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Use of CA15-3, CEA and prolactin for the primary diagnosis of breast cancer and correlation with the prognostic factors at the time of initial diagnosis

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The main goals of the clinical use of tumor markers are to evaluate the adequacy of the treatment, monitor recurrence and follow up response to the treatment applied. For this purpose a baseline level for the commonly used tumor marker must be known at the time of initial diagnosis, before any therapy, in order to compare with the tumor marker levels which will be obtained after the treatment and during the clinical follow-up. The aim of this study was to investigate the correlation, if there is any, of the baseline levels of CA15-3, CEA and prolactin (PRL) in patients with breast cancer with the most commonly used prognostic factors, i) the presence of distant metastasis, ii) the presence of axillary lymphatic invasion, iii) the number of invaded axillary lymph nodes, iv) tumor size and v) stage of the disease, for breast cancer. Baseline serum CA15-3, CEA and PRL levels of 172 patients with breast masses were determined prior to biopsy. The sensitivity and specificity of baseline CA15-3, CEA and PRL were; 23.2% and 95.3%,17.4% and 83.7%, 5.8% and 97.6%, respectively. At least one of the three tumor markers was high in 36% (31/86) of the breast cancer patients. Baseline CA15-3 levels were frequently higher than CEA in patients with bone metastasis (60% vs. 20%) and axillary lymphatic invasion (31.8% vs. 25%), and showed a better correlation with the stage of disease. Baseline tumor marker levels showed no statistically significant correlation with either the number of invaded axillary lymph nodes or tumor size. In conclusion, sensitivities and negative predictive values for baseline CA15-3, CEA and PRL were not satisfactory for primary diagnosis of breast cancer. Correlation of baseline CA15-3 was found superior to CEA and PRL in terms of stage of disease, presence of axillary invasion and distant metastasis.

Key words: breast cancer, tumor markers, primary diagnosis, prognostic factor

INTRODUCTION

APPROXIMATELY more than 700,000 breast cancer patients are diagnosed in the whole world annually and it remains the leading cause of death among women aged 40 to 55 years.[1] Determination of prognostic factors is one of the key decisions in the current management of primary breast cancer. Although several prognostic factors have been reported to be useful for this purpose, very few of these are sufficiently established at this time to be clinically helpful, except for the classic pathologic parameters. Serum tumor markers have little diagnostic value in screening or diagnosing breast cancer due to their low increase in early stage breast cancer.[2,3] On the other hand, tumor markers are widely used to evaluate the adequacy of the treatment, monitor recurrence and follow up response to the treatment applied. For this purpose a baseline level for the commonly used tumor marker must be known at the time of initial diagnosis, before any therapy, in order to compare with the tumor marker levels which will be obtained after the treatment and during the clinical follow-up. The aim of this study was to investigate the correlation, if there is any, of the baseline levels of

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Table 1 Histopathologic results of 172 patients

Histopathologic and cytologic findings	Number of patients
Malignant Patients	
Infiltrating ductal carcinoma	60
Mucinous carcinoma	6
Infiltrating lobular carcinoma	5
Ductal carcinoma *in-situ* (DCIS)	4
Medullary carcinoma	2
Invasive metaplastic carcinoma	2
Infiltrating ductal carcinoma and DCIS	1
Infiltrating ductal carcinoma with Paget's disease	1
Lobuler carcinoma *in-situ* (LCIS)	1
Infiltrating lobular carcinoma and LCIS	1
Infiltrating lobular carcinoma and DCIS	1
Inflammatory carcinoma	1
Tubulolobular carcinoma	1
Benign Patients	
Fibrocystic disease	39
Fibroadenoma	18
Gynecomastia	9
Fibrocystic disease and fatty necrosis	3
Ductal ectasia	3
Fibrocystic disease and ductal ectasia	2
Normal breast parenchyma	2
Adipose tissue	2
Intraductal papilloma	2
Granulation tissue	2
Fibroadenoma and ductal ectasia	1
Fibroadenoma and fibrocystic disease	1
Radial scar	1
Sclerosing adenosis	1

CA15-3, CEA and PRL in patients with breast cancer with the most commonly used prognostic factors, i) the presence of distant metastasis, ii) the presence of axillary lymphatic invasion, iii) the number of invaded axillary lymph nodes, iv) tumor size and v) stage of disease, for breast cancer.

MATERIALS AND METHODS

Baseline serum levels of CA15-3, CEA and PRL were determined for 172 patients (aged 16 to 89 years; mean age = 47.9 ± 15.2 years) with a palpable mass on physical examination and/or abnormal mammographic finding who would be candidates for biopsy. Of all 172 patients, 86 had breast malignancy and 86 had benign breast masses according to the final histopathological diagnosis (Table 1). Of all breast cancer patients, 22 had stage I, 50 had stage II, 6 had stage III and 8 had stage IV disease. For all malignant patients, the stage of the disease was determined by evaluating the presence of distant metastasis, the presence of axillary lymphatic invasion, tumor size

Table 2 Mean values of CA15-3, CEA and PRL in patients with breast lesions

Marker	Cut off	Malign	Benign	p value
		Mean ± SEM	Mean ± SEM	
CA15-3	38 U/ml	31.53 ± 4.46	17.44 ± 0.93	0.003
CEA	4.5 ng/ml	3.34 ± 0.48	2.46 ± 0.20	0.099
PRL	29 ng/ml	12.24 ± 0.90	11.51 ± 0.63	0.512

SEM: Standard error of mean

Table 3 Serum tumor markers for primary diagnosis of breast cancer

Marker	Sv, n (+/–)	Spc, n (+/–)	PPV (%)	NPV (%)	p value
CA15-3	23.2 (20/86)	95.3 (82/86)	83.3	55.4	< 0.001
CEA	17.4 (15/86)	83.7 (72/86)	51.7	50.3	0.838
PRL	5.8 (5/86)	97.6 (84/86)	71.4	50.9	0.246
CA15-3 + CEA	33.7 (29/86)	79.0 (68/86)	61.7	54.4	0.089
CA15-3 + PRL	26.7 (23/86)	93.0 (80/86)	79.3	55.9	0.001
CA15-3 + CEA + PRL	36.0 (31/86)	76.7 (66/86)	60.7	54.5	0.096

Sv: sensitivity, Spc: specificity, PPV: positive predictive value, NPV: negative predictive value

Table 4 The incidences of tumor marker positivity for different stages of breast cancer

Marker	Stage I (n = 22)	Stage II (n = 50)	Stage III (n = 6)	Stage IV (n = 8)	p value
CA15-3	16.6 ± 1.4 (0%)	24.9 ± 1.9 (22%)	53.3 ± 11.5 (66.6%)	62.5 ± 17.5 (62.5%)	< 0.001
CEA	2.4 ± 0.5 (4.5%)	2.9 ± 0.4 (22%)	6.2 ± 3.1 (66.6%)	4.3 ± 1.1 (50%)	0.063
PRL	11.0 ± 1.4 (0%)	12.0 ± 1.1 (6%)	18.3 ± 7.2 (33.3%)	11.9 ± 1.9 (0%)	0.805

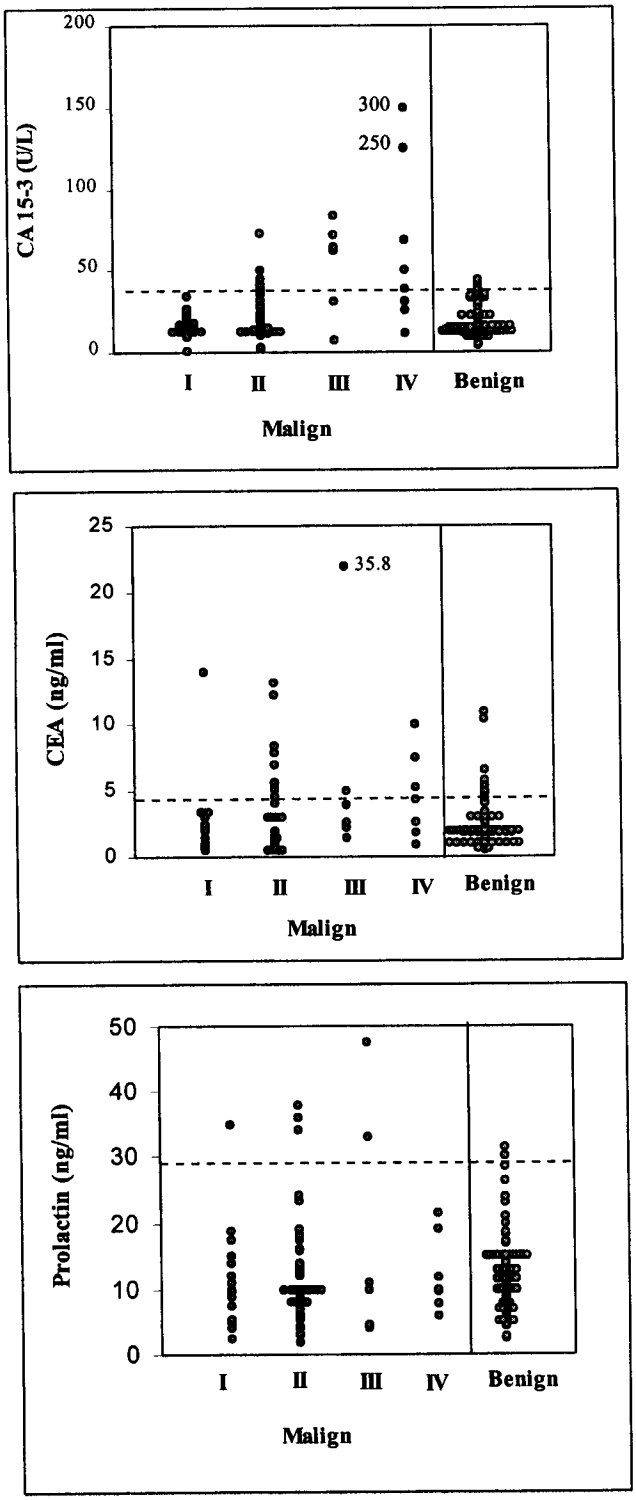

Fig. 1 The categorization of patients according to stage of disease and cut-off values.

and the number of invaded axillary lymph nodes. Finally, tumor marker levels were compared with each prognostic parameter at the time of initial diagnosis.

CA15-3 levels were determined by using an immunoradiometric assay method (Diagnostics Products Corporation, CA, USA) with a cut-off level of 38 U/m*l*. CEA and PRL levels were determined by a two-site chemiluminometric immunoassay method (Ciba Corning Diagnostic Corp., ACS CEA, MA, USA). A cut-off level of 4.5 ng/m*l* was used for CEA. On the other hand, expected PRL values for nonpregnant and postmenopausal females were 2.8–29.2 ng/m*l* and 1.8–20.3 ng/m*l*, respectively.

Statistical analyses were performed with Kruskal Vallis, independent sample t, Mann-Whitney-U, Chi-Square and Fisher Chi-Square tests. Pearson's correlation test was used to determine the relationships between all quantifiable data. Difference was regarded as statistically significant when p values < 0.05. All calculations were performed with SPSS for Windows, Version 6.0.

RESULTS

At least one of the three tumor markers was high in 36% (31/86) of the breast cancer patients. Among three serum markers, only CA15-3 levels were significantly higher in breast cancer patients than in patients with benign breast masses ($p = 0.003$) (Table 2). The sensitivity (23.2%), specificity (95.3%), positive (83.3%) and negative (55.4%) predictive CA15-3 values were found superior to CEA and PRL (Table 3). Combining CA15-3 with CEA demonstrated a higher sensitivity (33.7%), but, the specificity was decreased to 79.0%. On the other hand, despite its low specificity (76.7%), combining CA15-3 with both CEA and PRL showed the greatest sensitivity (36.0%) for the detection of breast cancer. For differentiation of malignant patients from benign ones according to cut off values, statistically significant p values were obtained with CA15-3 (Table 3).

Of all stage IV patients, five had bone, two had liver and one had lung metastases. Of all patients with bone metastases, three for CA15-3 and one for CEA had high tumor marker levels. In one of two patients with hepatic metastases, both CA15-3 and CEA were found to be high; opposite to PRL. None of the patients with bone or other distant metastasis had increased PRL.

CA15-3, CEA and PRL were high in 31.8% (14/44), 25.0% (11/44) and 4.5% (2/44) of patients with axillary invasion, respectively. No correlation was observed with the presence of axillary invasion and the positivity of CA15-3 ($p = 0.496$), CEA ($p = 0.989$) or PRL ($p = 0.497$). Among the patients with more than four metastatic axillary lymph nodes, CA15-3 and CEA were found to be high in 33.3% (5/15) and 20% (3/15), respectively, but none of these patients with more than four metastatic lymph nodes had distant metastasis. The correlation between the tumor marker level and number of metastatic lymph nodes was not statistically significant for CA15-3 ($p = 0.845$, $r = -0.021$), CEA ($p = 0.840$, $r = 0.022$) or PRL ($p = 0.722$, $r = -0.039$). The relationship between the number of metastatic lymph nodes and tumor marker levels is shown in Figure 2. On the other hand, no corre-

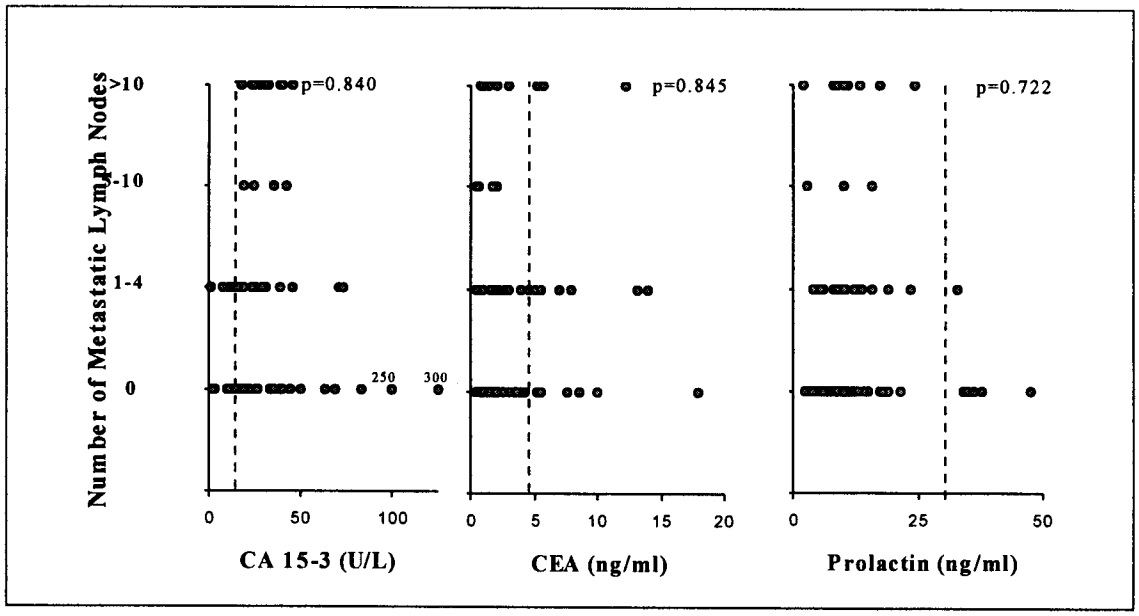

Fig. 2 The correlation of tumor marker levels with number of metastatic lymph nodes.

lation was found between tumor size and CA15-3 ($p = 0.099$, $r = 0.179$), CEA ($p = 0.300$, $r = 0.113$) or PRL ($p = 0.493$, $r = 0.075$) levels.

The positivity of CA15-3 and CEA in patients with stage-IV disease was 62.5% (5/8) and 50.0% (4/8), respectively. The increase in CA15-3 with the increasing stage of the disease was statistically significant ($p < 0.001$), but no statistically significant correlation was found between the stage of the disease and either CEA ($p = 0.063$) or PRL ($p = 0.805$) levels. The mean ± SD values for tumor markers for different stages of the disease and the categorization of patients according to cut-off values are shown in Table 4 and Figure 1, respectively.

DISCUSSION

A prognostic factor is defined as a biologic or clinical measurement associated with disease-free or overall survival in the absence of adjuvant systemic therapy. Determination of prognostic factors is especially important in the management of malignant patients and deciding on the therapy regimen. The most useful and consistent of the prognostic factors for breast cancer patients are tumor TNM stage, histologic tumor type, tumor size, presence of distant metastasis, presence of axillary invasion and the number of invaded lymph nodes. For example, as the number of invaded lymph nodes and tumor size increases, the survival rate decreases and the relapse rate increases. Other pathologic prognostic factors are histologic and nuclear differentiation, lymphatic and vascular invasion, sex steroid (estrogen and progesterone) receptor status, histologic tumor type and proliferative indices such as the mitotic index and S phase fraction.[4]

Tumor markers have little diagnostic value in screening or diagnosing breast cancer and they are mainly used to evaluate the adequacy of the treatment, monitor recurrence and follow up response to the treatment. The tumor marker of choice for breast carcinoma is CA15-3 with a sensitivity of between 20 and 30% at the time of primary diagnosis, and between 60 and 90% in the presence of distant metastases.[2] Another tumor marker used for breast cancer is CEA. The sensitivity of CEA at the time of primary diagnosis, for the diagnosis of recurrence, and the presence of distant metastases is between 27 and 75%.[2] Furthermore, it was postulated that some hormones such as PRL and somatomedin might regulate proliferation of cancer cells in a manner like growth factors produced by cellular oncogenes.[5] A close correlation was reported between the serum PRL level and tumor size, and poor differentiation of breast tumors in some reports.[3,6]

In a comparison of CA15-3 with CEA, we observed superior sensitivity with CA15-3 both for primary diagnosis and in patients with advanced disease and bone metastases, as reported in previous studies.[7–9] This present study has also defined the specificity of CA15-3 and CEA assay for breast cancer diagnosis. The specificity, positive and negative predictive values of CA15-3 were found superior to CEA. Superior sensitivity was obtained for the detection of breast cancer by combining CA15-3 with other tumor markers, especially with CEA. On the other hand, the best sensitivity was obtained for the detection of breast cancer by using CA15-3, CEA and PRL together, but when the three tumor markers were combined, specificity decreased from 95.3% to 76.7%.

CA15-3 levels were higher in high-risk patients with bone, liver and axillary metastases, similar to reported

studies[8–10] but, we believe that low CA15-3 level did not exclude metastases, and a given CA15-3 level alone could not be used to determine the stage of the disease. On the other hand, although an increase in CA15-3 was found more sensitive in the case of axillary invasion, no statistically significant correlation was found between the number of invaded lymph nodes and the level of any tumor marker.

A number of studies have shown that the increase in CA15-3 accompanies the increase in the stage of the disease.[11] It has been reported that 9% of women with stage I, 19% of women with stage II, 38% of women with stage III and 75% of women with stage IV breast cancer patients had high CA15-3 levels.[7] In the evaluation of our findings, we observed CA15-3 results comparable with these previous reports.[7,11] Interestingly, we obtained similar results for stage II and III patients with both CA15-3 and CEA.

In previous reports, PRL levels were found high in poorly differentiated tumors, and it has been postulated that the levels of PRL[3] can effectively reflect the disease status. It was also reported that there was a significant correlation between tumor size and plasma PRL.[6] In contrast to these studies, we could not find any correlation between PRL and either tumor size or the stage of the disease. Moreover, despite its high specificity (97.6%), PRL showed the worst sensitivity for primary diagnosis (5.8%) and staging of breast cancer.

CONCLUSIONS

In conclusion, although combining CA15-3 with CEA and PRL may increase the sensitivity for primary diagnosis, sensitivities and negative predictive values for baseline CA15-3, CEA and PRL indicate that they cannot be used in screening or diagnosing breast cancer. The correlation of baseline CA15-3 with stage of the disease, the presence of axillary invasion and distant metastasis was found superior to CEA and PRL.

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