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Clinical and Pathological Characteristics of *BRCA2* Positive Breast Cancer in Egyptian Female Patients

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ABSTRACT: Mutations in the *BRCA1* and *BRCA2* genes confer greater risk of developing breast cancer. Early age at onset is generally considered an indicator of genetic susceptibility to breast cancer. We determined whether tumor pathologic features and clinical features differ in patients with and without *BRCA2* mutations, the study was carried out on thirty breast cancer patients, divided as fifteen with familial breast cancer and fifteen with sporadic breast cancer. Seven cases of the familial breast cancer patients showed *BRCA2* mutaion. According to this study, there was statistically significant negative correlation between frequency *BRCA2* gene mutations and female age, there was negative correlation between *BRCA2* gene mutations and ER receptor, PR receptor and HER2/neu status (positivity and negativity) and positive correlation between gene mutations and the pathological grade of the tumor. However, this correlation did not reach a significant level. Three of the seven *BRCA2* patients weRe of triple negative molecular type (from total 5patient had triple negative type among the thirty patients). The ER positive *BRCA2* patients were mainly luminal B.

KEYWORDS: Breast cancer, molecular type, *BRCA2* gene, hormonal receptors.

I. INTRODUCTION

Mutations in the tumor suppressor genes *BRCA1*and *BRCA2* are believed to be responsible for the majority of hereditary breast cancer cases. It is estimated that women with *BRCA1* and *BRCA2* mutations have a lifetime risk of developing breast cancer as high as 87% [1].Breast cancer is a heterogeneous disease including several entities with different clinical behavior. Even tumors belonging to the same histological type can have different clinical course. Naturally, the largest group (ductal cancer) shows the highest heterogeneity. Additional information can be obtained from molecular subtyping of breast cancer and results in breast cancer classification into subgroups with different biological properties and response to treatment [2]. Despite enormous efforts to develop novel biomarkers of tumor behavior there have been few advancements beyond the use of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) in diagnostic practice [3].

II. MATERIALS AND METHODS

This prospective study was performed at biochemistry and pathology department, Benha University hospital. The study was carried out on thirty Egyptian females divided into two groups as fifteen female patients without a family history of breast &/or ovarian cancers and fifteen female patients with a family history of breast &/or ovarian cancers. Consents were taken from the subjects after being informed the aim of the study, full history was taken (Age, marital status, contraception and family history). All patients included were diagnosed to have invasive breast carcinoma. 5ml of venous blood from each subject were collected on tube containing EDTA, the sample mixed well and stored at -80 for further processing. DNA was extracted from the blood using G-spin™ Total DNA Extraction Mini Kit – (iNtRON

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Biotechnology, INC. - Korean Biotech Database). PCR was done for amplification of mutations in *BRCA2* gene [4]. Gel electrophoresis was done for separation of DNA bands; the bands were stained with ethidium bromide [5, 6]. Formalin fixed paraffin embedded sections of breast lesions were retrieved from the department of histopathology; H&E (Haematoxylin-Eosin) stain was done, for histopathological examination typing, histologic grading [7] and TNM pathologic staging [8]. Formalin fixed paraffin embedded tissue blocks of the primary tumor tissues were evaluated for the expression of ER, PR and HER2/neu by Immunohistochemistry IHC [9, 10].Statistical pacckage for social science (SPSS) and Microsoft Office Excel were used for data processing and data analysis. For all the tests, a p value of 0.05 or less was considered for statistical significance.

III. RESULTS

Clinical characteristics of the patient group are shown in table 1.

Table 1: Clinical characteristics of 30 breast cancer patients.

Patient	Tumor		Receptor status		Lymph node metastasis	Pathological type
	Stage	Size(cm)	ER	PR		
1	I	2x1.5x1.5	+++	+++	No	ILC
2	I	2x1.5x1.8	++	++	No	IDC
3	I	1.5x1.5x1.3	_	_	No	IDC
4	I	2x1.5x1.4	_	_	No	IDC
5	II	2x1.5x1.7	+++	+++	1/21	IDC
6	II	3x2.5x2	+++	++	No	IDC
7	II	1.5x1.5x1.8	++	+++	2/17	IDC
8	II	2x1.5x1.5	+	+	1/22	IDC
9	II	3x4x2.7	++	++	No	IDC
10	II	2x1.5x1.5	+	+	2/19	IDC
11	II	1.8x1.8x1.5	_	_	1/21	IDC
12	III	4x3+3x2.5	+	+	5/13	ILC
13	III	6x4x3.7	+++	+	5/25	ILC
14	III	4x3x2.3	+	++	6/28	ILC
15	III	7X6.5x5.5	+++	+++	10/23	IDC
16	III	7x6x5.5	+++	+	2/33	IDC
17	III	4x3.5x3.1	+++	+++	17/20	IDC
18	III	4x3.8x3	+++	+++	6/30	IDC
19	III	4x3x2.5	+	+	5/24	IDC
20	III	7x6x5.5	++	+	2/24	IDC
21	III	3.5x3.5x3	+	+++	9/31	IDC
22	III	3x2x1.5	+	+	13/33	IDC
23	III	6x5.8x5.5	+	+	3/17	IDC
24	III	3x3x2.7	++	+++	17/24	IDC
25	III	4x3.4x3.2	++	++	9/23	IDC
26	III	7x6.5x6.2	_	_	7/23	IDC
27	III	6x4.5x4	_	_	15/34	IDC
28	IV	5x4.5x4.3	++	+	21/32	ILC
29	IV	7x6.8x6	+	++	17/21	IDC
30	IV	5x3.5x3	+	++	3/17	IDC

IDC : Invasive ductal carcinoma , ILC: Invasive lobular carcinoma

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The age at diagnosis of *BRCA2* mutation carriers ranged from 32 to 48 years of age. The mean age at diagnosis for *BRCA2* carriers was 40 years whereas for non *BRCA2* carriers was 48 years. The majority of *BRCA1*-associated tumors were triplenegative. ER positive tumors in *BRCA2*-associated tumors were mainly luminal B, while for non *BRCA2* tumors it was mainly of luminal A subtype. The majority of *BRCA2*-associated tumors were grade II/III (86%).
There was statistically significant negative correlation between frequency *BRCA2* gene mutations and female age in the studied groups, r = -0.42, p<0.05 (figure1).

Figure 1: Correlation coefficient (r) between age and *BRCA2* gene mutations in the breast cancer groups.

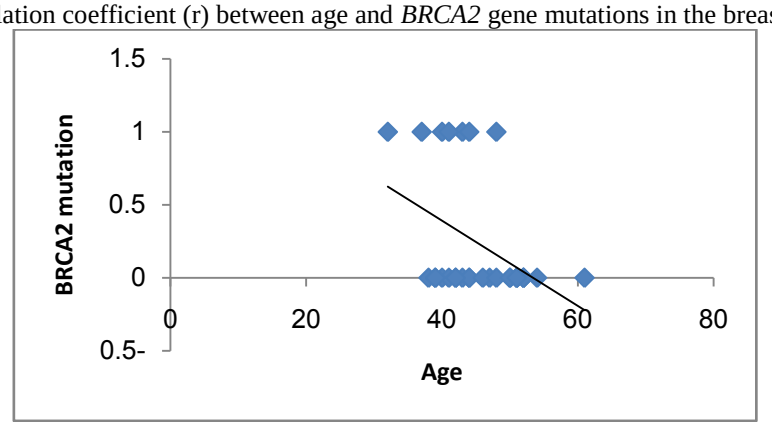

Figure 2: Correlation coefficient (r) between ER status and *BRCA2* gene mutations among patients with breast cancer.

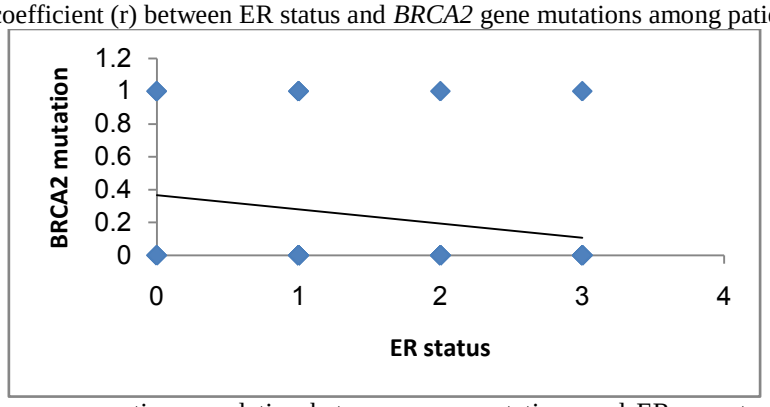

Figure2 shows that there was negative correlation between gene mutations and ER receptor status in patients with breast cancer groups with and without family history. However, this correlation did not reach a significant level. r = -0.21 and p>0.05

Figure 3: Correlation coefficient (r) between PR status and *BRCA2* gene mutations among patients with breast cancer.

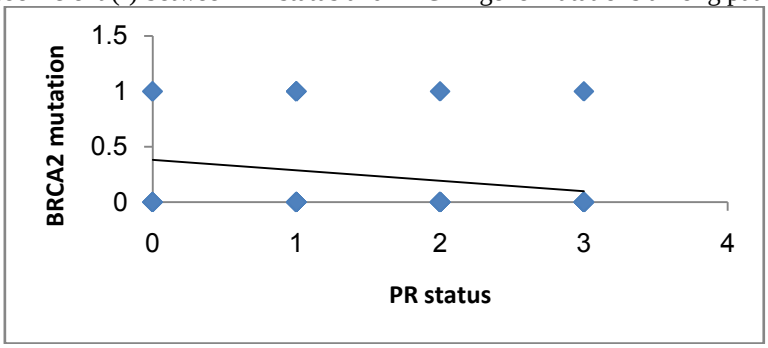

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Figure 3 shows that there is negative correlation between gene mutations and PR receptor status in patients with breast cancer groups with and without family history, however this correlation did not reach a significant level. r = -0.22 and p>0.05.

Figure 4: Correlation coefficient (r) between pathological grade of the tumor and *BRCA2* Gene Mutations Among Patients with Breast Cancer.

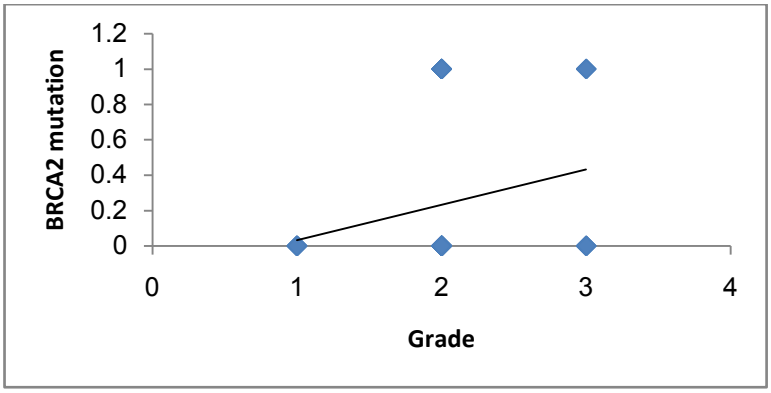

Figure 4 shows that there is positive correlation between gene mutations and pathological grade of the tumor in patients with breast cancer groups with and without family history. However, this correlation did not reach a significant level. r = 0.27 and p p>0.05.

IV. DISCUSSION

In this study, we identified clinical and pathologic characteristics of tumors in women with*BRCA2*-positive and*BRCA2*-negative breast cancer. According to this study, there was statistically significant negative correlation between frequency *BRCA2* gene mutations and female age in the studied groups. This also was found by Eerola et al (2005) [11]. However, studies demonstrate that *BRCA2* mutations were mostly found in breast cancer patients with disease diagnosis before the age of 50 years. Moreover, in cases with familial clustering of site-specific breast cancer, *BRCA2* mostly accounted for tumors diagnosed before age 40 years [12].

In this study we found that there was negative correlation between *BRCA2* gene mutations and ER receptor, PR receptor and HER2/neu status (positivity and negativity) and positive correlation between gene mutations and the pathological grade of the tumor in patients with breast cancer groups with and without family history. However, this correlation did not reach a significant level.

Previous reports describing the distribution of ER, PR, and HER-2/neu positivity in *BRCA* carriers have been inconclusive, mainly because in these studies, *BRCA1* and *BRCA2* mutation carriers were grouped together instead of being examined as two distinct groups [13]. However, some previous studies concluded that in comparison with non familial breast cancer group, the *BRCA2* cancers were more receptor-negative [14]. The frequency of ER-positive cancers among our non *BRCA2* cancers is quite high, which might be due to a later year of diagnosis than for *BRCA2* cancers and in general because of age distribution [14]. In this study triple negative cancers were associated with presence of *BRCA2* mutation and that ER positive tumors were mainly of luminal B subtype, and 86% of *BRCA2* positive tumors were of II and III pathological grade, this is in accordance to studies have demonstrated that breast carcinomas in younger or premenopausal women are more likely to exhibit biologic and prognostic features that are known to be associated with a high histologic grade, such as an absence of steroid hormone receptors, It has been hypothesized that this adverse pattern of prognostic indicators and the poorer clinical outcome of younger, premenopausal patients were secondary to the greater proportion of higher grade carcinomas found in these women [14]. However, some previous studies revealed results not similar to this study as they concluded that the pathology of *BRCA2*-related breast cancer was similar to that of *BRCA*-negative breast cancers [15, 16], also researches has demonstrated that *BRCA2*-associated breast cancers and sporadic breast cancers are equally likely to be triple negative [17] or to have tumor pathology similar to sporadic cases [18]. One previous study suggested that *BRCA2*-related cancers have tumor pathology that is between that of *BRCA1* and sporadic cancers [19].

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V. CONCLUSION

We concluded from this study that *BRCA2* tumors is associated with aggressive behavior and early onset tumors, further broad based studies are recommended on larger samples to identify markers indicating high possibilty of presence of gene mutations.

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