

Recurrent Breast Cancer Following Modified Radical Mastectomy and Risk Factors

Noufel Sh. Mutlak*

Ramiz Al-Mukhtar*

Nabeel S. Al-Dawoodi***

Tharwat I. Sulaiman**

MBChB, FICS

MBChB, FRCS

CBAS

CABS, FACS, FRCS

Summary:

Background: - Recurrent breast cancer is cancer that comes back following initial treatment. Risk factors of recurrence are lymph node involvement, larger tumor size, positive or close tumor margins, and lack of radiation treatment following lumpectomy, younger age and inflammatory breast cancer.

Objective: Asses the rate of recurrence for early breast cancer in Iraqi female patients, in relation to certain risk factors.

Patients and methods: A prospective study was conducted on 100 consecutive female patients, with stage I and stage II breast cancer treated by mastectomy and axillary dissection by the same team. Patients were assessed postoperatively every three months and recurrences were detected by physical examination and ultrasound of the bed of mastectomy and axilla. Statistical correlation using univariant analysis between recurrence rate and certain associated variables was done.

Results: Recurrence rate was found to be 13%. It was more common among both young (20-29) years & the (40 – 49) years age groups which was 16.7%. Most of recurrences (61.6%) occurred (within 12_19 months) after surgical treatment. Statistically significant associations were found between recurrence and the latency period between first complaint and surgical management, the grade of the tumor, the size of primary tumor, and the number of lymph nodes involved. There was no statistically significant association between the type of adjuvant therapy and the incidence of local recurrence.

Conclusions: the rate of recurrence after modified radical mastectomy is relatively high in our study. The same known risk factors related to the stage, grade and delay of treatment were detected, and close follow up especially at the first 20 months after surgery is recommended.

Keywords: breast cancer, recurrence, risk factors, adjuvant therapy.

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Introduction:

The two basic principles of treatment of early breast cancer are to reduce the chance of local recurrence and the risk of metastatic spread (1). The standard surgical treatment is mastectomy and axillary dissection or clearance, and although there is somewhat higher rate of local recurrence following conservative surgery, even if combined with radiotherapy, but the long term outlook in terms of survival remains unchanged. Radiotherapy to the chest wall after mastectomy is indicated in selected patients in whom the risks of local recurrence are high. Recurrence of cancer within the operative field following radical mastectomy results from incomplete removal of the tumor or involved node, from cutting across infiltrated lymphatics, from spillage of cancer cells into the wound or perhaps blood born metastasis that have implanted within the surgical field (2). Risk factors of recurrence are lymph node involvement, larger tumor size, positive or close tumor margins, and lack of radiation treatment following lumpectomy, younger age and inflammatory process. (3, 4). The ten years incidence of loco regional recurrence after mastectomy is approximately

15%, ranging from 5%_25% (5, 6) . Due to the above reasons patients with breast cancer used to be followed up for life to detect recurrence and dissemination.

The aim of this study is to assess the rate of recurrence for early breast cancer in a sample of Iraqi female patients, and to assess the risk factors for recurrence

Patients and methods:

A prospective study was conducted on 100 consecutive female patients, with stage I and stage II breast cancer treated by mastectomy and axillary dissection in the 1st surgical unit - Baghdad teaching hospital and AL_Rahma private hospital by the same surgical team during the period from the 1st of January 2007 to the 1st of March 2009. Follow up of the patients continued till the end of December 2010. The least follow up period was 2 years and seventeen patients were treated during this period but were excluded from the study because of failure to follow them. Patients were assessed by history taking, physical examination and investigations namely ultrasound of the abdomen, chest X-ray and skeletal survey to exclude distant metastasis before patients being incorporated in the study. The patients were from different

* Dept. of Surgery, Medical city – Baghdad teaching hospital

** department of surgery-college of medicine - university of Baghdad.

areas of Iraq, from different socioeconomic groups, different educational levels and of different ages. They received adjuvant therapy following surgery as follow , 31 patients received chemotherapy alone using one of the following chemotherapy regimens : (CMF regimen that consisted of 6 weeks cycle of cyclophosphamide, methotrexate and 5 fluorouracil),(CAF which consisted of adriamycin instead of methotrexate),(4AC 4 weeks cycle of adriamycin and cyclophosphamide then 4 weeks cycle of taxol) or (4AC then 4 weeks cycle of taxotere) , while 6 patients received only tamoxifen (20 mg/day for at least 2 years) , 31 patients received both (chemotherapy and hormonal therapy),18 patients received combination of chemotherapy and radiotherapy to the axilla and 14 patients received combination of radiotherapy, chemotherapy and hormonal therapy. Patients were assessed every three months and recurrences were detected by physical examination, chest x-ray, US examination of the site of mastectomy, axilla, infra and supraclavicular regions, and special imaging as required in the form of US of the abdomen, CT scan, and MRI of the chest and axilla, and biopsy with histopathological examination. The site of recurrence and the time interval from modified radical mastectomy and the appearance of recurrence were recorded. Statistical correlation using univariate analysis between recurrence rate and certain associated variables namely age, educational level, socioeconomic status, marital status ,parity , lactation , family history site of the primary tumor latency period between first complaint and surgical management in months, size histopathology of the primary tumor, and type of post operative adjuvant therapy was used .

Results:

Recurrence occurred in 13 patients (13%)and the recurrence rate was higher in both young (20-29) years &the (40 – 49) years age groups which was 16.7% but there was no significant association between age and recurrence rate. Most of recurrences (38.5%) occurred between 12_15 months after treatment. Local recurrence constitutes 53.8% of all recurrences while regional (axillary lymph nodes) was seen in 30.7% and the least was distant metastasis (15.3%). Level of education of the patients, socioeconomic status, marital status, parity, lactation, the use of contraceptive pills, and family history of breast cancer all showed no statistically significant correlation with recurrence of breast cancer following surgery (table1). The primary tumor was laterally located in 71%. Laterally located tumors had a higher recurrence rate (14%) than medially or centrally located tumors (10,3%) but this was statistically insignificant(table 5). Intra-ductal carcinoma of the breast was the most frequently diagnosed tumor, being reported in 87% of cases. lobular carcinoma had a higher recurrence rate (28.5%) as compared to patients with ductal carcinoma (12.6%), but the association between histopathological types & recurrence rate was statistically insignificant (table 4). Well differentiated tumor constituted 17% of all patients, while moderately differentiated tumor was found in 50% & poorly differentiated tumor constituted 33% .Patients with poorly differentiated tumor had a statistically significant higher recurrence rate

(27.2%) than other patients. (Table 4). Sixty three% of cases had their tumor size ranging between 2-5 cm and 5% of cases had tumor size > 5cm which had a statistically significant higher recurrence rate(60%) than patients with tumor size less than 2cm(6.2%) and 2_5cm (12.6%) (Table 4). Thirty three percent of patients had no lymph nodes involvement by the tumor in the histopathological reports, while 67% of the cases had positive lymph nodes. Patients with more than 4 lymph nodes involvement had a higher recurrence rate (27.5%) than patients with no or less than 4 lymph nodes involvement. (table 4). Thirty seven percent of patients had stage I disease while 63% were stage II. Patients with stage II had a statistically significant higher recurrence rate (19%) than patients with stage I (2.7%). (Table 4). Patients with a delay of treatment more than 12 months had a statistically significant higher recurrence rate (60%) than other patients. Although patients who received a single type of adjuvant therapy developed a higher rate of recurrence in comparison to those who received more than one adjuvant therapy but this association was statistically in-significant (table 7).

Table 1: Relation between independent variant and recurrence

	Total		Recurrence		P value
	No	%	No	%	
Age <30	6	6	1	16.7	0.881
30-39	14	14	2	14.3	
40-49	36	36	6	16.7	
50-59	30	30	3	10	
=>60	14	14	1	7.1	
Education Low	61	61	9	14.7	0.514
High	39	39	4	10.2	
Socioeconomic Low	67	67	10	14.9	0.415
High	33	33	3	9.09	
Parity Multipara	49	49	8	16.3	0.332
Nullipara	51	51	5	9.8	
Marital status Married	53	53	6	11.3	0.596
Non-married	47	47	7	14.8	
Lactation Lactating	35	35	7	20	0.127
Non- lactating	65	65	6	9.2	
Contraception use Positive	24	24	3	12.5	0.933
Negative	76	76	10	13.1	
Family history Positive	21	21	4	19	0.354
Negative	79	9	9	11.3	

P value >0.05 (Statistically not significant)

Table 2: Association of time after surgical treatment with local recurrence:

Time in months	Total	
	No	%
0-3 m	-	-
4-7 m	1	7.7
8-11 m	2	15.4
12-15 m	5	38.5
16-19 m	3	23.1
> 20 months	2	15.4

Table 4: Relation Of histopathological types, grade, stage, tumor size and number of lymph nodes with recurrence:

	Total		Recurrence		P value
	No	%	No	%	
Histopathology					0.784
Ductal	87	87	11	12.6	
Lobular	7	7	2	28.5	
Medullary	4	4	-	-	
Tubular	1	1	-	-	
Colloid	1	1	-	-	0.012*
Grade Well differentiated	17	17	1	5.8	
Moderate	50	50	3	6	
Poor	33	33	9	27.2	0.004*
Tumor size <2 cm	32	32	2	6.2	
2-5 cm	63	63	8	12.6	
>5 cm	5	5	3	60	0.031*
Lymph node None	33	33	2	6	
1-3	38	38	3	7.8	
4	29	29	8	27.5	0.019*
Stage1	37	37	1	2.7	
2	63	63	12	19	
*P value <0.05 (Statistically significant)					

Discussion:

In this prospective study of 100 Iraqi female patients who were followed up for median period of 2 years after being subjected to modified radical mastectomy, the rate of recurrence was (13%) and this is relatively high in comparison to other studies such as Andry et al where the rate was 14% after follow up of 5 years (5), and Jonas lundkvisit et al in Stockholm (1985–2005) who found a 5 years recurrence rate of 9.8% of loco regional and metastatic relapse (6). In this study the highest proportion of recurrences occurred between 12-19 months after primary

treatment, which is similar to studies of Morihiko Kimura et al (7). This drew attention to the importance of close follow up of our patients for the first two years after primary treatment since this is the period when most of recurrences occur. Andry et al, and Chen K. T. et al showed a significantly worse survival when recurrence occurs at first 18 months after modified radical mastectomy (5, 8). We need to follow our patients for a longer time to assess the effect of the timing of local recurrence on the overall survival. Certain factors associated with recurrence were surveyed and statistically significant associations were found between recurrence and the latency period between first complaint and surgical treatment as the risk of having recurrence for patients in whom the surgical treatment was delayed for more than one year after the first complaint was higher. The longer the delay in initiating surgical therapeutic option will allow the tumor more time to double itself to reach a bigger size and subsequently encountered with more lymph node involvement (9, 10, and 11). A primary tumor larger than two cm in diameter significantly increase the risk of recurrence compared to primary tumors smaller than 2 cm and this correlates with studies performed by Andry et al, Stenfick et al and others (5,7,12,13,14,15,) which confirmed that tumor size is one of the significant risk factors for recurrence. For any tumor to be clinically detectable, it's size should be more than one cm in diameter which equal to 109 cells (9). By this time shedding of cells through blood or lymphatics might occur. So it is important to intensify screening programs to discover tumor at smaller size <1 cm (at pre clinical status) and that needs diagnostic tools as ultrasound and/or mammography for female patients at risk of having carcinoma of the breast (16). The rate of recurrence in patients with more than 4 lymph nodes involved by primary tumor was significantly higher than that for patients with no lymph node involvement, and this correlates with Ismail Jatoui et al, Channdry et al findings and others (11,12, 17,18,19,20,21) which confirmed that those patients had a significantly worse outcome, and associated with higher recurrence rate. In general patients with stage II primary tumor had significantly higher risk of recurrence than those with stage I disease. Our results coincide with the results of the study performed by Morihiko kimura et al, and others who concluded that primary tumor size and number of lymph node involved were the two major indicators of recurrence (7, 13, and 17). In our study it has been found that poorly differentiated tumors were associated with a significantly higher risk of having recurrence compared to well differentiate tumors. This correlates with Amir R Razavi et al and Milad M et al studies (22, 23) who observed positive corellation between grade of tumor and recurrence rate as poorly differentiated tumors are rapidly dividing aggressive tumors reaching more advanced stage at early time. The association between recurrence rate and certain other variables namely; Age ,socioeconomic status , educational level ,site of the primary tumor, histopathology

of the primary tumor and type of post operative adjuvant therapy are weak and statistically not significant. Most of Iraqi patients with carcinoma of the breast are among age group of (40-49) years of age (Iraqi registry 1997)(24) which is similar to that in other countries as Nigeria (25, 26), while in USA population carcinoma of the breast affects older aged female , (above 60 years of age) (27) . Some studies as that done by Chung et al (28,29) pointed to the significance of younger age as a risk factor for recurrence, while other studies did not show that Youssef et al and others (30) which showed that age is not an independent variant. In our study the rate of recurrence was higher for patients in the age group (40-49) years age compared to elderly patient (60 + years) though it was not significant statistically. Recurrence rate is higher in low socioeconomic group of patients (although it was not statistically significant), since low socioeconomic status limit the ability of patient to gain adequate health care as Velanochi et al (31) stated in his study . Low educational level also is associated with increased the rate of recurrence as low education makes the patients less able to gain benefit from health educational programs , a finding correlate with Muller study (32) but this association was not statistically significant in our study. The site of the primary tumor was not significantly associated with increase recurrence in spite of the fact that laterally located primary tumor has slightly higher rate of recurrence than that with medially or centrally located tumor. This correlates with the results obtained by Fisher et al and other studies (13,33).The association between recurrence and histopathology of the primary tumor was weak and statistically not significant and this correlates with study done by Chung et al (34), who found that the rate of recurrence with invasive ductal carcinoma did not significantly differs from that of invasive lobular carcinoma for those who underwent modified radical mastectomy. This finding is different from results obtained by Andry et al study and others which showed that histology is a significant risk factor for recurrence (5,35) . The recurrence rate in other histopathological varieties (medullary, tubular and colloid) cannot be assessed because there was no recurrence detected within 2 years of observation in this study although it has been mentioned that those above varieties are relatively less aggressive and carries better prognosis (35, 36) . We observed in our study that in spite of post operative adjuvant therapy, it did not statistically show its desired effect seen in other trials of adjuvant chemo therapy (18, 37,38, 39, 40) and still we have an overall higher recurrence rates. This could be due to the influence of other factors like socioeconomic status and educational level (40) which interfere with proper therapy, correct timing of dose, correct dosing and inability to get effective drug because of cost. This combined effect still has its detrimental effect on our patients post operatively in addition for those factors discussed above . This is important since it has been found that in different therapeutic trials the dose response

curve for cytotoxic anti cancer drugs used in treatment of breast cancer is relatively steep that is small reduction in the administered dose will lead to disproportionately large decrease in the efficacy so it is important that full dose of drugs be administered according to the therapeutic protocol whenever possible. Arbitrary dose reduction to circumvent moderate and manageable toxicity should not be made as they substantially reduce the effectiveness of adjuvant therapy (41,39). The increased exposure to estrogen is associated with an increased risk for developing breast cancer, whereas reducing exposure is thought to be protective(42,43). In spite of that, the association between recurrence rate and marital status, lactation state and parity was statistically insignificant in this study and this correlates with studies done by Jonas lundkvist et al and others (44,6).

Conclusions:

The rate of recurrence after modified radical mastectomy for operable breast carcinoma in our study was 13% in 1st two years of follow up and most of these recurrences occurred between 12-19 months after surgery. Significant associations was found between rate of recurrence and the latency period between first complaint and surgical treatment (months), size of primary tumor , number of lymph nodes involved, stage of primary tumor and histopathological degree of differentiation of carcinoma of breast(grade). The association between the rate of recurrence and age at presentation, education level, socioeconomic states, marital states, parity, lactation state, family history, and histopathological type was not significant. The type of adjuvant therapy did not significantly effect the incidence of recurrence of breast cancer .

References:

1. Norman S. Williams, Christopher J. K. Bulstrode and P. Ronan O'Connell Bailey and Love ; *Short practice of surgery*, 25th edition.2008.
2. ACS surgery principles and practice, 2006, 6th edition.
3. Gieiger AM et al, *Recurrences and second primary breast cancer in older women with initial early stage disease. Cance* 2007;109:966 _974.
4. Greco M, Cascinelli N, Galluzzo D, Testori A, Baldini M Levene A. *Locally recurrent breast cancer after 'radical' surgery Eur J Surg Oncol* 1992;18:209–14.
5. Andry G, Sucin S, Vico P, Faverly D, Andry M, Verhest HA, Nogaret JM, Mattheiem W. *Recurrence after 649 modified radical mastectomy. Incidence and significance. European journal of surgical oncology* 1989,(15): 476_485.
6. Jonas lundkvist et al. *SSE/EFF paper series in economics and finance No.661.May 2007. Risk and mortality of recurrent breast cancer in Stockholm 1985_2005.*
7. Morihiko Kimura , Yasuhiro Yanagita , Tokihiro Koida

- ,Tomomi Fujisawa. Study of time-course changes in annual recurrence rates for breast cancer: data analysis of 2,209 patients for 10 years post-surgery. *Breast Cancer Res Treat* (2007) 106:407–411.
8. Chen KT, Chang KJ, Chang YZ, Wang SM, Chen KM. Factors effecting recurrence in breast cancer. *J. Formose Medicine* 1991;90(10):986_998.]
9. Guinee VF: *Epidemiology of breast cancer*, in Bland KI, Copeland EM III (eds): *The Breast: Comprehensive Management of Benign and Malignant Diseases*. Philadelphia: WB Saunders, 1998, p 339.
10. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status and survival in 24740 breast cancer cases. *Cancer* 1989; 63(1):181-187.
11. Andry G, Sucin S, Pratola D, Sylvester R, Leclercq G, Costa PMD, Legros N, Hooft MAT, Verhest A, Matthei W. Relation between estrogen receptor concentration and clinical and histological factors, their relative prognostic importance after radical mastectomy for primary breast cancer. *Eur. J. Cancer Clinic. Oncology* 1989 25(2):319-329.
12. Romano Demicheli, Gianni Bonadonna, William JM Hrushesky, Michael W Retsky and Pinuccia Valagussa. Menopausal status dependence of the timing of breast cancer recurrence after surgical removal of the primary tumor. *Breast Cancer Res* 2004, 6:R689-R696 (DOI 10.1186/bcr937).
13. Malone KE, Daling JR, Weiss NS, Knight BM, While E, Voigt LF. Family history and survival of young women with invasive breast carcinoma. *Cancer* 1996; 78(7):1417-1425.
14. Lee AKC, Loda M, Mackarem G, Bosari S, Delellis RA, Healthy GJ, Hughes K. Lymph node negative invasive breast carcinoma 1 cm or less in size (T1 a,b N0 M0) clinico pathological features and outcome. *Cancer* 1996; 79 (4): 761-771.
15. Hacene K, Doussal VL, Rousse J, Brunt M. Predicting distant metastasis in operable breast cancer patients. *Cancer* 1990; 66(9): 2034-2043.
16. Bodian CA, Perzin KH, Lattes R. Lobular neoplasia, long term risk of breast cancer and relation to other factors. *Cancer* 1996; 78(5):1024-1034.
17. Scotts Morrow M. Breast cancer making the diagnosis. *The surgical clinics of north America* 1999; 79(5):990-1007.
18. Richard KO, Nanda FC, Karen MK. A cost-effective analysis of axillary node dissection in post menopausal women with estrogen receptors positive breast cancer and clinically negative axillary L.N. *Surgery* 1999; 3(126):568-576.
19. Chaudary MA, Tong D, Millis R, Smith P, Fentim IS, Rubens RD. recurrence following mastectomy for early breast carcinoma. Efficacy of radio therapy at time of recurrence. *Eur. J. Surg. Oncology* 1997; 23(4):348-353.
20. Fisher B, Bauer M, Wickerham L, Radmond CK, Fisher ER. Relation of number of positive axillary node to the prognosis of patients with primary breast cancer. *Cancer* 1983; 52(9):1551-1557.
21. Nina Bijker, M. D. Emiel J. T. Rutgers, M. D., Ph. D. Johannes L. Peterse, M. D. Joop A. van Dongen, M. D., Ph. D. August A. M. Hart, M. Sc. Jacques H. Borger, M. D., Ph. D. Bin B. R. Kroon, M. D., Ph. D. Low risk of locoregional recurrence of primary breast carcinoma after treatment with a modification of the Halsted radical mastectomy and selective use of radiotherapy.
22. Amir R Razavi, Hans Gill, Olle Stål, Marie Sundquist, Sten Thorstenson, Hans Åhlfeldt, Nosrat Shahsavari, and the South-East Swedish breast cancer study group *BMC Medical Informatics and Decision Making* 2005, 5:29 doi:10.1186/1472-6947-5-29.
23. Milad M, Khalil A, Ismail NE, Mourad M. Estrogen and progesterone receptors versus some prognostic parameters in mammary carcinoma. *Med. J. Cairo Univ.* 1996; 64(1):35-42.
24. Iraqi cancer registry/ministry of health. 1997-1999.
25. Chiedozi LC. Morbidity, mortality and survival in the management of breast cancer in Nigeria. *Annals of Saudi medicine* 1995; 15(3):227-230.
26. Amir H, Kitiny JN, Parkin DM. A comparative study of carcinoma of the breast in an African population. *East Africa medical journal* 1994; 71(4):215-218.
27. Scott CEH, Jochimsen PR, Menck HR, Winchester DJ. An analysis of male and female breast cancer treatment and survival among demographically identical pairs of patients. *Surgery* 1999; 126(4):775-781.
28. Chung M, Chang HR, Bland KI, Wanebo HJ. Younger women with breast carcinoma have a poorer prognosis than older women. *Cancer* 1996; 77(1):97-102.
29. Wonshik Han, Seok Won Kim, In Ae Park, Daehee Kang, Sung-Won Kim, Yeo-Kyu Youn, Seung Keun Oh, Kuk Jin Choe and Dong-Young Noh, Young age: an independent risk factor for disease-free survival in women with operable breast cancer *BMC Cancer* 2004, 4:82 doi:10.1186/1471-2407-4-82.
30. Youssef A, Esmail S, Abdalla A, Anos F, Esmail N. Five years results of adjuvant CMF and post operative radio therapy in node positive premenopausal women with operable breast cancer randomization in timing of chemo therapy. *Egypt. J. Nat. Cancer. Inst.* 1995; 7(1):61-65.
31. Velanochi V, Yood MU, Bawle U, Wathanson SD, Strand VF, Talpos CB, Szymanski W, Lewis FR. Racial differences in the presentation and surgical management of breast cancer. *Surgery* 1999; 125(4):375-379.
32. Muller AG, Vanzyl JA, Joubert G. Analysis of prognostic factors in 568 patients treated for breast cancer by surgery. *Journal of Surgical Oncology* 1989; 42(15):126-131.
33. Havenga K, Welvaart K, Hermans J. Significance of local recurrence after mastectomy for breast cancer. *Surg Oncology* 1992; 1:363-9.

34. Chung MA, Cole B, Wanibo HJ, Bland KI, Chang HR. Optimal surgical treatment of invasive lobular carcinoma of the breast. *Ann. Surg. Oncology* 1997; 4(7):545-450.
35. Camel JW, Meyer JS, Feuer E, Miller BA. Recurrent breast cancer 1996;77(8):1459-1464.
36. The breast, in Mann C.V., Russell R.C.G, Williams N.S: *Bailey and love's short practice of surgery*, 22ed. London, Champion and Hall, 1995;(39)543-562.
37. International breast cancer study group. Duration and reintroduction of adjuvant chemo therapy for node positive premenopausal breast cancer patients. *Journal of clinical oncology* 1996;14(6):1885-1894.
38. Fisher B, Dignam J, Mamounas EP, Constantine JP, Wickerham DL, Redmond C, Wolmark N, Dimitrov NV, Bowmen DM, Glass AG, Atkins JN, Abramson N, Sutherland CM, Aron BS, Margolese RG. Sequential methotrexate and fluorouracil for the treatment of node negative breast cancer patients with estrogen negative tumors. Eight years results from national surgical adjuvant breast and bowel project (NSABP) B13 and first report of finding from NSABP-B19. Comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate and fluorouracil. *Journal of clinical oncology* 1996; 14 (7):1982-1992.
39. Early breast cancer trialists collaborative group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy 1992; 339(11):71-84.
40. Abdallah H, Barsoum M, Serafi M, Gayed A, Attar I, Khodary A, Zaghloul M, Nagger N, Khafaga Y, Monji M, Long term results of adjuvant chemotherapy in carcinoma of the breast, NCL_Cairo experience. *Med. J. Cairo. Univ.* 1996;64 (1): 85_92.
41. Foster RS, Bostwick J: *Breast in Davis JS, Drucker WR, Gamelli RL, Gann DS (eds): Clinical surgery, 1st edition. Washington DC, Mosby company CV. 1987 (42) 1275-1390.*
- 42 Hulka BS: Epidemiologic analysis of breast and gynecologic cancers. *Prog Clin Biol Res* 396:17, 1997. [PMID: 9108587].
43. Singletary SE: Rating the risk factors for breast cancer. *Ann Surg* 237:474, 2003. [PMID: 12677142].
44. T W Chapman ,EB Fish and M A Link ,Competing risks analysis for recurrence from primary breast cancer. *British Journal of cancer* (1999) ,1508_115.