I and II) in cases with a family history, 65.1% of patients versus 55.7% of late cases (III and IV) in patients who do not have a history of breast cancer with p = 0.02. By crossing the stage with the profile, it was early in 63.7% of triple-negative cases and late in 44.8% of cases in non-triple non-negative with p = 0.03. Distant metastasis was observed in 6.0% of non-triple negative case versus 0.3% of triple negative case with a p = 0.02.

The most common histological type was invasive ductal carcinoma and was observed in 80.3% of cases, followed by invasive carcinoma in 6.3%, invasive lobular carcinoma in 4.6% and other rare locations (medullary carcinoma infiltrating, infiltrating papillary carcinoma, mucinous carcinoma, micropapillary carcinoma, carcinosarcoma, ...) in 7.4% of cases. Infiltrating ductal carcinoma was more frequent in non triple-negative cases in 84.6% of cases versus 80.1% of non-triple-negative cases. On the other hand, rarest types were frequent in triple negative cases in 6.8% of cases, versus 3.6% with a p = 0.04. Regarding the histological grade (SBR Scarff-Bloom-Richardson), the most common in our sample is the SBR grade II in 54.0% of cases, followed by SBR grade III in 31.9% of cases, the grade I had noted in 3.9% of cases. By crossing histological grade with the tumor phenotype, high grade (SBR III) was found in 47.3% of cases in the triple negative, for cons, a medium grade (SBR II) was observed in 60.7% cases among non-triple negative with p <10-3.

The intersection of family history research with the age of occurred of breast cancer revealed that the age of breast cancer occurred was younger in cases with a family history breast cancer (48.5 ± 10.5 years vs. 50.4 ± 11.4 years for patients without a family history breast cancer with p = 0.03). By observing based on the phenotype of the tumor, the triple negative patients had a younger age (47.9 ± 11.7 years versus 50.0 ± 10.9 years for non-triple negative patients with a p = 0.03).

Table 2 The breast cancer occurrence of the tumor phenotype by Age and family history of breast cancer.

	Age (years)	P value
Family history of breast cancer		
OUI	48,5±10,5	0,03
NON	50,4±11,4	
Triple negative profile		
OUI	47,9±11,7	0,03
NON	50,0±10,9	

DISCUSSION

A family history is one of the most important risk factors for breast cancer development. Women with a first-degree history of breast cancer are twice as likely to develop breast cancer compared to women without breast cancer history. The study of genomic expression profiles provided a molecular classification of disease in clinically relevant subgroups.

In this study, we collected 1277 cases of breast cancer supported by Mohammed VI center for the treatment of cancers; almost all were female in 99.5% of cases. In our series, the notion of family history was found in 13.5% of cases. According to the literature, the frequency of breast cancer with a family history of breast cancer varies from 15 to 20% (Colditz and al., 1993). Several authors report that frequency; moreover, Jacobi and al.,(2003) showed that 13.0% of cases of familial cancer, including 64.3% of cases are of the first degree and 34.7% of cases are of the second degree (Jacobi and al., 2003).

The frequency of 13.4% was also observed by Molah and colleagues (2015). In the Swedish familial cancer data, 16.0% of women with breast cancer had a breast cancer history of first degree (Kharazmi and al., 2012). A family history of breast cancer has been proposed as one of the most important predictors of hereditary breast cancer (Evans and al., 2002). In our series, hormone receptor positivity was noted to estrogen in 55.9% of cases and progesterone in 49.3% of cases, 16.4% were triple negative and 83.6% of non-triple-negative cases. Our results are similar to those of the literature that TN breast cancer accounts for 12-17% of all breast cancers (Millikan et al., 2008, Foulkes and al., 2010.).

TN Breast cancers are more common in younger women, premenopausal, before age 50 (Beaur and al., 2007). Our study revealed that TN have a younger age compared to non TN tumors (47.9 ± 11.7 versus 50.0 ± 10.9 with p = 0.03). According to the literature, some authors even report an age below 40 years. Moreover, Bauer and al. (2007) conducted a large cohort case-control study of 6370 cases of TN breast cancer compared 44.704 cases of non TN that TN cancer was more common among young women under 40, with an OR 1 , 53 (95% CI 1.37 to 1.7). Similar results were reported by Millikan and al. (2008) in a large cohort study, case-control study of 1424 breast cancer compared to 2022 controls (The Carolina Breast Cancer Study), after adjustment for ethnic groups, the prevalence of TN phenotype of cancer was nearly 5 times greater among women less than 40 years (OR = 4.5; 95% CI 2.7 to 7.3). Similar results were also observed by Carey and al. (2006). The TN breast cancers are associated with a worse prognosis, with more risk of distant metastasis, local and regional recurrences (Bauer and al., 2007). In our study, distant metastasis was observed in 17.2% of cases in TN and 5.4% of cases among non-TN with P = 0.02.

TN breast cancers form a morphologically heterogeneous entity. Infiltrating ductal carcinoma was more frequent in non triple-negative cases in 84.6% of cases versus 80.1% of non-triple-negative cases. However, the other rare types were frequent in triple negative cases in 6.8% of cases compared to 3.6% with a p = 0.04. Our results are consistent with those described in the literature, that the non-specific cell carcinoma and other rare locations are the most common in TN (Broisserie-Lacroix and al., 2014). The majorities of the TN tumors are tumors with high histological grade and a high proliferation index (Carey and al., 2006). In our series, SBR grade III was found in 47.3% of cases in TN by against an average grade SBR II in 60.7% of cases among non TN with p <10-3. There are some TN, which are low-grade, low proliferative secreting such as carcinomas and adenoid cystic carcinomas (Bauer and al., 2007). However, large differences

in the clinical presentation, of evolutionary profile, response to treatment, regional and general prognosis reflects the heterogeneity of TN tumors.

In our series, the study of family history with the age of occurred of breast cancer revealed that the age of breast cancer onset was younger in cases with a family history of breast cancer (48 5 ± 10.5 years vs. 50.4 ± 11.4 years for patients without a family history breast cancer with p = 0.03). Similarly, at diagnosis, the stadium was early (I and II) in cases with a family history, 65.1% of patients versus 55.7% of late cases (III and IV) in patients who do not have a family history breast cancer with p = 0.02. However, knowledge of a high family risk allows to evidencing a specific and early screening. Recent studies published by Kharazmi and al. (2016) showed that patients with a family history were younger (<40 years) and diagnosed at an earlier stage of diagnosis.

CONCLUSION

Breast cancer is a complex and heterogeneous disease associated with clinical, pathological and biological causes that differs from a population to another. The TN breast cancers are associated with a worse prognosis and represent 16.4% of cases in our center.

Family history of breast cancer has proved to be as one of the most important predictors of hereditary breast cancer. Our data are consistent with the literature emphasizing that patients with breast cancer family are diagnosed at an early age.

Conflict of interest

The authors declare that there are no conflicts of interest.

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