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## RESEARCH ARTICLE

### AGE AS AN INDEPENDENT PROGNOSTIC FACTOR IN BREAST CANCER.

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#### Abstract

**Introduction:** Breast cancer is the commonest cancer among females in both developed and developing countries [1]. In the field of breast cancer, in most of the articles, young woman is defined to be below the age of 35 or the age of 40 [2]. The results of the National Population-Based Cancer Registry Program in Egypt, showed that, among females, the proportion of breast cancer was 32 % of all female cancers [3]. In study applied in Gharbia over 10 years (1999-2008), the result was that the majority of breast cancer cases during the study period were diagnosed among women aged 40 – 49 years (31.8%) and among women aged 50–59 years (29.8%) [4] one decade younger than the corresponding age in western countries.

**Patients and methods:** This was a retrospective study in which the records of patients presenting with breast carcinoma who were admitted to the unit of Surgical Oncology and to the Clinical Oncology and Nuclear Medicine department, Alexandria Main University Hospital from January 2005 to December 2013 were collected. These patients were followed for 5 years after completion of their treatment.

**Results:** There was higher incidence of hormone positive tumors in older patients with a significant difference statistically ( $p < 0.001$  for ER receptors and  $p < 0.010$  for PR receptors). there is a significant reduction in the disease-free survival ( $p < 0.001$ ) and overall survival ( $p < 0.001$ ) in patients who developed breast cancer before 40 years.

**Conclusion:** Hormone-positive tumors are more common in patients older than 40 years which may indicate a better prognosis in this age group. Younger age at diagnosis of breast cancer is an adverse prognostic factor for relapse of the disease even when effective adjuvant therapy is given. This based on disease free survival and overall survival are worse in young age group.

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#### Introduction:-

Breast cancer is the commonest cancer among females in both developed and developing countries [1]. In the field of breast cancer, in most of the articles, young woman is defined to be below the age of 35 or the age of 40 [2]. The results of the National Population-Based Cancer Registry Program in Egypt, showed that, among females, the proportion of breast cancer was 32 % of all female cancers [3]. In study applied in Gharbia over 10 years (1999-

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2008), the result was that the majority of breast cancer cases during the study period were diagnosed among women aged 40 – 49 years (31.8%) and among women aged 50–59 years (29.8%) [4], one decade younger than the corresponding age in western countries. Breast cancer in Egypt has been reported to be biologically more aggressive disease than that in Western countries with predominance of premenopausal patients with late presentation in advanced stages [5,6]. The incidence of breast cancer among young females in Africa and Middle East reaches up to 20% of cases. The aetiology of this high incidence may be attributed to genetic or environmental factors [7]. Young patients diagnosed with breast cancer usually have a worse prognosis than older patients [8]. Young women diagnosed with breast cancer experience the same problems experienced by their older counterparts like abdominal pain, hair loss and bone aches in addition to the problems of infertility, early menopause, changed body image and sexuality [9]. Age is considered as an independent prognostic factor. Breast cancer occurring young women tends to have an aggressive behaviour such as HER2 over-expression and triple negative subtypes and is more likely to be diagnosed in a late stage. This may explain the poor outcome of younger patients as regarding the locoregional recurrence and the overall survival [10, 11]. Breast conserving therapy in women younger than 35 years is associated with higher risk of local recurrence than older patients [12].

### Patients and methods:

This was a retrospective study in which the records of patients presenting with breast carcinoma who were admitted to the unit of Surgical Oncology and to the Clinical Oncology and Nuclear Medicine department, Alexandria Main University Hospital from January 2005 to December 2013 were collected. All available records and blocks for these patients were retrieved. 5 years follow up period for these patients after completion of treatment.

#### In this study, we divided all patients in to two groups:

1. Group I: patients presenting with Breast carcinoma at age  $\leq 40$  years.
2. Group II: patients presenting with Breast carcinoma at age  $>40$  years.

Exclusion criteria for this study included:

1. Male breast cancer
2. Patients with pathology rather than carcinoma
3. Patients without data about pathological assessment and patients without follow-up records.

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov, Shapiro and D'agstino tests were used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using **Chi-square test (Fisher or Monte Carlo)**. **Mann Whitney test** was used to compare between two groups for abnormally distributed quantitative variables. **Kaplan-Meier** Survival curve was used. Significance of the obtained results was judged at the 5% level.

### Results:-

The study was done on 3820 cases diagnosed with breast cancer in the period between January 2005 to December 2013 with follow up period of 5 years.

Some of the reports were deficient in some parts.

Patients younger than 40 years at the time of diagnosis represents 15.6% of all cases (fig. 1)

There was a higher incidence of cribriform insitu carcinoma in younger patients. More breast conserving surgeries and oncoplastic procedure were done for young patients. Mastectomy was done in most of the cases. (table 1)

Table 2 shows the different parameters studied and comparing both age groups in relation to these parameters. There was higher incidence of hormone positive tumors in older patients with a significant

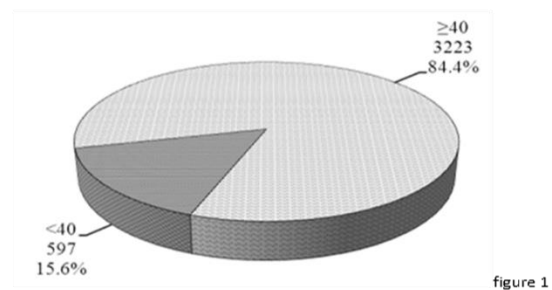


Figure 1: Age distribution among the studied group

difference statistically ( $p < 0.001$  for ER receptors and  $p < 0.010$  for PR receptors)

Table 3,4 and figure 2 show that there is a significant reduction in the disease-free survival ( $p < 0.001$ ) and overall survival ( $p < 0.001$ ) in patients who developed breast cancer at age younger than 40 years.

By the end of the study (5 years), 31 patients in the young group died from the disease and 16 patients in the old group died from the disease with statistical significance ( $p < 0.001$ )

**Table 1:-** Comparison between the two age groups according to different parameters

	Age (years)		Test of sig.	p
	<40	≥40		
<b>Multiplicity</b>	<b>(n = 122)</b>	<b>(n = 539)</b>		
Single	109(89.3%)	491(91.1%)	$\chi^2 = 0.398$	0.820
Multifocal	9(7.4%)	32(5.9%)		
Multicentric	4(3.3%)	16(3%)		
<b>Neoadjuvant Type</b>	<b>(n = 389)</b>	<b>(n = 1877)</b>		
No	367(94.3%)	1757(93.6%)	$\chi^2 = 0.298$	0.585
Yes	22(5.7%)	120(6.4%)		
<b>Response to Neoadjuvant</b>	<b>(n = 10)</b>	<b>(n = 50)</b>		
Partial response	6(60%)	27(54%)	$\chi^2 = 1.214$	0.622
Poor response	4(40%)	16(32%)		
Complete path response	0(0%)	7(14%)		
<b>Type of surgery</b>	<b>(n = 490)</b>	<b>(n = 2421)</b>		
No	9(1.8%)	21(0.9%)	$\chi^2 = 15.696$	0.004*
BCT	41(8.4%)	114(4.7%)		
Oncoplastic	0(0%)	1(0.04%)		
Mastectomy	438(89.4%)	2278(94.1%)		
Mastectomy & Recon	1(0.2%)	2(0.1%)		
Quadrantectomy	1(0.2%)	5(0.2%)		
<b>T size</b>	<b>(n = 297)</b>	<b>(n = 1581)</b>		
Median (Min. – Max.)	4 (0.1 – 18)	3.50 (0 – 17)	U=221920.5	0.130
<b>Pathology Types</b>	<b>(n = 438)</b>	<b>(n = 2192)</b>		
IDC	420(95.9%)	2051(93.6%)	$\chi^2 = 3.468$	0.063
ILC	3(0.7%)	56(2.6%)	$\chi^2 = 5.820^*$	0.016*
DCI	2(0.5%)	9(0.4%)	$\chi^2 = 0.019$	1.000
Mixed	5(1.1%)	51(2.3%)	$\chi^2 = 2.460$	0.117
Medullary	5(1.1%)	12(0.5%)	$\chi^2 = 2.006$	0.183
Paget dis with IDC	0(0%)	5(0.2%)	$\chi^2 = 1.001$	0.598
Mucinous	1(0.2%)	6(0.3%)	$\chi^2 = 0.028$	1.000
LCIS	0(0%)	1(0.05%)	$\chi^2 = 0.200$	1.000
Cribiform	2(0.5%)	0(0%)	$\chi^2 = 10.017^*$	0.028*
Paget disease with DCIS	0(0%)	1(0.05%)	$\chi^2 = 0.200$	1.000
<b>Tumor grade</b>	<b>(n = 317)</b>	<b>(n = 1528)</b>		
1	15(4.8%)	59(3.9%)	$\chi^2 = 2.349$	0.672
2	255(80.4%)	1281(83.8%)		
3	47(14.8%)	188(12.3%)		
<b>LV invasion</b>	<b>(n = 180)</b>	<b>(n = 841)</b>		
Yes	104(57.8%)	469(55.8%)	$\chi^2 = 0.243$	0.622
No	76(42.2%)	372(44.2%)		

$\chi^2$ , p:  $\chi^2$  and p values for **Chi square test** for comparing between the two groups U, p: U and p values for **Mann Whitney test** for comparing between the two groups: Statistically significant at  $p \leq 0.05$

**Table 2:-**Comparison between the two age groups according to different parameters

	Age (years)		Test of sig.	p
	<40	≥40		
<b>Pathological T</b>	<b>(n = 298)</b>	<b>(n = 1503)</b>		
0	0(0%)	1(0.1%)	$\chi^2 = 3.679$	0.469
1	44(14.8%)	281(18.7%)		
2	178(59.7%)	870(57.9%)		
3	62(20.8%)	275(18.3%)		
4	14(4.7%)	76(5.1%)		
Median (Min. – Max.)	2(1 – 4)	2(0 – 4)	U=213583.0	0.155
<b>Pathological N</b>	<b>(n = 337)</b>	<b>(n = 1577)</b>		
0	91(27%)	475(30.1%)	$\chi^2 = 3.241$	0.356
1	90(26.7%)	429(27.2%)		
2	98(29.1%)	456(28.9%)		
3	58(17.2%)	217(13.8%)		
Median (Min. – Max.)	1(0 – 3)	1(0 – 3)	U= 251672.5	0.113
<b>Stage</b>	<b>(n = 296)</b>	<b>(n = 1451)</b>		
0	0(0%)	1(0.1%)	$\chi^2 = 4.502$	0.356
1	18(6.1%)	103(7.1%)		
2	116(39.2%)	638(44.0%)		
3	158(53.4%)	697(48.0%)		
4	4(1.4%)	12(0.8%)		
<b>Stage Level</b>	<b>(n = 296)</b>	<b>(n = 1450)</b>		
Early stage	122(41.2%)	673(46.4%)	$\chi^2 = 3.436$	0.179
Locally advanced	170(57.4%)	766(52.8%)		
Metastatic	4(1.4%)	11(0.8%)		
<b>ER score</b>	<b>(n = 309)</b>	<b>(n = 1351)</b>		
Negative	70(22.7%)	200(14.8%)	$\chi^2 = 11.378^*$	0.001*
Positive	239(77.3%)	1151(85.2%)		
<b>PR test</b>	<b>(n = 309)</b>	<b>(n = 1411)</b>		
Negative	79(25.6%)	269(19.1%)	$\chi^2 = 6.640^*$	0.010*
Positive	230(74.4%)	1142(80.9%)		
<b>HER2</b>	<b>(n = 90)</b>	<b>(n = 373)</b>		
Positive	18(20%)	59(15.8%)	$\chi^2 = 0.151$	0.697
Negative	72(80 %)	314(84.2%)		
<b>KI</b>	<b>(n = 48)</b>	<b>(n = 171)</b>		
Low	26(54.2%)	100(58.5%)	$\chi^2 = 0.285$	0.593
High	22(45.8%)	71(41.5%)		

$\chi^2$ , p:  $\chi^2$  and p values for **Chi square test** for comparing between the two groups

U, p: U and p values for **Mann Whitney test** for comparing between the two groups

\*: Statistically significant at  $p \leq 0.05$

### Discussion:-

Breast cancer in females before the age of 40 years is uncommon and reaches nearly 7% of all cases at diagnosis in United States. According to many epidemiological studies in the last twenty years, this group of patients has raised special interest for being associated with poorer prognosis when compared to cases diagnosed over the age of 40. The majority of these studies were done in Europe and United States [13,14].

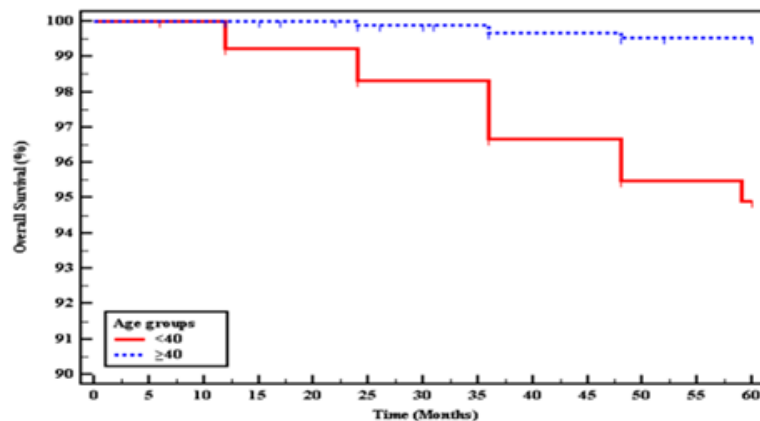


Figure (2): Kaplan-Meier survival curve for Overall survival

Since breast cancer is considered a potentially curable disease, a more aggressive approach may be needed if it is confirmed that young patients with breast cancer have increased incidence of relapse and low survival [15].

In the United States, a large retrospective cohort study of 243,012 breast cancer patients diagnosed between 1988 and 2003, showed that only 6.4% were younger than 40 years old [16]. While in our study, we found that patients diagnosed with breast cancer account for 15.6% of cases. This disparity is attributed to differences in population structure with more young population in Egypt; median age of females' population in Egypt is 24 years at 2016 while in USA median age is 38 years at 2016. Also, Egyptian female life expectancy, while increasing greatly in the last 50 years from approximately 49 years in 1960 to 74 years for 2016, is still currently lower than the USA 2016 estimate of 82 years.

In the current study, no significant association with age groups as regard the presence of lymphovascular invasion, although there was a higher incidence of presence of lymphovascular invasion in the young group, a finding similar to that reported in many published series [17]. On contrast Song et al [18] showed LVI was significantly associated with young patients aged  $\leq 40$  years, also Cancellato et al [19] concluded that there were higher percentages of tumors with LVI in young patients.

In our study; there was no statistically significant difference in the distribution of TNM stage between two age groups. These results were consistent with many studies [20, 21]. In contrast, several studies concluded that the percentage of patients diagnosed with more advanced stages was higher in the young patients than the older patients [22, 23]. While LIN et al [15] concluded that younger patients ( $< 50$  years) were significantly associated with higher frequencies of stage I than older patients ( $\geq 50$  years).

In the current study, there were more ER and PR negative cases in the younger age group than in the older age group with statistical significance. This matches with the results of many studies that showed the same results [19, 22].

In the current work, there was no significant difference in HER-2 positivity between 2 age groups, which is consistent with other published works analysing series of young patients [24, 25]. While many studies concluded that HER2 positivity is more frequent in young patients which inversely affect the prognosis of young breast cancer patients [19, 22 and 26].

In our study, the 5 years disease free survival was less in young patients with higher relapse rate with statistical significance. Also, the overall survival was less in the young age group. This is not explained by the primary size of the tumor or the lymph node status as they were more or less the same in both groups with no statistical significance.

These results are consistent with results from many published data which reported that Being 40 or younger is an independent risk factor for relapse in operable breast cancer patients [17, 22 and 27].

**Table 3:-** Comparison between the two age groups according to different parameters

	Age (years)		Test of sig.	p
	<40	≥40		
<b>Luminal subtypes</b>	<b>(n = 58)</b>	<b>(n = 205)</b>		
A	14(24.1%)	71(34.6%)	$\chi^2 = 4.590$	0.332
B Her2 -ve	13(22.4%)	49(23.9%)		
B Her2 +ve	13(22.4%)	44(21.5%)		
Her2 Enriched	5(8.6%)	15(7.3%)		
Triple -ve	13(22.4%)	26(12.7%)		
<b>Hormonal status tumor</b>	<b>(n = 326)</b>	<b>(n = 1487)</b>		
Negative	54(16.6%)	143(9.6%)	$\chi^2 = 13.326^*$	<0.001*
Positive	272(83.4%)	1344(90.4%)		
<b>Disease free survival event</b>	<b>(n = 281)</b>	<b>(n = 1231)</b>		
Free	156(55.5%)	851(69.1%)	$\chi^2 = 19.064^*$	<0.001*
Mets	125(44.5%)	380(30.9%)		
<b>5yr dis free months</b>	<b>(n = 261)</b>	<b>(n = 1147)</b>		
Median (Min. – Max.)	48 (0 – 60)	48 (0 – 60)	U=133373.5*	0.004*
<b>Overall survival event</b>	<b>(n = 284)</b>	<b>(n = 1234)</b>		
Alive	274(96.5%)	1230(99.7%)	$\chi^2 = 25.823^*$	<0.001*
Died	10(3.5%)	4(0.3%)		
<b>5yr OS (months)</b>	<b>(n = 259)</b>	<b>(n = 1141)</b>		
Median (Min. – Max.)	60 (6 – 60)	60 (12 – 60)	U= 141503.5	0.211

$\chi^2$ , p:  $\chi^2$  and p values for **Chi square test** for comparing between the two groups

U, p: U and p values for **Mann Whitney test** for comparing between the two groups

\*: Statistically significant at  $p \leq 0.05$

**Table 4:-** Kaplan-Meier survival curve for overall survival

Age groups	Mean (months)	% End of the study	Log rank	
			$\square$	p
<40	58.8	94.9	27.672*	<0.001*
≥40	59.9	99.5		

#### Conclusion:-

1. Hormone-positive tumors are more common in patients older than 40 years which may indicate a better prognosis in this age group.
2. Younger age at diagnosis of breast cancer is an adverse prognostic factor for relapse of the disease even when effective adjuvant therapy is given. This based on disease free survival and overall survival are worse in young age group.

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