

# Survival of breast cancer in very young women <35 years treated in Tripoli/Libya

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## Abstract

**Study objective:** To study survival of breast cancer in very young age women < 35 years over the period between 2000-2005. To relate recurrence rate and survival to risk factors as lymph node involvement, and Estrogen and progesterone status.

**Design and Setting:** Non-randomized retrospective study in patients with breast cancer confirmed by biopsy in Oncology department in TMC.

**Patients:** 552 patients were seen, 93 patients < 35 years representing 16.8% were included in this study .

**Results:** Patients < 35 represent 16.8%. Their stages were not different from older patients, No difference in tumor grade. In the majority of the patients under 35 years estrogen and progesterone receptor status were negative (55.6%), but the majority of the patients over 35 years were estrogen and progesterone receptor positive (55.5%) (p=0.035). Visceral metastases were more common in the under 35 years (50%) versus (29%) in patients above 35 years (p=0.04). Overall survival rate in very young age at 1<sup>st</sup> , 2<sup>nd</sup> and 5<sup>th</sup> years was 94.5%, 85% and 74% respectively, while overall survival rate in patients above 35 years at 1<sup>st</sup> , 2<sup>nd</sup> and 5<sup>th</sup> years was 96%, 89% and 81% respectively regardless of age. (p=0.04).

Overall recurrence rate at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years and survival rate was better in node negative patients than node positive patients regardless of age (p=0.01).

Overall recurrence rate at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years and survival rate was better in estrogen positive patients than in estrogen negative patients p=0.04.

**Conclusion:** women < 35 have a poor prognosis despite a similar stage and grade to older women. They have more estrogen and progesterone negative status tumors (p=0.035) and greater tendency to develop visceral metastases than older women.

## Introduction

The prognosis of breast cancer in young women is thought to be worse than older women however this issue is heavily debated. About 2% of patients with breast cancer are <35 years old at diagnosis. (1, 2). Breast cancer at young age tends to be more aggressive and associated with poor prognosis compared with

older patients. Tumors in young women were less differentiated, high grade, has high proliferating fraction and had more vascular invasion and negative steroid hormone receptors (3-6). One study concluded that younger patients with ER-positive tumors had a significantly worse prognosis than younger patients with ER negative tumors. (7)

Also they have reduced efficacy of adjuvant chemotherapy for these very young patients with endocrine responsive tumors. (8)

The occurrence of early -onset breast cancer has been associated with mutation in BCRA1 and BRCA2 genes. The majority of breast cancer patients found to have BRCA1 and BRCA2 reveal a family history of breast cancer and /or ovarian cancer in at least one first degree relatives. (9-11)

Women diagnosed with breast cancer at age of < 35 years are likely to have BRCA1, BRCA2 mutation in up to 15-30%.

These mutations are frequently associated with higher histological grade, lack of estrogen receptors, and high proliferating rate. (12-14)

The age at diagnosis was still a significant predictor with each year younger than 45 years adding 5% to the relative risk of death from breast cancer. (15)

## Aims of the study

1-To study Patients characteristics and stage at disease presentation in young < 35 years and older than > 35 years.

2-To study the various predictive and prognostic factors affecting survival (hormone receptor status, and lymph node status and age respectively ) in women younger than 35 years in comparison to older women.

3-To compare between these two groups regarding survival rate at 1<sup>st</sup> , 2<sup>nd</sup> , 5<sup>th</sup> years.

## Materials and Methods

552 breast cancer patients who were registered in Oncology clinic in Tripoli Medical Center between Jan. 2000-Dec.2005. The Ethical committee in Tripoli Medical Center approve the study.

Their files were reviewed and information collected include age, family history, menopausal status, lesion characteristic (site, size), status of Lymph node, stage of disease according TNM staging system, type of surgery, histopathology, Estrogen and progesterone status, type of treatment either adjuvant chemotherapy and radiotherapy, site of recurrence, overall recurrence, overall survival after 1, 2, and 5 years.

Patients were divided into two groups as group 1 < 35 years and groups 2 > 35 years. Frequency of all questions was calculated and t and Z test used to calculate level of significance between variables.  $p < 0.05$  was considered significant.

Kaplan Meier curves used for survival analysis to study the effect of age and hormone receptor status and lymph node involvement in two groups.

## Results

552 patients were diagnosed with breast cancer in Tripoli Medical Center in period between 2000-2005 with mean age of 45 years and 56% were premenopausal. 1.8% were male. 93 (16.8%) of patients were less than 35 years. Among these patients < 35 years, 17.7% has positive family history of breast cancer in contrast only 14.8% in patients > 35 years had family history of breast cancer ( $p = 0.3$ ). The clinical and pathological characteristic status grouped as group 1 (< 35 years) and group 2 (> 35 years). Table-1.

Tumor size in group 1 tends to be large T3 and T4 ( $p = 0.05$ ), while group 2 have small sized tumor (T1 and T2) ( $p = 0.04$ ).

Both groups has more positive lymph node, it was 58% in group 1 and 60.8% in group 2. There were no significant difference in lymph node involvement between these two groups ( $p = 0.189$ ).

Regarding hormone receptors, 55.5% of group 2 patients have positive hormonal receptors while only 44.4% of group 1 patients have positive hormonal receptors, This means younger women tend to have more hormone negative receptor ( $p = 0.035$ ).

Tumor grade was assessed in 38% of patients, there was no statistical difference in tumor grade between two groups  $p = 0.89$ .

HER-2 receptor was assessed only in 17.8% of all patients, 33% had strong positive HER-2 receptor by immunohistochemistry study. There was no difference between two groups, 33% in group 1 vs. 30% in group 2.

In group 1, mastectomy and Axillary clearance was done in 75.3%, lumpectomy and Axillary clearance was done in 19.4% and only biopsy was done in 5.4%, in group 2, mastectomy and Axillary clearance was done in 76.6%, lumpectomy and Axillary clearance was done in 15.2% and only biopsy was done in 6.2%. ( $p = 0.6$ ).

Adjuvant chemotherapy was given to 86% of group 1, in form of Anthracycline based chemotherapy in 78.5% of patients and Taxane –Anthracycline based treatment was given in 7.5% of cases while 82.8% of group 2 received chemotherapy, 70% received

CAF (Cyclophosphamide, Adriamycin and 5-fluorouracil). 5.4% received CMF (Cyclophosphamide Methotrexate and 5-fluorouracil). 7.4% received Taxanes based chemotherapy. ( $p = 0.6$ ).

58% of all patients received adjuvant radiotherapy to chest wall and the axilla that had breast conserving surgery or locally advanced tumors, or more than 3 positive lymph node. Tamoxifen was given to those who are positive estrogen and /or progesterone receptors or unknown receptor status. 50.5% of group 1 received Tamoxifen while it is given to 71.9% of group 2 ( $p = 0.001$ ), because there was more positive receptor status in patients > 35 years.

Ovarian ablation was done in 34.3% of group 1. It was done by LHRH analogue in 97% of patients and 3% by radiotherapy.

Higher proportion of patients in group 1 developed visceral metastases 50% as liver, lung, brain) compared with 29% in patients group 2 ( $p = 0.04$ ).

Isolated bone metastases were observed in 25% of patients in group 1 and 28% in patients group 2. 25% of patients group 1 has local recurrence while only 15.6% patients in group 2 developed local recurrence.

There was difference in cumulative recurrence rate in both groups at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years. Overall cumulative recurrence rate in patients of group (1) was 10.8%, 22.9%, and 32.4% at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years versus 13.8%, 23.4% and 36.4% in patients group 2 at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years.

Overall survival rate was better in women more > 35 years at 5 years. Overall survival rate in patients of group 1 are 94.5%, 85%, and 74.3% at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years versus 95.4%, 88.8% and 81% in patients of group 2 at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years ( $p = 0.01$ ).

Regarding hormone receptors status patients who are estrogen receptor positive had better survival than those with negative hormone receptors  $p = 0.04$  fig -1.

In group 1 patients with ER positive receptors, had overall survival at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years of 95%, 90% and 85%, while ER negative receptors patients, had overall survival at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years 95%, 77%, 73%  $p = 0.05$ .

In patients in group 2 with ER- positive receptors had overall survival at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years of 97%, 89.6% and 82.9%, where ER negative receptors overall survival at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years 95%, 83%, 71% ( $p = 0.04$ ).

Patients who were under 35 years and were ER positive had a similar survival to those who were ER positive and over 35 years, 95%, 90% and 85% vs 97%, 89.6% and 82.9%, at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years. ( $p = 0.82$ )

Patients who were under 35 years and were ER negative had a similar survival to those who were ER negative and over 35 years, 95%, 77%, 73% vs. 95%, 83%, 71%, at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years. ( $p = 0.46$ )

Lymph node involvement was a very powerful prognostic of survival in both groups, patients < 35 years without nodal involvement had a survival of 100%, 95% and 88.9% at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years while those whose lymph node were involved had a survival of 93.6%, 82.1%, and 60% at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years.

Patients > 35 years without nodal involvement had a survival of 100%, 99% and 95% at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years while those whose lymph node were involved had a survival of 95.2%, 86%, and 77% at 1<sup>st</sup>, 2<sup>nd</sup> and 5<sup>th</sup> years.

The presence of positive lymph node had more adverse effect on survival in group 1 < 35 years than older group 2 > 35 years, 93.6%, 82%, and 60% in patients < 35 years versus 95%, 86%, and 77% at 1<sup>st</sup>, 2<sup>nd</sup>, and 5<sup>th</sup> years in patients > 35 years.  $p = 0.014$ .

Patients who were node negative had similar survival in both groups, 100%, 95%, 88.9% in group 1 vs. 100%, 99%, 95% in group 2 at 1<sup>st</sup>, 2<sup>nd</sup>, and 5<sup>th</sup> years ( $p = 0.3$ ) fig -2

## Discussion

Young breast cancer reported to have worse prognosis than older group and some studies shows no difference between two groups, it's a matter of controversy and still under study.

Young women below 35 years of age represent less than 2% of the total breast cancer population in Western countries. (1, 2)

In our study 16.8% of patients were below 35 years which is significantly different from other results. In fact it represents the highest recorded percentage reported. 67% of our patients are below 50 years. 56% are premenopausal.

In Colleoni et al study, 4.7% of patients are very young < 35 years, and only 47% are less than 50 years (7).

N. Elsaghir et al study, only 8.1% of patients are < 35 years old, 53% are < 50years, and 44% are premenopausal (16). In Korean study, 14.6% of patients are less than 35 years (18).

Young patients has poor prognostic factor than older group, they have more bigger tumor size as T3and T4 and more negative hormone receptor which is similar to other studies Colleoni, El saghir, Elisabette study, the Korean study and A Chan et al. (7, 16, 17, 18, 19, 20). Regarding lymph node involvement, it was no difference between the two groups, which is similar to Colleoni (7) and Alsaghir(13) studies, but Korean study shows more lymph node positive involvement in young patients (P=0.024) (18,19).

In our study patients who are less 35 years have poor survival and more visceral metastases than patients who are more than 35 years. In our study, Patients who have positive estrogen receptors have better survival than those with negative receptor tumor in both groups, and there was no difference in survival between patients who are less than 35 years and more 35 years if they were Estrogen positive or negative.

N. Elsaghir study, it shows poor survival in positive receptors in young women than old women but not in negative receptors status (16).

In Colleoni et al, younger patients with Estrogen positive tumors had significantly worse prognosis than old women (7).

In Elisabetta et al study shows that five year survival was not different in the three groups 91%, 90%, and 89% for very young, young and old age respectively. In our study, patients less than 35 years who had positive lymph node had worse survival (p=0.014) than patients more than 35 years, but no effect on survival if it was negative lymph node, which shows similar results to Elsaghir study(16) Tumor grade and vascular invasion has negative impact on survival in patients who are less than 35 years which was not studied in our patients because of small number of patients(7). In some studies, among young and older breast cancer patients treated, outcome measures were similar in both groups of women. There was no significant difference in tumor characteristic, local disease relapse and distant metastases in both groups. (21)

## Conclusion

Women less than thirty five years have a poor prognosis despite a similar stage and grade to older women. These women have more estrogen and progesterone negative status tumors (p=0.035), and have greater tendency to develop visceral metastases than older women.

Patients who have positive estrogen receptors have better survival than negative receptors in both groups. No difference in survival between patients who are less than 35years and those older than 35 years if they had similar hormone receptor status. Patients less than 35 years who had positive lymph node had worse survival than patients more than 35 years, but no effect on survival if it was negative lymph node. (p=0.014), but those patients with negative lymph nodes have similar survival to older patients with negative lymph nodes.

## Tables

Table 1. Patients characteristic

Variable	Group 1 < 35years	Group 2 >35 years	P Value
1-Age	93	459	
2-Tumor Size			
T1+T2	31(33%)	199(43%)	0.04
T3+T4	47(50%)	186(40%)	0.05
3-Lymph Node			
Positive	54(58%)	279(60.8%)	
Negative	22(23.6%)	114(24.8%)	0.163
4-Stage			
I	2(2%)	15(3.3%)	0.57
II	34(36.6%)	203(44.2%)	0.173
III	37(39.8%)	150(32.7%)	0.187
IV	11(11.8%)	47(10.2%)	0.649
5-Histopathology:			
Ductal(IDC)	70(75%)	375(81.7%)	NS
Lobular(ILC)	9(9.7%)	36(7.8%)	NS
Medullary	4(4.3%)	11(2.4%)	NS
Mixed ILC+IDC	2(2.2%)	8(1.7%)	NS
Other	5(5.4%)	23(5%)	NS
6-Grade( known)	31(33.3)	183(39.9%)	
I	4(12.9%)	11(6%)	NS
II	16(51.6%)	104(56.8%)	NS
III	11(35.5%)	68(37.2%)	NS
7- Hormone receptor status:			
E.R Positive	28(44.4%)	166(55.9%)	
Negative	35(55.6%)	131(44.1%)	0.035*
PR Positive	29(46%)	175(58.9%)	
Negative	34(53.9%)	122(41.1%)	0.03*
8-Recurrence			
Visceral	12/24(50%)	39/134(29%)	0.044*
Bone	6/24(25%)	38/134(37.9%)	
Local	6/24(25%)	21/134(15.6%)	
9-Overall			
1 <sup>st</sup> year	(9.6%)	(13.8%)	0.519
Recurrence			
2 <sup>nd</sup> year	(22.9%)	(23.4%)	0.941
Rate			
5 <sup>th</sup> year	(44.4%)	(36.4%)	0.514
10-Overall			
1 <sup>st</sup> Year	(95%)	(96%)	
Survival			
2 <sup>nd</sup> Year	(86.5%)	(90%)	
5 <sup>th</sup> Year	(68.5%)	(81.4%)	0.01*

## Figures

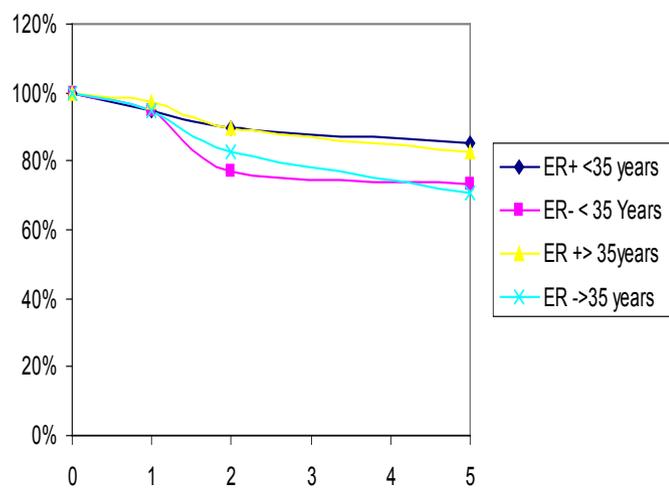


Fig 1. Overall survival in hormone positive and negative in both groups 1 and 2

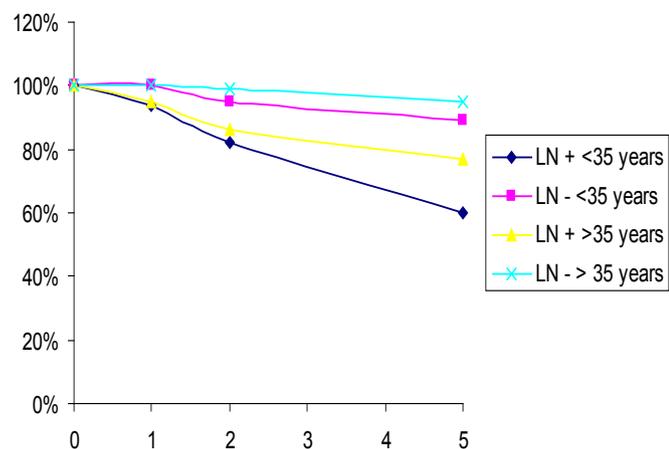


Fig 2. Overall survival in Lymph node positive and negative in both groups 1 and 2

## References

1. Parkin DM: Global Cancer statistics in the year 2000. *Lancet Oncol* 2:533-543, 2001.
2. Surveillance, Epidemiology, and End Results (SEER) program public – use CD-ROM (1973-1997). National cancer institute, DCCPS, cancer Surveillance Research Program, cancer statistics branch, released April 2000, based on the August 1999 submission.
3. Walker RA, Lee E, Webb MB, Dearing L et al Breast carcinoma occurring in young women (< 35 years) are different. *Br J Cancer*.1996; 74:1796-1800.
4. Adami HO, Malaker B, Holmberg L et al. The relation between survival and age at diagnosis in breast cancer. *N Engl J Med* 1986; 315:559-563.
5. Chung M, Chang HR, Bland KI, Wanebo HJ. Younger women with breast carcinoma have a poorer prognosis than older women. *Cancer* 1996; 77:1838-1843.
6. Winchester DP, Osteen RT, Menck HR. The national cancer data base report on breast carcinoma characteristics and outcome in relation to age 1996; 78:1838-1843.
7. Colleoni M., Rotmensz N., Robertson C., Orlando L., Viale G., Renne G., Luini A., et al .very young women (< 35 years) with operable breast cancer: features of disease at presentation . *Annals of Oncology* 2002; 13:273-279.
8. Pagani O , O'Neill A, Castiglione M et al .prognostic impact of amenorrhea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement : results of the International Breast Cancer Study Group (IBCSG) Trial VI *Eur J Cancer* 1998;34:632-640.
9. Robson M, Gilewski T, Hass B et al: BCRA-associated breast cancer in young women. *J Clin Oncol* 16:1642-1649, 1998.
10. Garber J: inherited breast cancer: increasingly familiar territory. *J Clin Oncol* 16:1639-1641, 1998.
11. Ford D, Easton DF, Peto J:estamite of the gene frequency of BCRA1 and its contribution to breast and ovarian cancer incidence. *Am J Hum genet* 57:1457-1462,1995.
12. Turchetti D, Cortesi L,Federico M et al . BRCA 1 mutation and clinicopathological features in sample of Italian women with early –onset breast cancer. *Eur J cancer* 2000; 36:2083-2089.
13. Peto J, Collins N, Barfoot R et al. prevalence of BRCA1 and BRCA2 gene mutations in patients with early –onset breast cancer. *J Natl Cancer Inst* 1999; 91:943-949.
14. Robson M, Gilewski T,Haas B et al BRCA- associated breast cancer in young women. *J Clin Oncol* 1998; 16: 1642-1649.
15. Aebi S, De Ridder M, Vlastos g, et al (2006) young age is a poor prognostics factor in women with stage I breast cancer *Eur J Cancer Suppl* 4,121.
16. Elsaghir N, Muhieddine Seoud , Mazen K Khalil , Maya Charafeddine, Ziad K Salem , Fady B Geara and Ali I Shamseddine.Effect of young age at presentation on survival in breast cancer. *BMC Cancer*; 2006; 6:194
17. Elisabetta Rapiti, Gerald Fioretta , Helena M.Verkooyen, Georges Vlastos, Peter Schäfer , André- Pascal sappino et al, survival of young and older breast Cancer patients in Geneva from 1990-2001. *European Journal of Cancer*. 2005; 41: 1446-1452.
18. Sei Hyun Ahn, Byung Ho Son , Seok Won Kim, Seung Il Kim, Joon Jeong, Seung-sang Ko, Wonshik Han. Poor outcome of hormone receptor-positive breast cancer at very young age is due to Tamoxifen resistance: nationwide survival data in Korea- a report from the Korean breast cancer society. *Journal of Clinical Oncology*2007; 25:2360-2368.
19. Jeong Kyeung Kim, Beom Seok Kwak Jung Sun Lee, Soo Jung Hong, Hee Jeong Kim, Byung Ho Son, and Sei Hyun Ahn. Do very young Korean Breast Cancer Patients have worse outcomes? *Annals of surgical Oncology* 2007; 14:3385-3391.
20. A.Chan, M. Pintilie, K Vallis , C.Giroud, P. Goss. Breast cancer in women< or= 35 years: review of 1002 cases from a single institution. *Ann Oncol*,2000 Oct; 11(10):1255-62.
21. N. Siddiqui, M.K.Siddique , I.A.Muazzam, R.Faiz, N.Anwer, F.Badar, Breast cancer in very young Pakistani women at a cancer hospital in Lahore. *J Clin Oncol* 26:2008(May suppl; abstr 11596)