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Carcinoembryonic Antigen (CEA) and Beta Human Chorionic Gonadotropin (Beta-hCG) as Markers in Breast Cancer

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Abstract.- Serum tumour markers, carcinoembryonic antigen (CEA) and beta human chorionic gonadotropin (β-hCG) were studied in 65 postmenopausal and 49 premenopausal postoperative breast cancer patients with stage I, II, III and IV. Serum levels of these tumour markers were assessed before and during chemotherapy and/or radiotherapy. Serum CEA concentration was significantly higher (>5 ng/ml) in 7.9% (6/76) of patients with local and 60.53% (23/38) of patients with advanced breast cancer ($P<0.001$) compared to controls. The concentration of β-hCG also increased (>7 mIU) in 25% (19/76) and 36.8% (14/38) of patients without and with metastatic disease, respectively ($P>.05$). Following unilateral mastectomy serial monitoring of these two tumour markers was carried out in 82 patients before and after the initiation of therapy. Five distinct patterns of marker levels were observed. In three patterns the marker levels increased, decreased and remained unchanged during disease progression, regression and stationary clinical state. Whereas, the other two patterns were paradoxical to the disease. CEA and β-hCG serum levels in patients with metastatic breast cancer correlated with the extent of disease and postoperative values obtained before and after the initiation of therapy were found to be clinically useful markers which could be utilized for prognostic purposes.

Key words: Breast cancer, carcinoembryonic antigen, hCG.

INTRODUCTION

Molecular markers are extremely useful in screening, diagnosis and treatment of various types of cancers (Waalkes *et al.*, 1984). At present, there have been contradicting reports regarding the usefulness of the serum carcinoembryonic antigen (CEA) and beta human chorionic gonadotrophin (β-hCG) as markers for breast cancer (Falkson *et al.*, 1982). Some authors have indicated that CEA levels in tissue or plasma correlate positively with disease recurrence (Falkson *et al.*, 1982; Mansour *et al.*, 1983). Serum levels of CEA have also been correlated with disease activity and response to therapy in patients with metastatic disease (Lokich *et al.*, 1978; Mughal *et al.*, 1983; Theriault *et al.*, 1989). On the other hand some researchers have reported that CEA can not aid in predicting disease relapse and is not an independent prognostic factor in breast cancer (Veronesi, 1982). Like CEA, controversy also exists for the role of β-hCG in breast cancer. Cove *et al.* (1979) found no evidence to support the suggestion that β-hCG is produced by breast tumour or could be used as tumour marker in breast cancer. Whereas, Tormey *et al.* (1977) observed elevated levels of β-hCG in preoperative, postoperative and metastatic breast cancer. An unusual glycoprotein has also been found in high concentrations in the serum of breast cancer patients (Bradlow *et al.*, 1979; Mughal *et al.*, 1983). Different patterns of marker levels have also been reported in response to postoperative chemotherapy and/or radiotherapy (Lokich *et al.*, 1978; Lamerz *et al.*, 1979; Mughal *et al.*, 1983). In the present report we have studied the serum levels of CEA and β-hCG in response to chemotherapy and/or radiotherapy in postoperative breast cancer patients.

MATERIALS AND METHODS

Patients and serum samples

Serum samples from 114 patients which have undergone unilateral mastectomy were analysed for carcinoembryonic antigen (CEA) and beta human chorionic gonadotropin (β-hCG). Patients included in this study were operated one month to three years prior to the initiation of therapy. Sixty five women were postmenopausal and 49 premenopausal with stage I, II, III and IV breast cancer. Staging was in according with the Tumour, Node, Metastasis (TNM) classification (1978). Mean age of the patients was 49 years. In 76 patients no signs of metastases were found (stage I and II) at the time of investigation whereas in 49 cases different degree of metastases could be demonstrated (stage III, IV). Thirty two patients were lost during the follow-up and in 82 patients 5-15 serial determinations

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of CEA and β-hCG were carried out at 1-3 months interval over a period of 6-18 months. During this period patients were treated by hormonal (Tamoxifen) and/or cytostatic drugs (*e.g.* 5-Fluorouracil, Cyclophosphamide, Adriamycin, Methotrexate, Novantrone etc.) or radiotherapy (Gamma rays, high energy X-ray). The treatment was not changed on the basis of tumour marker levels as the results were not available at the time of treatment. The patients were evaluated at 1-3 months interval by history, physical examination, complete blood counts, chest X-ray film, liver function studies, urea and creatinine. Liver and bone scanning were performed for the identification of the metastases and brain scanning was carried out when indicated on clinical grounds. Blood samples were drawn between 8 AM and 10 AM, allowed to clot at 4°C, then serum was separated by centrifugation at 2000 g for 30 min. Serum was stored at -20°C until used for assays.

Tumour marker assays

Serum CEA was mesured by sandwich immunoradiometric assay and β-hCG by Amerlex-M radioimmunoassay kits supplied by Amersham (U.K.) according to the instructions provided by the manufacturer. The inter and inraassay coefficients of variations were 9.3 and 7.4% for CEA and 10.4 and 8.2% for β-hCG, respectively. The sensitivity of the CEA assay was 0.5 ng/ml and for β-hCG assay was 0.65 mIU/ml. The normal values for the serum CEA and β-hCG in the age matched control subjects (n=32) were less than or equal to 5.0 ng/ml and less than or equal to 7 mIU/ml respectively. The significance of tumour marker changes was assessed by Student's t test.

RESULTS

The levels of serum CEA were significantly higher in 7.9% (6/76) of patients with local and 60.53% (23/38) of patients with metastatic breast cancer (Fig. 1, P<.001) compared to the age matched controls. A scattergram of the results shows the range of CEA values from <1.0-47 ng/ml in patients with metastatic disease (Fig. 2A). Serum β-hCG concentration was also higher in 25% (19/76) of the patients without metastases and 36.8% (14/38) of the patients with metastases but not significantly different from the patients without metastases (Fig. 1, P>.05). The scattergram of the results showed the range of serum β-hCG values to be <1.0-130 mIU/ml in patients with local breast cancer and <1.0-240 mIU/ml in patients with advanced breast cancer (Fig. 2B). In these patients

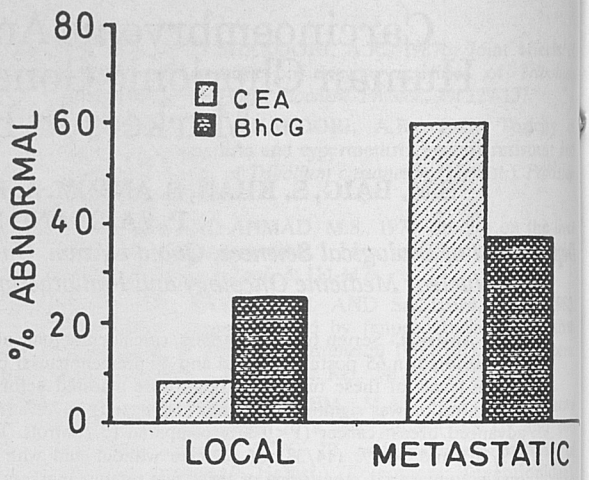

Fig. 1. Percentage of postoperative abnormal levels of CEA and β-hCG in local and metastic breast cancer patients (n=114).

the correlation of the tumour markers and stage of the disease was also investigated (Fig. 2). In patients with stage II, III and IV, the serum CEA levels were significantly higher from stage I patients and concorded with the disease status (P<.01, .05 and .01 respectively). The serum levels of β-hCG were also determined in all four stages of the disease but changes observed were not significantly different between the stage II-IV (Fig. 2B, P>.05). When both the markers (CEA and β-hCG) were determined together in the same patients, the percentage of patients with abnormal levels was higher than when the markers were studied individually (Fig. 3). In the patients with local breast cancer the percentage of abnormal levels was 29% (22/38) and for metastatic disease it was 76%.

Follow-up studies for CEA

The follow-up constituted serial monitoring of the marker over a prolonged period after the initiation of therapy. Different patterns of marker levels were observed in patients during the study period and may be divided into five groups.

Group I (n=46, 56%) had constantly normal CEA levels (<5 ng/ml). Thirty one (67%) remained free of metastasis, whereas, in 15 (33%) different levels of metastases were identified.

Group II (n=2, 33%) showed a continuous significant increase (Fig. 4A, P<.05) of serum CEA levels. Eleven patients (91.6%) developed clinical progression of the disease during the monitoring period. In only one patient a stationary clinical state was observed. Clinical remission was not identified in any of the patients.

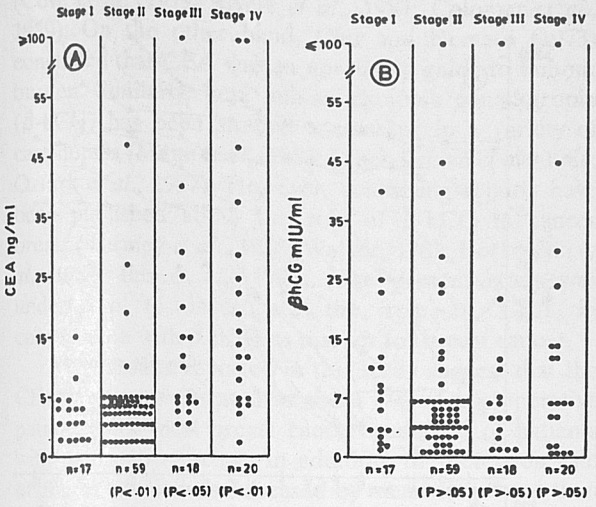

Fig. 2. A scattergram showing the range of marker values in individual patients, serum CEA values (A) and serum β-hCG values (B). The stages on top of each section refer to the clinical stage of the breast cancer. The numbers (n) at the bottom are number of patients included for each stage. The numbers in parenthesis at the bottom are P-values calculated in each case.

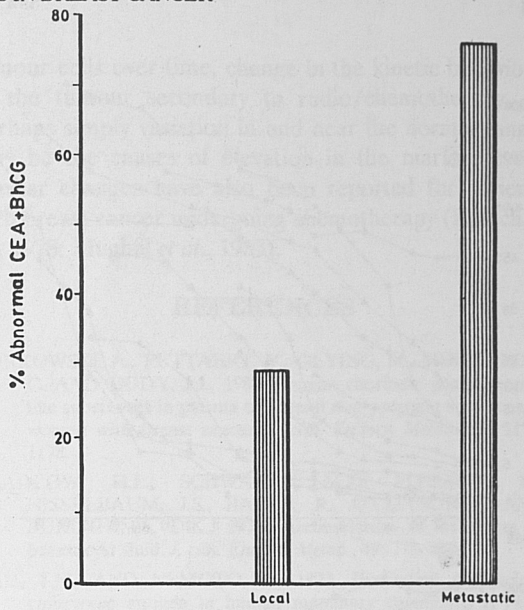

Fig. 3. Percentage of patients with abnormal levels of CEA and β-hCG. The values for both markers were determined in the same patient.

Group III (n=9, 25%) consisted of patients showing decreasing CEA concentrations (Fig. 4B) but these changes were not significant (P>.05). Clinical remission was observed in 6, progression in 1 and stationary state in 2 patients.

Group IV (n=7, 19%) comprised of the patients with unchanged or slightly fluctuating CEA levels. Most of the patients (86%) maintained a stationary clinical state whereas, one patient showed clinical progression.

Group V (n=8, 22%) consisted of patients with strongly varying serum CEA levels (Fig. 4C) in concordance with the clinical state of the patients.

Follow-up studies for β-hCG

Different patterns for serum β-hCG were also observed during the monitoring period of breast cancer patients in the follow-up period after the initiation of therapy. These patients could also be divided into five groups.

Group I (n=49, 60%) showed constantly normal levels of β-hCG (<7 mIU/ml), thirty two patients remained free of metastases and 17 developed advanced breast cancer.

Group II (n=9, 27%) showed a significant continuous increase of β-hCG levels (Fig. 5A, P<.05). Most of the patients (89%) were with progression disease, except one patient, who showed no disease progression inspite of the increasing marker level.

Group III (n=6, 18%) comprised of patients with decreasing serum levels of β-hCG (Fig. 5B, P<.05). In five patients the marker levels concorded with the disease, while in one patient paradoxical pattern was observed.

Group IV (n=8, 24%) comprised of patients with slightly varying levels of β-hCG. Six patients maintained stationary clinical state, whereas 2 patients exhibited a fluctuating pattern.

Group V (n=10, 30%) consisted of patients with strongly fluctuating β-hCG levels throughout the monitoring period in concordance with the clinical state (Fig. 5C).

DISCUSSION

The lack of a specific and sensitive biomarker for breast carcinoma has made many investigators to study combination of markers (Coombes *et al.*, 1977). Carcinoembryonic antigen (CEA) is included in all studies of such combinations. CEA fulfills the initial requirements of a satisfactory tumour marker. Its levels are frequently raised, often to a considerable degree, and more commonly is raised in advanced than in local disease (Tormey *et al.*, 1977). According to other reports abnormal CEA levels correlated with clinical and pathological disease stages of breast cancer

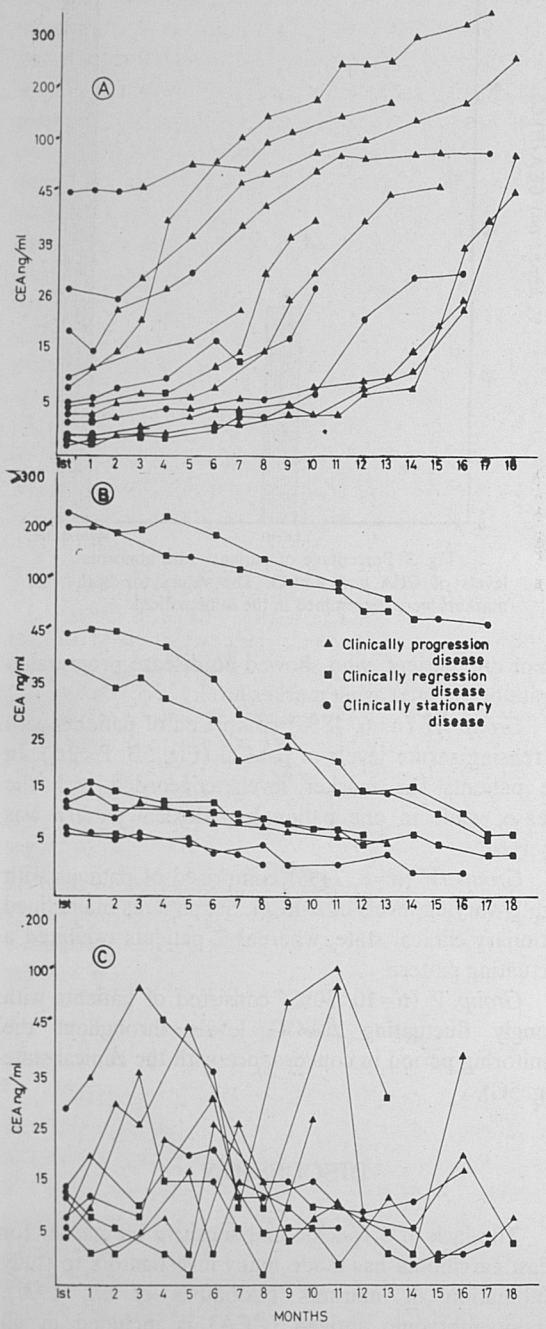

Fig. 4. Follow-up of serum CEA levels in post-operative breast cancer patients undergoing radio/ chemotherapy. A, Patients showing progression (clinically progressing disease, n=11; clinically stationary disease, n=1); B, patients showing regression (clinical remission, n=6; clinical progression, n=1; clinically stationary state, n=3); C, patients showing fluctuations (n=8, marker levels in concordance with the clinical state in all patients).

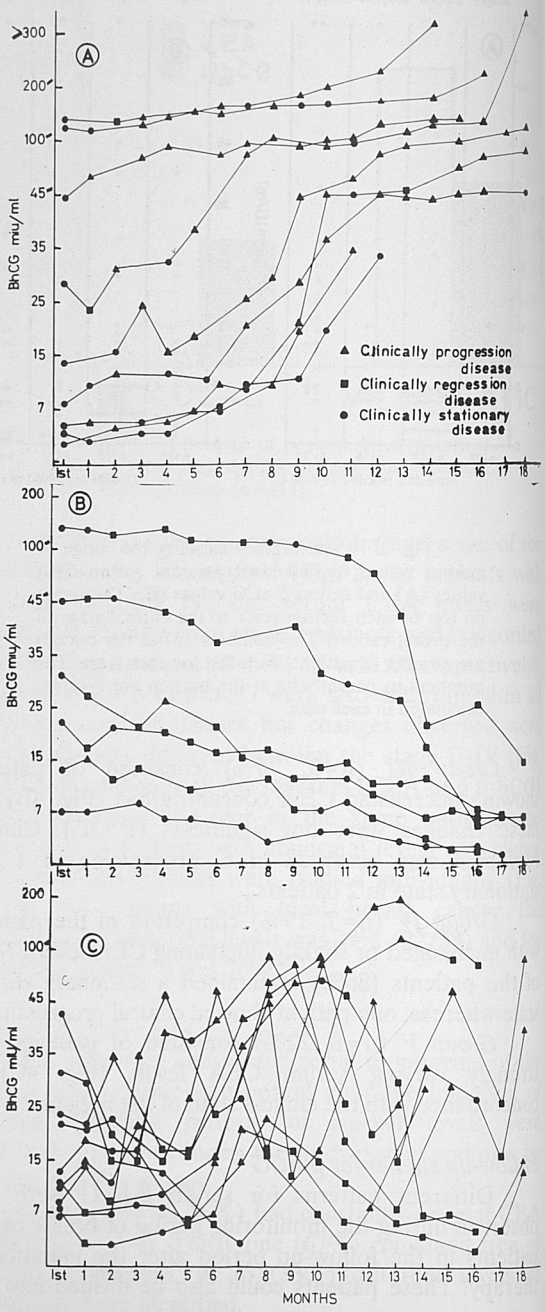

Fig. 5. Follow-up of serum β-hCG levels in postoperative breast cancer patients undergoing radio/chemotherapy. a) patients showing progression (clinically progressing disease, n=8; clinically stationary state, n=1); b) patients showing regression (clinical remission, n=5; clinically progressing disease, n=1); c), patients showing fluctuations (n=10, marker levels in concordance with the clinical state in all patients).

(Cove *et al.*, 1979; Myers *et al.*, 1987; Colomer *et al.*, 1989). On the other hand, Chu and Nemato (1973) concluded that CEA was an unreliable guide to tumour burden. Similarly, beta human choionic gonadotropin (β-hCG) has been studied as marker in a variety of carcinomas (Mann *et al.*, 1983; Jones-Brown *et al.*, 1984; Ozturk *et al.*, 1987). However, conflicting reports have been published about the role of β-hCG in cancer breast (Tormey *et al.*, 1978; Walker, 1982; Borkowski *et al.*, 1984; Iles *et al.*, 1990). The present study was undertaken to investigate the role of CEA in combination with β-hCG as marker for breast cancer.

The results reported in this study suggest that the CEA levels are elevated in about 8% of postoperative patients with local breast cancer and 60% of patients with metastatic disease. In addition, the detection rate of abnormalities was increased by measuring more than one biochemical marker. Our data further suggest that serial marker values can be used to follow-up the effectiveness of therapy in breast cancer patients. In the present study, we observed five distinct kinetic patterns of CEA and β-hCG in the breast cancer patients undergoing radio/chemotherapy in the follow-up period. Our study demonstrates that elevated circulating levels of serum CEA and β-hCG in advanced breast cancer correlated with extent of metastatic disease. Moreover, the present study also suggests that CEA is more sensitive and reliable marker than β-hCG in patients with advanced breast carcinoma.

Changes in the serum levels of β-hCG were similar to that of CEA. Thus changes in the marker levels in postoperative breast carcinoma are not unique to the CEA. Some of the CEA and β-hCG kinetic patterns are easily understood when a direct correlation between clinical state and serum marker level is made *i.e.* a therapy which causes a disease regression will bring down the serum tumour marker level. Whereas, increases and decreases of serum marker levels paradoxical to the clinical state are the causes of controversy. In this paradoxical phenomenon the low levels of markers may be due to reduced tumour volume, reduced synthesis, reduced marker release into the blood and increased marker catabolism (Kiang *et al.*, 1990).

According to previous reports (Tormey *et al.*, 1975; Waalkes *et al.*, 1980; Waalkes *et al.*, 1983), immediate postsurgical and after initial course of antitumour drugs the levels of biomarkers in a variety of carcinomas, remain elevated despite clinical response to therapy and may last for several months. The reasons for this paradoxical result are not known at present. But lysis of tumour cells over time, change in the kinetic behaviour of the tumour secondary to radio/chemotherapy, or perhaps simply variation in and near the normal range, may be the causes of elevation in the marker levels. Similar changes have also been reported for patients with breast cancer undergoing chemotherapy (Kokich *et al.*, 1978; Mughal *et al.*, 1983).

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