Effect of Family History on Clinical and Pathological Characteristics of Breast Cancer: a Hospital-Based Study in Egypt

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Running title: Familial and sporadic breast cancer

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Abstract:

Background: Breast cancer is the most common female malignancy. The family history of breast cancer increases the risk of the disease**.**

Objectives: To assess the frequency of familial breast cancer among breast cancer patients attending oncology outpatient clinics in Menoufia University Hospital and to compare the clinical and pathological characteristics of familial and sporadic breast cancer. **Methods:** The study was conducted on 150 women with familial or sporadic breast cancer who were attending oncology outpatient clinics, Menoufia University Hospital for follow up or receiving treatment. The participants were interviewed by predesigned questionnaire to assess risk factors for breast cancer. Data on different characteristics of the tumors were gathered from patients' medical records. **Results:** Familial cases represented 18.7% of studied breast cancer patients. The age of onset seems to be younger in familial breast cancers (P=0.008). Percentage of familial breast cancer cases was significantly more prevalent among premenopausal females (P=0.007). Percentage of studied cases who breastfed their babies, had bilateral breast cancer, had triple negative breast cancer and with larger tumor size (T4) was significantly more prevalent among familial than sporadic breast cancer cases (P=0.023, 0.006, 0.000, 0.000 respectively). About 63% of sporadic cases were among hormonal contraceptive users versus 43% in familial group (P=0.040). There was no significant difference between familial and sporadic groups regarding histological type was observed. **Conclusion:** Familial cases represented 18.7% of studied breast cancer patients. Familial breast cancer seems to affect premenopausal young women and tends to present at the larger size, bilateral and triple negative tumors.

Key words: breast cancer, family history, tumor characteristics.

Introduction:

Breast cancer (BC) is the commonest female malignancy accounting for 22.9% and 37.7% of all female cancers all over the world and in Egypt, respectively .(1) Breast cancer in Egypt seems to have a bad prognosis with 29% mortality. It is the most common cause of death among women with cancer worldwide.(2) The family history of breast cancer increases the risk of the disease, and the risk depends on the number of relatives, type of the tumor and age at diagnosis among relatives who have had breast cancer.(3)

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Genetic predisposition, such as mutations in BRCA1 and BRCA2 genes, probably contribute to increasing risk of subsequent breast cancers, particularly in women diagnosed at a young age.(4) Many studies documented that familial breast cancer has many specific clinical features compared to sporadic cases. Breast cancer cases with positive family history tend to present at younger age, bilateral breast cancer, advanced tumor stage, lymph node involvement and negative hormone receptors with a bad prognosis.(5)

However, other studies found no significant differences between familial and sporadic breast cancer regarding age at diagnosis, histological features, and tumor stage and hormone receptors status. (6)

The family history of breast cancer is considered as a significant risk factor in the etiology of this disease. Based on the above-mentioned view, there was a need to conduct the current study to assess the frequency of familial breast cancer among breast cancer patients attending oncology outpatient clinics in Menoufia University Hospital and to compare the clinical and pathological characteristics of familial and sporadic breast cancer among the studied participants.

Methods:

This study was a cross-section comparative study conducted in oncology outpatient clinics of Menoufia university hospital, Menoufia Governorate, Egypt. It was carried out throughout the period from February 2016 to September 2016.The sample size was calculated based on the familial breast cancer prevalence 5 – 10% (7) and a number of registered breast cancer patients in Oncology outpatient clinics, Menoufia University Hospital which was 1500 **(** obtained from Oncology outpatient clinics records, 2015). Using online Raosoft sample size calculator, at 95% confidence level and 5% margin of error, the sample was estimated to be 115 and increased to 148 to avoid data loss.

The study included previously diagnosed breast cancer patients attending outpatient oncology clinic for follow up or receiving treatment. Male patients were

excluded. An interview was conducted with each participants using a pre-designed validated questionnaire to obtain information about different clinical characteristics related to breast cancer including age at diagnosis, age at menarche, parity, breastfeeding history, menopause status, and contraceptive history.

A detailed medical record review was done to obtain data about clinical and pathological characteristics of breast cancer among the studied cases (tumor localization, histological type, tumor size, lymph node involvement, pathological stage and hormone receptor status). The studied cases were divided into two groups: Familial Breast Cancer (FBC) including patients with positive family history (n=28) and Sporadic Breast Cancer (SBC) group including sporadic patients without any family history of breast cancer (n=120). The family history was considered as positive when the patient had one or more relative with breast cancer within three generations.

Ethical approval:

The study was approved by the ethical committee of the faculty of medicine, Menoufia University. An official permission letter was obtained from the authorities and directed to local administrators in Oncology outpatient clinics in Menoufia University Hospital. Written consent was taken from each participant in the study after simple clarification of the study objectives and methodology.

Statistical Analysis:

Data were analyzed using Statistical Package of Social sciences (SPSS) software (Statistical Package for the Sociable Sciences, version 20, SPSS Inc. Chicago, IL, USA). Data was expressed through:

Qualitative data were expressed as number and percentage and analyzed by using Chi-squared test(X^2) to detect the relation between different qualitative variable. Quantitative data were expressed as mean $\pm$ SD and analyzed by using Student t-test for comparison of two independent normally distributed quantitative variables.

Results:

This study found that patients with familial breast cancer represent 19% of the studied breast cancer patients (Figure 1). Among cases with FBC; 75% of them have the positive family history in first degree relatives. About 57 % of relatives with BC was diagnosed at 40 -50 years old (Table1). The age of onset appears to be younger in FBC

patients with a mean age of 45.8 years compared to 50.8 years in the SBC patients (P = 0.008). Also, FBCs are more likely to be presented in premenopausal period 78.6% (P = 0.007). However, there was no statistical difference between the two groups as regards mean age at menarche and parity (Table 2).

There was a statistically significant difference between FBC group and SBC group as regard breastfeeding as 65% of the SBC had negative breastfeeding history versus 42.9% in the FBC group (P-value 0.03). There was a statistically significant difference between FBC group and SBC group regarding hormonal contraceptive use as 64.2% of sporadic patients are among hormonal contraceptive users versus 43% in familial group (P=0.038). (Table 2)

Regarding tumor localization; the current study showed that bilateral breast cancer was significantly more prevalent among familial than sporadic breast cancer cases (P=value 0.006) (Table 2).

As regards histological features of the tumor, invasive ductal carcinoma (IDC) was identified as the predominant histological type in both groups (89.3% and 90% respectively). There was a statistically significant difference between FBC group and SBC group regarding tumor size as T4 tumors were observed in patients of FBC group with the frequency of 25% versus 2.5% in patients of SBC group (P=0.001). (Table 3) The results regarding hormonal status had showed that the expression of estrogen receptor (ER), progesterone receptors (PR) and *human epidermal growth factor 2 receptors (Her2)* showed no significant difference between FBC and SBC groups. However, triple negative BC is significantly more prevalent among familial than sporadic breast cancer cases (P=0.001). (Table 3)

Discussion:

Carcinoma of the breast is considered the most commonly diagnosed cancer among females and it is the second leading cause of cancer-related deaths among them.[8,9] One of the major risk factors for breast cancer is the family history of the disease.[10] Out of 150 studied breast cancer cases, 19% had a positive family history of the disease**.** This is in concordance with a study conducted in Morocco by Tazzite et al.[11] who found that the frequency of breast cancer family history among their studied cases

was 18.4%. However**,** Destounis et al.[12] found that out of 388 studied breast cancer patients 39% reported a positive family history of the disease.

In the current study, more than 90% of relatives of FBC patients were diagnosed above the age of 40 years old, this is similar to finding of **Brewer** et al [3] study which found that more than 85% of affected relatives were diagnosed after the age of 45 years old. The present study found statistically significant difference between Familial and Sporadic breast cancer patients as regard mean age at diagnosis; Familial breast cancer women were diagnosed at an early age**.** This is in agreement with results of Tazzite et al [11] and Molino et al study [13] which found a lower mean age in patients with the positive family history of breast cancer**.**

Moreover, a study in Egypt [14] stated that family history of breast cancer has been observed in a series of young Egyptian women diagnosed with breast cancer. About 12% of their cancer patients aged 35 years old and younger. Also, the present study reported a significant difference between familial and sporadic breast cancer patients regarding menopausal status as a percentage of premenopausal women were higher among familial cases**.**

Similarly, Jiang et al study [15] noted a significantly higher frequency of premenopausal women among the FBC patients and they recommended that FBC patients may benefit from screening and surveillance for early detection of the disease. Breast cancer is hormone-dependent cancer, and the effect of hormonal factors -such as breastfeeding and hormonal contraception- on the familial risk of this disease has been previously studied.[16]

This study found statistically significant difference between both groups regarding breastfeeding; as a higher percentage of the sporadic group had negative breastfeeding history**.** This is supported by Lambertini et al. study [17] which confirmed the protective effect of ever breastfeeding against hormone receptor-negative breast cancer, which is more common in younger women. Also, Toss et al [18] found a protective effect of breastfeeding only in triple negative breast cancer which represent only 15% of breast cancer cases and this explains the results of the present study which found that breastfeeding had no protective effect against familial breast cancer.

The present study reported that hormonal contraceptive use was significantly more prevalent among patients with sporadic breast cancer. This is in agreement with a study conducted by Work et al[19] who reported that hormonal contraceptive use was significantly higher among sporadic than familial breast cancer patients, while in contrast to Tazzite et al[11] who reported that there is no significant difference between familial and sporadic cases as regarding hormonal contraceptive use.

This study showed no significant difference between familial and sporadic breast cancer cases as regard age at menarche, age at first delivery and parity. The same finding was reported by results of several studies.[17,18,20] Horn et al [21] explained this finding by the fact that familial breast cancer is more frequently hormone receptor negative tumors, while age at menarche, age at first delivery and parity seems to modify mostly the incidence of hormone receptor-positive tumors.

In the current study; ductal carcinoma is the most common histological form in both groups. This comes in parallel to results of Saxena et al study [22] in New Delhi which revealed that Infiltrating duct carcinoma was the commonest form among familial and sporadic breast cancer patients. However, in previous publications, [23, 24] invasive lobular carcinoma was believed to be associated with family history of breast cancer.

As regard tumor size; the present study showed a significantly higher percentage of T4 tumors in patients with positive family history. This disagrees with Arpino et al [25] who found no significant relation between tumor size and familial or sporadic breast cancer. Also, this study reported that bilateral breast cancer was significantly more frequently in the FBC group. This is inconsistent with Verkooijen et al [26] and Margolin et al [6] who stated that bilateral breast cancer is more likely to be presented in patients with positive family history than those with negative family history.

In the current study, triple negative breast cancer was significantly more prevalent among familial breast cancer cases. These findings were in agreement with a study conducted in Egypt,[27] which reported that triple negative breast cancer is commonly overexpressed in cases with positive family history compared to cases with negative family history. Also, Aysola et al [28] stated that triple negative breast cancer accounts for 15% of all breast cancer cases, with worst prognoses in young African American women.

Conclusion: Familial cases represented 19% of studied breast cancer patients. Familial breast cancer seems to affect premenopausal young women and tends to present at a larger size, bilateral and triple negative tumors. Findings of this study may be helpful to identify familial breast cancer and allow developing a careful follow-up for susceptible patients.

Declaration:

There was no conflict of interest and there were no funding agencies.

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الملخص العربى

تأثير التاريخ العائلي على الخصائص الاكلينيكيه والمرضيه لسرطان الثدي: دراسه بالمستشفى فى مصر

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الخلفية: ان سرطان الثدي هو اكثر الامراض الخبيثة شيوعا بين الإناث. التاريخ العائلي للإصابة بسرطان الثدي يزيد من خطر التعرض لهذا المرض. **الأهداف:** وتهدف هذه الدراسه الى تقييم الخصائص المختلفة لسرطان الثدي في المرضى الذين يعانون من سرطان الثدي العائلي و من لم يكن لديهم تاريخ عائلى للمرض بين المترددين على العيادات الخارجية للأورام في مستشفى جامعة المنوفية. **المنهجية و طرق البحث:**وقد أجريت الدراسة على 150 امرأة مصابة بسرطان الثدي ممن يترددن على العيادات الخارجية لأمراض الأورام، بمستشفى المنوفية الجامعي للمتابعة أو تلقي العلاج. تمت مقابلة المشاركين من قبل استبيان سابق لتقييم عوامل الخطر لسرطان الثدي بالإضافة الى جمع البيانات عن الخصائص المختلفة لهذه الأورام من السجلات الطبية للمرضى. **النتائج:**وقد اظهرت النتائج ان الحالات ذات التاريخ الإيجابى للمرض تمثل 18.7٪ من مرضى سرطان الثدي فى العينة المختارة. و تبين أن الإصابة بسرطان الثدي العائلي يبدأ فى سن مبكر بالمقارنة بمن لم يكن لديهم تاريخ عائلى للمرض. .وكانت النسبة المئوية لحالات سرطان الثدى العائلى أكثر انتشارا بين الإناث قبل انقطاع الطمث. كما أنه وجد بنسبة أعلى بين السيدات اللائى أرضعن أطفالهن طبيعيا، و من كان لديهم سرطان الثدي الثنائي، سرطان الثدي السلبى للهرمونات، وكان حجم الورم الأكبر (T4) أكثر انتشارا بينهم. وكان حوالي43% منهم بين مستخدمي وسائل منع الحمل الهرمونية مقابل63٪ في المجموعة الأخرى . لم يكن هناك فرق ذو مغزى إحصائى بين المجموعتين فيما يتعلق بالنوع النسيجي للمرض. **الخلاصة:** وخلصت الدراسه الى ان الحالات العائلية تمثل 18.7٪ من مرضى سرطان الثدي المدروسة. يبدو أن سرطان الثدي العائلي يبدأ فى الظهور قبل انقطاع الطمث، يتميز بكبر الحجم والأورام الهرمونية السالبة و الأورام الثنائية .

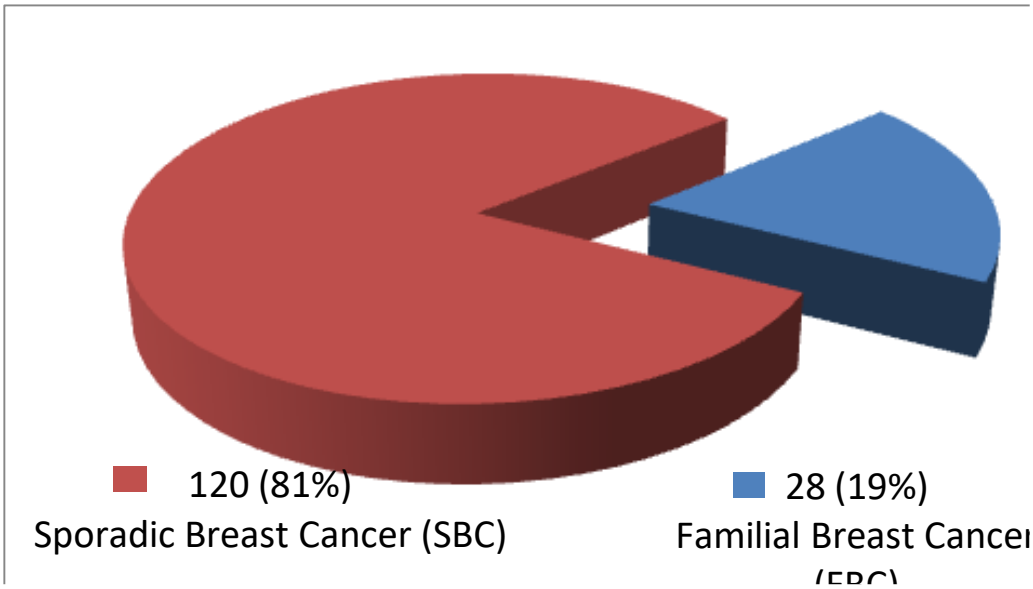

Figure (1): Distribution of breast cancer patients according to breast cancer family history.

Table (1): Breast Cancer history among relatives of patients with familial breast cancer

Breast cancer history in relatives	N(28)	%
Degree of relativity		
▪ First degree relatives	21	75
▪ Second degree relatives	3	10.7
▪ First and second degree relatives	4	14.3
Age at diagnosis in relatives		
▪ 30-40	2	7.1
▪ 40-50	16	57.2
▪ >50	10	35.7

Table (2): Comparison between familial and sporadic breast cancer regarding clinical characteristics related to breast cancer

Clinical characteristics	FBC (N=28)		SBC (N=120)		Total (N=148)		Student t-test	P
	FBC		SBC		Total		X^2	
	N=28	%	N=120	%	N=148	%		
Parity								
▪ Nulliparious	6	21.4	18	15	24	16.2	0.691*	0.406
▪ Parious	22	78.6	102	85	124	83.8		
Breast feeding								
▪ Yes	16	57.1	42	35	58	39.2	4.67	0.030**
▪ No	12	42.9	78	65	90	60.8		
Menopausal status								
▪ Pre-menopause	22	78.6	56	46.7	78	52.7	9.27	0.002**
▪ Post-menopause	6	21.4	64	53.3	70	47.3		
Hormonal contraceptive use								
▪ Yes	12	42.9	77	64.2	89	60.1	4.3	0.038**
▪ No	16	57.1	43	35.8	59	39.9		
Tumor localization								
▪ Unilateral	25	89.3	120	100	145	98	13.6**	0.006**
▪ bilateral	3	10.7	0	0	3	2		
age at diagnosis in years Mean ± SD	45.8 ± 7.9		50.8 ± 11.4		49.9 ± 11		2.738	0.008**
age at menarche in years Mean ± SD	12.3 ± 1.9		12.3 ± 2.3		12.3 ± 2.2		0.110	0.912

FBC: familial breast cancer**; SBC:** sporadic breast cancer

***Fisher exact test** ****statistically significant**

Table (3): Comparison between familial and sporadic breast cancer regarding pathological characteristics of breast cancer

Pathological characteristics	FBC		SBC		Total		X^2	P
	N=28	%	N=120	%	N=148	%		
Histological type								
▪ IDC	25	89.3	108	90	133	89.9		
▪ ILC	3	10.7	10	8.3	13	8.8		
▪ Mixed IDC&ILC	0	0	2	1.7	2	1.3	0.447	0.799
Tumor size								
▪ T1	3	10.7	13	10.8	16	10.9		
▪ T2	10	35.7	74	61.7	84	56.7		
▪ T3	8	28.6	30	25	38	25.7		
▪ T4	7	25	3	2.5	10	6.7	19.8	<0.001**
Estrogen receptors status								
▪ ER+	23	82.1	106	88.3	129	87.2	0.778*	0.378
▪ ER-	5	17.9	14	11.7	19	12.8		
Progesterone receptors status								
▪ PR+	22	78.6	95	79.2	117	79	0.005	0.944
▪ PR-	6	21.4	25	20.8	31	21		
Her2 receptors status								
▪ Her2+	6	21.4	44	36.7	50	33.8	2.3	0.125
▪ Her2-	22	78.6	76	63.3	98	66.2		
Triple negative BC								
▪ Yes	5	17.9	0	0	5	3.4	23.1*	<0.001**
▪ No	23	82.1	120	100	143	96.6		

FBC: familial breast cancer**; SBC:** sporadic breast cancer**; Her2:** human epidermal growth factor 2

***Fisher exact test** ****statistically significant**