Review

Breast cancer in Egypt: a review of disease presentation and detection strategies

S. Omar,[1] H. Khaled,[1] R. Gaafar,[1] A.R. Zekry,[1] S. Eissa[1] and O. El-Khatib[2]

SUMMARY Carcinoma of the breast is the most prevalent cancer among Egyptian women and constitutes 29% of National Cancer Institute cases. Median age at diagnosis is one decade younger than in countries of Europe and North America and most patients are premenopausal. Tumours are relatively advanced at presentation. The majority of tumours are invasive duct subtype and the profile of hormone receptors is positive for estrogen receptors and/or progesterone receptors in less than half of cases. This overview examines genetic changes, potential and established predictive and prognostic markers and end results of surgery, radiotherapy and systemic therapy for early, locally advanced and metastatic disease stages. Disease presentations common to the region and early detection strategies are presented.

Incidence

Breast cancer is the most common cause of cancer death among women worldwide. Incidence rates are high in more developed countries whereas rates in less developed countries and in Japan are low but increasing. In the United States of America (USA) each year more than 180 000 women are diagnosed with breast cancer. If current rates of increase remain constant, a woman born today has a 1 in 10 chance of developing breast cancer [*1*].

In Egypt, breast cancer is the most common cancer among women, representing 18.9% of total cancer cases (35.1% in women and 2.2% in men) among the Egypt National Cancer Institute (NCI) series of 10 556 patients during the year 2001 [*2*], with an age-adjusted rate of 49.6 per 100 000 population [*3*].

Biology

During the last two decades, progress has been made in defining some of the critical processes associated with the development of breast cancer. It is now generally accepted that malignant transformation involves genetic and epigenetic changes that derail common regulatory mechanisms and result in uncontrolled cellular proliferation and/or aberrant programmed cell death or apoptosis. These cellular abnormalities are frequently associated with molecular alterations involving certain types of genes, such as proto-oncogenes and tumour suppressor genes, as a result of genetic predisposition and/or exposure to physical, chemical, biological or environmental factors.

These biological alterations are reflected in many clinical and pathological aspects of

[1]*National Cancer Institute, University of Cairo, Cairo, Egypt.*
[2]*World Health Organization Regional Office for the Eastern Mediterranean, Cairo, Egypt.*
Received: 06/11/01; accepted 25/04/02

the disease. As an example, the natural history of breast cancer is markedly heterogeneous. Some patients suffer aggressive forms of the disease with rapid recurrences and short survival while others show a good response to current therapeutic modalities and have longer survival rates. Many of the predictive and prognostic factors that are currently known to affect tumour behaviour are based on these genomic alterations.

Loss of heterozygosity (LOH) analysis has been used to study most types of cancer and has been the basis of subsequent investigations to identify and clone the genes involved in tumour development. Deletions on the short arm of chromosome 3 have been detected in many human malignancies. In one report [*4*], 45 women presenting to the NCI with invasive duct carcinoma of the breast were investigated for LOH using 10 highly polymorphic micro-satellite markers distributed over the short arm of chromosome 3. LOH was observed in 87% of the cases examined. The highest LOH was detected at the *3p 14–13* region (43%), followed by region *3p 14.2–14.1* (21%) and region *3p 21.1–14.3* (21%). These results suggested that at least three or more tumour suppressor gene regions are present on the short arm of chromosome 3 (including the fragile histidine triad (FHIT) gene present on region *3p 14.2–14.1*) and that their deletion may play an important role in breast cancer tumourigenesis.

In another study [*5*], the presence and the prognostic significance of allelic imbalances such as micro-satellite instability (MSI) and LOH in chromosomes 2, 11, 13 and 17 were reported. The DNA from 29 Egyptian patients who were followed for up to 5 years were analysed using a panel of 24 markers. The frequencies of allelic imbalances in these markers ranged from 30%–55% and were highest for *D11S912, D2S171, TP53* and *D17S855*. Using multivariate analysis, it was observed that only the pathological and clinical stage, and allelic imbalances at *D2S171, D11S912* or *D17STP53*, generated significance predictive models for survival.

The role of the mismatch repair gene *MSH2* in breast cancer development was also investigated using 9 micro-satellite polymorphic markers located at the area of the *MSH2* gene on the chromosome 2p16 [*6*]. The study included 33 samples of invasive breast carcinoma, 15 samples of carcinoma *in situ* and 19 samples of epithelial hyperplasia obtained from 56 patients. LOH was detected in 44.6% of the cases. The highest frequency of LOH was reported in invasive breast carcinoma (74.4%), carcinoma *in situ* (16.3%) and epithelial hyperplasia (9.3%). MSI was reported in 62.5% of studied patients and was 51.5% in invasive breast carcinoma, 28.8% in carcinoma *in situ* and 20.45% in epithelial hyperplasia. The study concluded that defects involving the *MSH2* gene could promote breast cancer progression through well-defined stages of epithelial hyperplasia and carcinoma *in situ* [*6*].

Amplification of *ErbB-1* and *c-ErbB-2* genes has been shown in human breast cancer. Expression of these genes results in production of epidermal growth factor receptor (EGFR) and *c-ErbB-2* receptors respectively. A body of data has indicated that overexpression of the receptors is associated with poor prognosis. Tissue EGFR and *c-ErbB-2* were determined in the membrane fractions of histopathologically verified malignant and normal tissue from the same breast of 94 patients [*7*]. These values were also determined in 48 tissue specimens of benign mastopathies. Also, serum *c-ErbB-2* was quantified in 105 breast cancer patients as well as in 48

patients with benign breast disease. Patients were followed with serial determination of serum *c-ErbB-2* for 1 year and clinically for 3 years to detect any distant metastases or recurrence. The levels of tissue and serum *c-ErbB-2* were significantly higher in breast cancer patients than benign breast disease or normal controls. Moreover, preoperative serum *c-ErbB-2* levels showed prognostic value better than that of tumour size, EGFR, nodal involvement and tissue *c-ErbB-2*. Disease recurrence, however, was more frequent among patients with negative EGFR. There was also an inverse correlation between estrogen receptor levels and EGFR levels in malignant tissues.

To further evaluate the predictive potential of EGFR, EGFR was quantified biochemically using an enzyme immunoassay in another report by the same authors [*8*]. The study included 94 samples of malignant and normal tissue from the same breast as well as 40 benign mastopathies. The mean level of EGFR in malignant tissues showed a significant decrease from the control benign tissues. No cut-off point could be determined between malignant and non-malignant tumours due to the large overlap in their values. Also, no relation could be found between mean EGFR values and age of the patient, menstrual status, clinical stage, type and grade of cancer or lymph node involvement.

Clinicopathologic features

Breast cancer in Egyptian patients has a younger age distribution with the majority of cases occurring at 30–60 years of age. The median age is 46 years, one decade younger than the corresponding age in Europe and North America. Most patients are premenopausal (60.5%) with a female to male ratio of 44:1.

Late presentation of most patients is a characteristic feature and the inflammatory type of breast cancer is relatively more frequent. Thus, in an NCI series [*9*], clinical T1, T2, T3 and T4 lesions were 1.2%, 30.0%, 26.4% and 42.4%, respectively. The mean tumour size was 4.5 cm. The frequency of axillary lymph node metastases was 75%. The number of positive nodes was 1–3 in 23%, 4–10 in 22% and more than 10 in 17% of patients.

The most common tumour was invasive duct carcinoma (83.4%), while intraductal carcinoma was present in 1.5% of cases. Invasive lobular, medullary and mucoid carcinoma were detected in 7.1%, 1.6% and 2.3% of cases respectively. Pathologic grading showed a low incidence of grade I (5.4%). Grades II and III tumours were 66.0% and 28.6% respectively. Multiple tumours were found in 1.5% and were mostly of the lobular subtype; bilateral presentation occurred in 0.6% of cases [*10*].

The profile of hormone receptors as determined by immunohistochemistry was positive for estrogen receptors (ER) in 40.9%, for progesterone receptors (PR) in 31.4% and for both receptors in 27.2% of cases.

Diagnostic evaluation

Histopathologic confirmation of the diagnosis of malignancy is essential before any surgical intervention is attempted. Fine needle aspiration cytology may be done in special centres where the necessary expertise is available. This simple procedure can prevent unnecessary surgery. In a series of studies to evaluate the accuracy, sensitivity, specificity, and positive and negative predictive values of the procedure, one study included 990 samples from fine

needle aspiration cytology of breast lesions performed during the 3 years January 1994 to December 1996 at the Cytopathologic Unit of the NCI [*11*]. The cytological diagnoses were compared with the results of the histological examinations of the same lesions. The overall accuracy rate of the study was 70.0%. The sensitivity of the study was 92.4% and the specificity was 100%. The positive predictive value for carcinoma was 100%, negative predictive value for absence of carcinoma was 85.6% and efficiency of the test was 94.7%. In another study, the diagnostic results of another more simplified fine needle sampling technique without aspiration were compared with those of the routine classic fine needle aspiration technique in a series of 115 female patients having both benign and malignant breast tumours. Insufficient cellular yield was recorded in 6.8% of the lesions in those examined with fine needle alone, whereas it was 8% in those smears obtained by aspiration technique. With the new technique, trauma was reduced and better sampling of the tumour was directly obtained with more accuracy and precision [*12*].

Breast imaging is an important tool for diagnosis of different breast lesions. Although mammography is a relatively good and cost-effective method, it has some inherent weaknesses that limit its sensitivity and specificity. The role of magnetic resonance mammography in diagnosis of breast cancer was assessed in a series of 24 cases with pathologically proven breast cancer [*13*]. The results were compared with those of mammography and ultrasonography of the breast. Magnetic resonance mammography showed an overall sensitivity of 100% in tumour detection. These data suggest that mammography may be included in the diagnostic work-up of selected cases.

The role of technetium-99m-sestamibi (Tc-99m MIBI) in differentiating benign from malignant breast lesions and the effect of lesion site, size and histopathologic characteristics including tumour grading, hormone receptor status and carcinoma *in situ* on the diagnostic validity of this non-invasive procedure were evaluated. Scintimammography using Tc-99m MIBI had a high diagnostic accuracy of detecting malignant lesions, especially those larger than 1 cm in diameter with high-grade subtypes and with ER positive status [*14,15*].

End results of therapy

During the last two decades, substantial progress has been made in the treatment of early as well as late stages of breast cancer. For the first time, breast cancer mortality rates are decreasing in most countries. In the following part of this review, treatment results from studies in Egypt are presented.

Early stage disease

A follow-up study was conducted on 408 women with operable breast cancer treated at the NCI during January 1980–December 1983. All patients except 6 were subjected to a radical mastectomy at that time; 224 patients received adjuvant postoperative radiotherapy and 73 patients were treated by adjuvant CMF combination therapy [cyclophosphamide, methotrexate, 5-fluorouracil] for 6 courses. These adjuvant regimens were conducted in relation to tumour size and lymph node involvement. In June 1987, multivariate analysis was conducted for those patients and multiple stepwise regression analysis was done on the various prognostic factors to elicit a prognostic index. Age had no effect, whereas staging had a strong effect on

survival as evidenced by different rates of survival in relation to tumour extent. T1 lesions had a survival of 60.7% in contrast to 19.6% for T4 lesions and clinical nodal affection (N), N0 66.9%, N1a 54.6%, N1b 25.9% and N2 3.5%. The first 3 years were a critical period for patients, especially those with T4 lesions and N2 category. Using stage grouping as a prognostic discriminator, it was found that stage I patients fared better than stage II patients, who in turn did better than stages IIIa and IIIb patients. While 5% of stage I patients died during the first 6 months, 19.7% of the poorest prognosis group, stage IIIb, continued alive and free of recurrence for the first 3.5–5 years. Either this was due to the biologic heterogeneity effect or staging was not sufficient to predict prognosis. This result was also supported by multivariate analysis, which showed no independent prognostic effect for clinical staging.

In contrast, however, tumour size showed a prognostic effect of survival, which seemed to be indirect through the lymph node metastasis and not through the tumour grades. This was supported by the non-significant relationship detected between tumour size and grade. The histopathologic types (favourable and unfavourable) and grade gave significant discrimination, which was indirect through nodal metastasis in comparison with the unfavourable group (56.0% versus 70.6%). Also, grade I patients had a survival rate of 65% while for grades II and III cases it was 30%.

Axillary lymph node metastasis had the most significant prognostic power of all the prognostic factors. The results indicated that patients with 4–9 and > 9 nodes had a far worse prognosis. Capsular invasion was also a powerful prognostic factor in multivariate analysis. The clinical diagnostic accuracy of axillary nodes was 66.6% and 78.4% for the clinically negative and clinically positive lymph nodes respectively.

A more recent series was conducted at the same institute between 1994 and 1998 and included 400 patients. The median age of patients was 46 years (range 21–76 years). Of these 400 cases, 261 (65%) were postmenopausal and 139 (35%) were premenopausal. While all cases in the 1980–84 series had modified radical mastectomy as their primary treatment followed by adjuvant radiotherapy (55%) or chemotherapy (24%), in the 1994–98 series modified radical mastectomy was the primary treatment for 83% and conservative surgery was done for the remaining 17%. Adjuvant radio/chemotherapy was given to 85% of these cases. Tumour size was below 2 cm in 13%, between 2–4 cm in 54% and > 4 cm in 33% of cases. Pathological axillary lymph node involvement was absent in only 14 of the 400 cases (3.5%) examined, while 1–3, 4–6, 6–10 and > 10 positive nodal affection was present in 16.5%, 11%, 13% and 56% of cases respectively.

At a median observation time of 49 months the 5-year disease-free survival rate was 60.1% for the patients included in the 1994–98 series compared with 37.2% for those included in the 1980–84 series. Survival rate was significantly adversely affected by postmenopausal status, tumour size more than 2 cm in diameter, grade III tumours, positively axillary lymph nodal affection and being ineligible for conservative surgery as primary treatment.

In another study [*16*] using high-dose adjuvant chemotherapy with autologous peripheral blood stem cell transplantation in node positive breast cancer, 53 premenopausal patients with node-positive (≤ 6) breast cancer were randomly allocated to

receive 1 cycle of high-dose CECb regimen [cyclophosphamide 6 g/m^2 divided on 3 days, etoposide 1500 mg/m^2 divided on 3 days and carboplatin 800 mg/m^2 divided on 2 days] versus 6 cycles of conventional dose CEF regimen [cyclophosphamide 600 mg/m^2, epirubicin 75 mg/m^2 and fluorouracil 600 mg/m^2], all given intravenously on day 1, and repeated every 21 days. The high-dose regimen used peripheral blood stem cells as a stem cell rescue. The CECb (n = 27) and CEF groups (n = 26) were similar with respect to different prognostic factors. In the CECb group, the mean times to neutrophil and platelet recovery were 10.29 and 11.00 days respectively. The mean time of empiric antibiotic therapy was 8.59 days. The complications of the high-dose regimen were mild (grades II and III) and were mainly gastrointestinal (vomiting, diarrhoea and mucositis). In both groups of the study, there were no life-threatening complications or treatment-related mortality. At a median follow-up period of 30 months, the 3-year disease-free survival of the CECb group (50.5%) was better than that of the CEF group (29.4%), but the difference did not reach statistical significance (P = 0.137). The 3-year overall survival of CECb cases (82.8%) was slightly higher than that of the CEF cases (76.9%), but the difference was also statistically insignificant (P = 0.763). It was concluded that further follow-up and additional studies would be required to evaluate the role of high-dose adjuvant chemotherapy in high-risk breast cancer patients [*16*].

Because more patients recently presented with early lesions that may not necessitate radical surgery, conservative treatment results, pattern and determinants of recurrence were evaluated in a series of 60 patients presenting to the NCI with T1-T2, N0-N1, M0 stages [*17*]. In this group of patients, disease-free survival was 83% and 78% at 5 and 10 years respectively. Disease recurrence occurred in 11 patients (18.3%); 6 patients had local recurrence, 2 had ipsilateral nodal recurrence, 2 had distant metastases and 1 had contralateral primary tumours. The most important factor that affected treatment failure was the ability to achieve a negative margin exceeding 2 cm of normal tissue around the tumour. Other factors included tumour size, associated *in situ* components and nodal involvement.

The ability to assess such local failure after breast conserving therapy was addressed in another study [*18*]. The aim was to evaluate triple assessment (clinical examination, cytology and mammography) and magnetic resonance imaging in the differentiation of post-treatment changes and local recurrence of breast cancer after conservative therapy. In 25 cases studied, the sensitivity of cytological examination, mammography and magnetic resonance imaging (MRI) was 66.0%, 77.8% and 100% respectively. However, false positive results of MRI examination were seen in 2 patients (specificity 87.5%). The authors therefore suggested that when triple assessment is inconclusive, MRI is a more accurate technique in diagnosing tumour recurrence than scan formation but that the interpretation of data should be cautious during the first postoperative years.

Treatment of the axilla by surgery, i.e. axillary lymph node dissection, with or without radiotherapy remains an integral part of the management of breast cancer patients. This procedure is an effective staging process that defines prognosis and further management of patients as well as being essential for local control of the disease in the axilla [*19*]. The pattern of axillary lymph node metastases in Egyptian patients was examined in a series of 50

women with operable breast cancer who underwent axillary lymph node dissection as part of their primary therapy [*19*]. The median number of identified nodes in the dissection was 18.5 lymph nodes. Pathologic involvement of lymph nodes was found in 41 cases (82%), 46% had 1 to 3 positive nodes and 24% had 4 to 9 positive nodes. The frequency of lymph node metastases was 80% at level I, 34% at level II, 20% at level III and 4% at brachial lymph nodes (Table 1). Thus, complete axillary lymph node dissection is still advised for patients with invasive breast cancer as many Egyptian patients present with relatively advanced cases.

Optimization of the best line of systemic adjuvant therapy for early breast cancer patients has been the main objective of many clinical trials worldwide throughout the past three decades. The NCI was scientifically affiliated in the 1976 to the South West Oncology Group clinical trials cooperative group, sharing in its different study protocols in the field of cancer chemotherapy. In one of these studies, the relative efficacy of the CMF-VP combination regimen [cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone] and the drug melphalan given on adjuvant basis was evaluated in a randomized study of 80 Egyptian patients. At 15-year follow-up, there was a significant difference both in disease-free and overall survival rates in favour of the CMF-VP regimen compared with melphalan ($P = 0.001$) [*20*]. This was subsequently followed by a phase III clinical trial evaluating the role of postoperative chemotherapy and radiotherapy in our patients using the 1980s standard CMF regimen. This study confirmed the value of adjuvant therapy for breast cancer patients presenting to NCI.

Table 1 **Incidence of positive nodes ($n = 41$) in different levels of axillary lymph nodes**

Level of positive axillary lymph node	No. of cases	%
Level I alone	23	56.1
Levels I and II	8	19.5
Levels II and III	9	22.0
Level III alone	1	2.4
Total	41	100.0

Source: [19].

There is, however, a continuing controversy about the timing and sequence of these two important postoperative treatment modalities. The type, dose, timing and sequence of both adjuvant chemotherapy and radiotherapy have been addressed by a group of investigators at Ain Shams University [*21,22*]. The prediction of the clinical course of a primary breast tumour is very difficult. It would be useful to identify individual patients who have a high or low risk of relapse in order to plan the appropriate treatment for each patient. This would help to spare the potential toxicity of unneeded therapy, while patients whose tumours are most likely to recur could be given the option of aggressive adjuvant therapy.

Many prognostic factors have been studied and identified and include tumour size, lymph node status, estrogen receptor status, pathologic subtype and patient age. An index known as the Nottingham prognostic index was previously described by Haybittle et al. [*23*]. Using this index with 410 female patients with breast cancer, it was found that the Nottingham prognostic index was not applicable to our patients since 99.3% of cases were allocated to the poor prognosis group. Hence, the cut-off values were modified and the NCI prognostic index succeeded in dividing patients

into two main groups. The prognosis of patients with prognostic index > 3.2 was poorer than those with prognostic index ≤ 3.2 with *P*-value of < 0.001, necessitating the use of more aggressive systemic therapy for this group of patients [*24*].

The influence of age at diagnosis of breast cancer on prognosis has been evaluated in another study [*25*] in which 1208 premenopausal Egyptian women with stage I–III disease were followed. Patients were divided into three groups and the clinical and pathological characteristics and treatment methods were balanced between the three groups. It was found that 15-year actuarial overall survival rates were 24% for women aged < 35 years, 31% for 3540 years and 52% for > 40 years (Figure 1). It was concluded that young age in premenopausal Egyptian women may carry poorer prognosis and should be considered as an adverse prognostic factor when deciding treatment policy.

The increasing application of systemic adjuvant therapies to patients with earlier stage disease, even those with a lower risk of breast cancer recurrence, extends the absolute benefits of adjuvant therapy to more women. However, it also exposes a greater proportion of women with breast cancer to the potential of late complications of the adjuvant therapy. In particular, tamoxifen therapy has been used as a long-term standard adjuvant therapy for many patients, particularly those with ER/PR positive tumours. Recently an increasing number of reports suggest a possible association between tamoxifen and induction of endometrial pathologies including cancer. Therefore 50 postmenopausal breast cancer patients receiving tamoxifen for long periods and 30 matched postmenopausal breast cancer patients not receiving tamoxifen were examined by pelvic and transvaginal ultrasonography followed by endometrial cytology [*26*]. It was reported that the patients on tamoxifen therapy had a thicker endometrium (9.9 mm) and that the difference was highly significant when compared with the control group ($P < 0.001$). The sonographic evaluation showed abnormal endometrial appearance in 21 tamoxifen-treated women. Cytology of the 50 patients undergoing tamoxifen treatment showed 8 had cystic hyperplasia, 9 simple hyperplasia with associated polyps in 3 cases, 13 with atrophic changes and 16 with normal endometrium. In the control group, only 1 patient had an abnormal ultrasonographic finding that proved to be simple hyperplasia on cytological examination. Based on these findings, it was concluded that all postmenopausal breast cancer patients undergoing tamoxifen treatment should have periodic ultrasonographic examinations and that those with endometrial pathology should undergo cytology or biopsy for sonographically abnormal lesions [*26*].

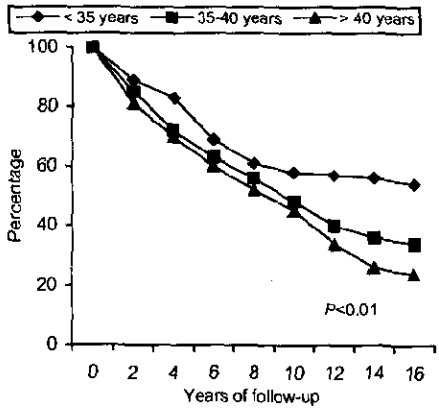

Figure 1 **Actuarial overall survival by age groups of 1208 patients. Source: [25]**

Anthracycline-containing regimen is now the standard treatment for most patients needing adjuvant chemotherapy. However, acute and chronic dose-related cardiomyopathy is a major limitation to the optimal use of this group of chemotherapeutic agents. The validity of monitoring serum troponin I and serum creatine kinase-MB isoenzyme (CK-MB) versus the standard echocardiography for early diagnosis of cardiotoxicity in 31 breast cancer patients treated by adjuvant FAC therapy [5-fluorouracil, doxorubicin, cyclophosphamide] was assessed [*27*]. The study demonstrated that the use of serial serum monitoring of cardiac troponin I as an early sensitive detector of acute myocardial injury could be of value to such patients.

It has been suggested that there is an increased incidence of thrombosis in cancer patients treated with chemotherapy. In a series of 40 patients, prothrombin time, partial thromboplastin time, protein C and protein S were estimated before and after receiving six cycles of adjuvant CMF regimen. The mean levels of the four tested parameters were statistically significantly decreased after CMF chemotherapy. However, none of the patients manifested any thromboembolic complications. It was suggested that patients with a decrease in protein C and protein S after chemotherapy should be monitored closely to prevent thromboembolic complications [*28*].

Locally advanced and metastatic disease

Some of the potential benefits of preoperative chemotherapy in primary operable and locally advanced breast cancer are to improve patient survival and support the more frequent use of breast conserving treatment modalities, especially in cases with early stage disease.

As the NCI is currently a member of the European Organization for Research and Treatment of Cancer, we have participated in EORTC trial 10902 in which preoperative neoadjuvant therapy using four cycles of FEC60 [5-fluorouracil, epirubicin, cyclophosphamide] were compared in a randomized trial versus the same regimen administered postoperatively to eligible cases with stages T1c, T2, T3, T4b, N0 to N1 [*29*]. A total of 698 cases were enrolled in the study, 42 from Egypt. The conclusion was that the use of neoadjuvant chemotherapy yields similar results in terms of progression-free and overall survival and locoregional control compared with conventional postoperative chemotherapy.

In another study at the Department of Oncology, University of Alexandria, the role of neoadjuvant chemotherapy in combined modality treatment of locally-advanced breast cancer cases was assessed in a trial of 111 patients [*30*]. Patients were randomized into two groups: the study group A (61 patients) and the control group B (50 patients). Group A patients received three cycles of neoadjuvant FAC therapy [5-fluorouracil 500 mg/m^2, adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every three weeks]. Lumpectomy and axillary dissection were performed for patients achieving downstaging to ≤ T2 followed by external irradiation (45 Gy/4.5 weeks) and boost to tumour bed by iridium-192 or electron beam (15–20 Gy). Those whose tumours were still > T2 after chemotherapy and irradiation underwent simple mastectomy and axillary dissection. All group A patients received 5 cycles of adjuvant FAC and, in addition, postmenopausal women were given tamoxifen (20 mg/day). Complete and partial responses of the primary tumour and nodal disease after

neoadjuvant chemotherapy and external irradiation were 80%, while downstaging to ≤ T2 was achieved in 51%. Group B patients were operated on either by modified radical mastectomy or simple mastectomy with axillary dissection followed by external irradiation (45 Gy/4.5 weeks), then six cycles of adjuvant chemotherapy CMF for premenopausal or tamoxifen (20 mg/day) for postmenopausal women. Follow-up ranged between 14 and 36 months. The locoregional and distant relapse rates were 13.2% and 10.5% versus 28.3% and 17.4% for groups A and B respectively. Median disease-free survival was 16 and 15 months for both groups A and B. Actuarial disease-free survival at 1 and 3 years was 89% and 54% for group A compared with 73% and 12% for group B. Median overall survival was 20 months for group A versus 19 months for group B, with actuarial survival of 96% and 65% at 1 and 3 years for group A compared with 83% and 25% for group B.

Treatment of recurrent, metastatic and inoperable locally advanced disease is essentially palliative. Treatment options include mainly hormonal manipulation, chemotherapy and other supportive and palliative measures.

The response to endocrine therapy and its relationship to the clinical features of the disease were studied in 84 Egyptian patients with advanced disease through an Anglo-Egyptian Health Agreement Collaborative Study [*31*]; 24 premenopausal patients were treated by oophorectomy (1/20 objective response) while 60 postmenopausal patients received tamoxifen (14/57 objective response). The outcome for postmenopausal patients was similar to that found in a parallel study at Guy's Hospital in London. The value of systemic chemotherapy was assessed in several studies.

As with hormonal therapy, patients with advanced or recurrent breast cancer can be palliated by single agent or combination chemotherapy and those who achieve a good response may enjoy prolonged control of their disease.

As second line therapy in patients who have relapsed or were refractory to first line therapy, Gad El-Mawla et al. have tried ifosfamide instead of cyclophosphamide in the classic combination of CMF. Among 24 patients, a complete remission was achieved in 3 patients (12.5%) and a partial response in another 3 patients (12.5%). The efficacy of ifosfamide-containing chemotherapy as second-line therapy was demonstrated [*32*].

The effect of the drug epirubicin as a single agent front-line therapy in metastatic breast cancer was studied in 1991 for a group of 40 patients. The patients were divided into two groups (20 patients each) and the first group received 30 mg/m^2 weekly. In the second group, epirubicin was given as 90 mg/m^2 every 3 weeks. While cardiac monitoring, including endomyocardial biopsy, revealed no serious cardiac toxicity, clinical results were 35.3% overall response in group I and 50% overall response in group II [*33*].

The search for new chemotherapeutic agents and the better use of existing drugs have been continuously researched for the treatment of all types of cancers including breast cancer. In 1997 the efficacy and tolerability of the combination of vinorelbine and 5-fluorouracil was tested as a first-line treatment in a cohort of 31 patients with metastatic and recurrent disease. The combination was tolerable, with only grade I and II toxicity in most patients. An overall response rate of 55% was detected (16/29 patients) and complete remission rate was documented in 14%

(4/29 patients). Responses occurred in all disease sites, particularly in locoregional disease [*34*].

The proven activity of paclitaxel in patients with advanced disease encouraged another group of researchers to investigate the combination of paclitaxel and doxorubicin [*35*]. They compared the combination to the standard FAC regimen in 57 and 58 cases respectively in a single blind randomized phase III clinical trial. The overall objective response rates in both groups were 68.4% and 48.3% in group I and group II respectively. At a median follow-up time of 35 months, the median time to treatment failures were 10.4 months and 7.6 months. The median overall survival was 22.0 months and 22.2 months respectively. The authors noted that paclitaxel and doxorubicin combination is an effective and tolerable therapy with superior overall response rate and time to treatment failure when compared with the standard FAC regimen.

Because metastases commonly invade bone in many cases with consequent development of complications including progressive and severe pain, a comparative study to manage bone pain was conducted on a group of 60 females with metastatic breast cancer. The patients were randomly allocated to receive either pamidronate disodium, calcitonin or a combination of the 2 drugs. Significant decrease in bone pain scoring was found in the pamidronate and in the combination group, while calcitonin was found to be more hypocalcaemic with rapid action. This suggested that the combination of the 2 drugs benefited from the rapid onset of calcitonin and the delayed but more prolonged action of pamidronate [*36*].

In some cases with recurrent and locally advanced breast cancer, the situation may be distressing to both patient and treating physician. Excision of such lesions was tried in 23 women with the use of transverse rectus abdominis myocutaneous flap and latissmus dorsi myocutaneous flap as palliative measures, with reasonable outcomes in terms of morbidity and mortality [*37*].

The need for additional prognostic indicators to improve the identification of breast cancer patients with different levels of risk has led in the last 10 years to the use of a plethora of potential markers. In a prospective study, the response of 60 recurrent or metastatic breast cancer cases to therapy on the basis of the tumour EGFR and ER status was examined. A total of 28 patients received hormonal therapy (tamoxifen) and 38 received the CEF chemotherapy regimen [*38*]. In the group receiving hormonal therapy, 10/12 (83.3%) of the ER-positive and 4/13 (30.8%) of the ER-negative cases responded ($P = 0.02$). While none of the 6 women with EGFR-positive tumours responded to hormonal therapy, 14/19 (73.7%) of EGFR-negative did ($P = 0.003$). In the group receiving chemotherapy, 17 of the 18 (94.4%) ER-positive tumours and 7 of 12 (58.3%) ER-negative cases responded ($P = 0.03$). Furthermore, 19 of 21 (90.5%) EGFR-negative cases showed an objective response compared with 5 of 9 (55.6%) EGFR-positive cases ($P = 0.02$). When analysed in relation to ER status and EGFR expression, the 2-year time to progression in the chemotherapy group was 36.1% for the ER-positive and 0% for the ER-negative cases ($P = 0.001$). Furthermore, it was 25.8% for the EGFR negative versus 0% for the EGFR positive cases ($P = 0.001$). In the hormonal group, the 2-year time to progression was 83.3% and 30.8% for the ER-positive and negative cases ($P = 0.003$) and was 73.7% and 0% for the EGFR-positive and negative cases ($P = 0.001$)

respectively. A total of 83% of the ER-positive and 83.9% of the EGFR-negative cases in the hormonal group survived for 2 or more years, while in the CEF group 53.9% of ER positive and 41.0% of EGFR negative survived for 2 or more years. It was concluded that EGFR status appeared to be a useful marker for predicting lack of response to endocrine therapy and chemotherapy giving complementary information to ER.

Also, the correlation between erythrocyte glutathione (GSH) level and thyroid hormone level in response to chemotherapy, as well as the potential prognostic value of serum osteocalcin in patients with advanced breast cancer, was examined in two subsequent studies [*39,40*] with very interesting results. In the first study, those who responded to the FEC regimen showed statistically significant lower levels of T3, T4 and GSH as compared to non-responders. In the second study, serum osteocalcin levels were increased in patients with bone metastases but decreased in those with visceral metastases.

Inflammatory breast cancer

Inflammatory carcinoma is one of the most aggressive types of breast cancer. This type of cancer has been considered a clinicopathological entity characterized by diffuse browny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. A strikingly high incidence of this form of breast cancer has been described in Tunisia and Egypt compared with reports from Europe and North America. It is unclear, however, whether this difference is related to basic biological characteristics of the disease or variability in diagnostic criteria. Two types have been distinguished: a primary type in which inflammatory changes appear simultaneously with the carcinoma; and a secondary type in which the inflammatory manifestations appear in the breast with long-standing carcinoma.

The poussee evolutive (PEV) staging system for tumour evolution is usually adopted for staging patients with inflammatory breast cancer. In a study of 73 patients classified according to this staging system at the NCI in the 1980s [*41*], 48 cases were diagnosed as inflammatory (PEV2 and PEV3) and 25 were non-inflammatory (PEV0 and PEV1). The histopathology verified 45 cases of which 35 had primary type and 10 had secondary type; 29% of the inflammatory cases were postmenopausal. The median age of such cases was 42 years with a peak incidence in the fifth decade of life (44%). Bilateral breast involvement was encountered in 4 cases. All inflammatory breast cancer cases had lymph node involvement at presentation, 75% had axillary and 25% had both axillary and supracalvicular node involvement. A great number of cases occurred during pregnancy (27%). Bigger tumour size at presentation (mean 7.2 cm) was also observed. The majority of inflammatory breast cancer cases were ER-negative (73%). The relation between evolutionary phase and 5-year relapse-free survival are presented in Table 2. It was clear from this study that cases with inflammatory breast cancer needed more aggressive systemic chemotherapy and that chemotherapy must be given prior to local primary treatment.

Prevention and early detection

As breast cancer represents an important public health problem, primary prevention should be given the highest priority in the fight against the disease. Early detection

Table 2 **Relation between evolutionary phase and 5-year relapse-free survival**

Evolution phase	No. of patients	% survival
PEV0	233	46.0
PEV1	56	26.0
PEV2	65	18.5
PEV3	14	21.4
Total	368	

$P < 0.001$.
Source: [38].

must be considered the best second choice for reducing mortality. Breast self-examination, physical examination by the treating physician, ultrasound and mammography have been used along with other procedures to detect breast cancer early.

There are no studies from Egypt on prevention. However, evaluation of the effect of breast self-examination training programmes on knowledge, attitude and practice of a group of 122 working women was conducted at Ain Shams University [*42*]. Only 10.6% and 11.5% of the total sample had satisfactory knowledge about breast cancer and breast self-examination. While the majority of cases mentioned lack of knowledge, 50% were afraid and worried to discover breast cancer. After implementing the programme, a remarkable improvement in participant knowledge, attitude and practice was observed.

While a wide-scale early detection trial using routine mammographic examination conducted at the Italian Hospital in Cairo has produced very interesting results, another study has investigated how to approach cases with non-palpable mammographically detected lesions. It included 27 patients for whom mammographic wire localization technique was used to direct biopsy taking. Results were very satisfactory and no serious complications were encountered in the procedure. This technique allowed accurate diagnosis and prompt treatment of such early cases [*43*].

In another study, 60 women who had solitary mammographic findings were given mammographically guided stereotactic core biopsy together with post-localization-defined, speculated and partially ill-defined densities whereas it ranged between 67% and 76% for asymmetrical densities, focal parenchymal distortion, asymmetrical ducts and clusters of microcalcifications. The overall accuracy rate was 81.4%. For the latter mammographic findings it was advised to shift to conventional open therapy [*44*].

References

1. Ries LAG et al. *SEER cancer statistics review, 1973–1997.* Bethesda, Maryland, National Cancer Institute, 1999.
2. Elatar I. *Cancer registration, NCI Egypt 2001.* Cairo, Egypt, National Cancer Institute, 2002 (http://www.nci.edu.eg/Journal/nci2001%20.pdf, accessed 1 April 2004).
3. Ibrahim AS et al. *Cancer profile in Gharbiah, Egypt. Methodology and results.* Cairo, Ministry of Health and Population Egypt and Middle East Cancer Consortium, 2002.
4. Abdel-Wahab AA. Frequent allelic losses at the short arm of chromosome 3p in invasive ductal carcinoma of breast in

Egypt. *Journal of the Egyptian National Cancer Institute*, 2000, 12(2):145–50.

5. Zekri AR et al. Allelic instability as a predictor of survival in Egyptian breast cancer patients. *International journal of oncology*, 1999, 15:757–67.
6. Bahnassi A et al. The role of allelic imbalance at chromosome 2p16 in breast cancer progression. *Journal of Egyptian National Cancer Institute*, 2000, 12:211–20.
7. Mansour OA et al. Tissue and serum c-ErbB-2 and tissue EGFR in breast carcinoma: three years follow-up. *Anticancer research*, 1997, 17:3101–6.
8. Mansour OA et al. Epidermal growth factor receptors: status and effect on breast cancer patients. *Anticancer research*, 1997, 17:3107–10.
9. El-Bolkainy MN. *Topographic pathology of cancer*, 2nd ed. Cairo, National Cancer Institute, Cairo University, 2000:87.
10. Mokhtar N. *Cancer pathology registry*. Cairo, Department of Pathology, National Cancer Institute, 1991.
11. El-Gemeie E, El-Didi M, Nouh A. Fine needle aspiration of breast lesions: the experience of the Egyptian National Cancer Institute. *Journal of the Egyptian National Cancer Institute*, 1997, 9(3): 239–46.
12. Salih AM, El-Morsy B, Mohamed NH. Cytopathological diagnosis of breast lesions among Egyptians by fine needle sampling without aspiration: using only the needle. *Journal of the Egyptian National Cancer Institute*, 1996, 8(2):203–11.
13. El-Badawi M, Zaki I, Tantawi S. Magnetic response mammography: diagnostic potentials in breast cancer. *Journal of the Egyptian National Cancer Institute*, 1999, 11(1):91–8.
14. Ali R, Zedan A. Differentiation between malignant and benign breast lesions using technetium-99m sestamibi. *Journal of the Egyptian National Cancer Institute*, 1996, 8(2):225–9.
15. Saber RA. Assessment of breast carcinoma by 99mTc-sestamibi scintimammography: effect of lesion site, size and histopathological characteristics. *Journal of the Egyptian National Cancer Institute*, 2000, 12:183–9.
16. Omar S, Contesso G, Khaled H. *Breast cancer*, 4th ed. Cairo, National Cancer Institute, Cairo University, 2001.
17. El-Naggar MH et al. Determinants of recurrence after conservative treatment of breast cancer. *Journal of the Egyptian National Cancer Institute*, 1999, 11(2): 99–108.
18. Abdalla H et al. Detection of local recurrence after breast conserving therapy. *Journal of the Egyptian National Cancer Institute*, 2001, 13(2):93–9.
19. Zaghloul AS et al. Pattern of axillary lymph node metastasis from breast cancer in Egyptian patients. *Journal of the Egyptian National Cancer Institute*, 2001, 13(1):1–8.
20. Gad-El-Mawla N et al. Adjuvant chemotherapy of primary breast cancer: single agent versus combination chemotherapy. The Egyptian experience. *Journal of the Egyptian National Cancer Institute*, 1993, 6:225–32.
21. Youssef A et al. Five year results of adjuvant CMF and postoperative radiotherapy in node positive premenopausal women with operable breast cancer randomization in timing of chemotherapy. *Journal of the Egyptian National Cancer Institute*, 1995, 7(1):61–5.
22. Youssef A et al. Concomitant adjuvant epirubicin containing chemotherapy and postoperative radiotherapy in premenopausal patients with respectable breast carcinoma and more than three

positive axillary nodes: A pilot study. *Journal of the Egyptian National Cancer Institute*, 1995, 7(2):169–74.

23. Haybittle JL et al. A prognostic index in primary breat cancer. *British journal of cancer*, 1982, 45:361–6.

24. El-Mongy M et al. Prognostic index in breast cancer: evaluation and correlation with treatment results. *Journal of the Egyptian National Cancer Institute*, 1997, 9(3):191–9.

25. El-Gantiry M. Breast carcinoma in 1208 premenopausal Egyptian patients: Treatment results at fifteen years with emphasis on age as a prognostic factor. *Journal of the Egyptian National Cancer Institute*, 1997, 9(1):1–10.

26. Abu Rabia A, Helal M, Mohamed NH. Ultrasonographic appearance of the endometrium in postmenopausal breast cancer patients on long-term tamoxifen therapy. *Journal of the Egyptian National Cancer Institute*, 1999, 11(2):189–95.

27. Sedky L et al. The value of troponin measurement in assessment of anthracycline induced cardiotoxicity in breast cancer patients. *Journal of the Egyptian National Cancer Institute*, 2000, 12(1): 35–40.

28. Abou Taleb FM, El-Nemr NM, al-Husseiny H. Thrombogenesis in patients with breast cancer treated with adjuvant CMF protocol. *Journal of the Egyptian National Cancer Institute*, 2000, 12(2): 125–9.

29. Van der Hage JA et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer, trial 10902. *Journal of clinical oncology*, 2001, 19(22):4224–37.

30. El-Noweim SA et al. Combined modality approach of locally advanced breast cancer with conservative surgery. *Journal of the Egyptian National Cancer Institute*, 1995, 7(1):123–30.

31. Richards MA et al. Advanced breast cancer in Egyptian women: clinical features and response to endocrine therapy. *European journal of surgical oncology*, 1992, 18:219–23.

32. Gad El-Mawla N et al. Ifosfamide, methotrexate and 5-fluorouracil: effective combination in resistant breast cancer. *Cancer chemotherapy and pharmacology*, 1999, 26(suppl.):S85–6.

33. Gad El-Mawla N et al. A phase II study of epirubicin in breast cancer. *Anti-cancer drugs*, 1991, 2:371–4.

34. Osman I, El-Hattab O. Phase II study of Vinorelbine (Navelbine) with 5-fluorouracil infusion in metastatic infusion in metastatic and recurrent breast cancer. *Journal of the Egyptian National Cancer Institute*, 1997, 9(2):127–31.

35. Ali NM, El-Hattab O. Paclitaxel plus doxorubicin combination as first line treatment in metastatic breast cancer patients: comparison with fluoruocil, doxorubicin and cyclophosphamide regimen (a single blind randomized clinical trial). *Journal of the Egyptian National Cancer Institute*, 1999, 11(2): 151–6.

36. El-Wasseef MM et al. Pamidronate disodium versus calcitonin: a comparative study in the management of malignant bone pain in metastatic breast cancer patients. *Journal of the Egyptian National Cancer Institute*, 2001, 13(2):109–15.

37. Naguib SF. Salvage surgery for recurrent and locally advanced breast cancer. *Journal of the Egyptian National Cancer Institute*, 1999, 11(3):197–203.

38. Gaafar R et al. Prognostic significance of epidermal growth factor receptor and

estrogen receptor in advanced breast cancer. *Journal of the Egyptian National Cancer Institute*, 1996, 8(2):231–9.

39. Hashem T et al. The correlation between erythrocyte glutathione level and thyroid hormones levels in blood and response to chemotherapy in patients with advanced breast cancer. *Journal of the Egyptian National Cancer Institute*, 1996, 8(1):39–44.
40. Shouman SA, Saber MM, El-Marzabany M. The potential value of serum osteocalcin in patients with metastatic breast cancer. *Journal of the Egyptian National Cancer Institute*, 1995, 7(2):199–205.
41. Omar S et al. End result of breast cancer therapy. II. Clinical immunological and hormonal profile of inflammatory carcinoma of the breast. A: Clinicopathological aspects. *Cancer prevention and therapy*, 1989, 1:29–41.
42. Seif NY, Aziz MA. Effect of breast self-examination training programme on knowledge, attitude and practice of a group of working women. *Journal of the Egyptian National Cancer Institute*, 2000, 12(2):105–15.
43. Naguib S et al. Mammographic wire localization for non-palpable breast cancer. *Journal of the Egyptian National Cancer Institute*, 1999, 11(1):1–8.
44. Hafez MH, Selim A. Accuracy of stereostatic core biopsy for non-palpable breast lesion. *Journal of the Egyptian National Cancer Institute*, 1998, 10(3): 333–9.

Regional consultation on early detection and screening of breast cancer

The World Health Organization organized a Regional Consultation on Early Detection and Screening of Breast Cancer in Cairo, Egypt from 21 to 24 October 2002. The objectives of the Consultation were: to promote early screening and detection of breast cancer in the Region; to establish cost-effective measures for reducing mortality of breast cancer; to have international views and experience on detection and management of breast cancer; and to review previous regional guidelines for the management of breast cancer (1995). Experts from Egypt, Lebanon, Qatar, Tunisia, United Kingdom, United States of America, and the International Agency for Research on Cancer as well as WHO concerned staff participated in the Consultation.