Prolactin Serum Level in Patients with Breast Cancer

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Abstract

Background: Previous studies have suggested that prolactin may serve as an indicator of disease progression in breast cancer.

Objectives: To evaluate the use of PRL as a serum tumor marker in patients with breast cancer.

Methods: PRL serum level was determined in 99 breast cancer patients and compared with CA 15-3 serum level.

Results: Elevated serum level of PRL (>20 ng/ml) was found in 8 of 99 patients (8.1%). A stratified analysis of prolactin levels according to therapy revealed that PRL levels was increased in 8 of 55 untreated patients (14.5%), but not in patients who received hormonal or chemotherapy in the 3 months preceding the test (0/42 patients, $P=0.009$). However, mean PRL level was similar in patients with no evidence of disease activity and in patients with active disease (10.2 vs. 8.2 ng/ml, NS). In comparison, CA 15-3 mean level was significantly lower in patients with no evidence of disease as compared to patients with active disease (18.2 vs. 144.7 units/ml, $P<0.001$). PRL level was increased in 6 of 60 patients (10%) with no evidence of disease and in 2 of 39 (5.2%) with active disease (NS). In comparison, CA 15-3 level was increased in 3 of 60 patients (5%) with no evidence of disease and in 24 of 39 (61.5%) with active disease ($P<0.001$).

Conclusions: PRL levels are decreased following hormonal or chemotherapy in patients with breast cancer and there is no correlation between PRL serum level and the state of disease. Further studies are needed to clarify a possible clinical significance of hyperprolactinemia in a subset of patients with breast cancer.

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Breast cancer cells synthesize and secrete biologically active prolactin. PRL has a role in carcinogenic processes of the breast, possibly due to its stimulatory effect on the immune system [1–6]. Bhatavdekar et al. [7,8] reported that PRL serum levels correlate with the state of disease and inversely correlate with survival in breast cancer patients, although contradictory observations were reported by other investigators [9,10]. In addition, PRL levels decrease following hormonal or chemotherapy in patients with breast cancer [11–14]. Therefore, it was suggested that PRL may be used in the management and follow-up of patients with breast cancer by playing the role of a serum tumor marker [7,8].

In previous studies we demonstrated that CA 15-3 serum level correlates with disease activity in breast cancer patients [15–18]. The aim of the present study was to evaluate the use of PRL serum level, compared to CA 15-3, as a serum tumor marker in patients with breast cancer.

Materials and Methods

Previously, we determined CA 15-3 serum levels in 312 patients with breast cancer using immunoradiometric assay (CIS Bio-International, France) [15–18], The cutoff level for CA 15-3 was defined as 35 units/ml. The serums were stored at -70°C.

In the present study, PRL level was measured in 99 stored consecutive serum samples using an immunoradiometric assay (Promed, Holland) [19]. The cutoff level for PRL was defined as 20 ng/ml. Student's *t*-test and two-tailed Fisher's exact test were used to compare means of PRL and CA 15-3 levels and some of the patients' characteristics. Chi-square tests were performed to compare frequencies of increased PRL and CA 15-3 serum levels. Statistical analysis was performed using the Medata report generator [20] and the Epi-Info version 6.0 [21]

Results

The study population consisted of 99 women with breast cancer. Increased PRL levels were demonstrated in 8 of the 99 (8.1%). Demographic and clinical details of the patients with normal PRL (PRL<20 ng/ml) and hyperprolactinemia (PRL>20 ng/ml) are presented in Table 1. A stratified analysis of prolactin levels in 97 patients in the study (98%), according to therapy, revealed that PRL levels were increased in 8 of 55 untreated patients (14.5%), but not in any of the 42 patients who received hormonal or chemotherapy for 3 months preceding the test ($P=0.009$). PRL mean level was significantly lower in

PRL = prolactin

Table 1. Demographic and clinical details of breast cancer patients with hyperprolactinemia and normal PRL

	Hyperprolactinemia (n = 8)	Normal PRL (n = 91)
Age (yr)		
Mean (SD)	49.7 (10.3)	57.5 (12.4)
Median	49.5	57.0
Range	35–64	34–86
Stage at diagnosis		
I	2 (25%)	20 (23%)
II	5 (62.5%)	49 (56.3%)
III	1 (12.5%)	10 (11.5%)
IV	0 (0%)	8 (9.2%)
Clinical state		
No evidence of disease	6 (75%)	54 (59.3%)
Active disease	2 (25%)	37 (40.7%)
PRL level (ng/ml)		
Mean (SD)	40.7 (22.8)	6.7 (2.6)
Median	33.1	5.0
Range	20.1–77.9	5–14.1
CA 15-3 level (units/ml)		
Mean (SD)	15.71 (9.5)	72.6 (133.0)
Median	18.5	21.0
Range	3.1–29.0	3.5–575.0
Receptor state		
ER and PR positive	5 (62.5%)	34 (52.3%)
ER positive and PR negative	2 (25%)	11 (16.9%)
ER negative and PR positive	0 (0%)	5 (7.7%)
ER and PR negative	1 (12.5%)	15 (23.1%)

Table 2. PRL positivity rate and serum levels in breast cancer patients according to therapy.

	No. (%) of patients with increased level	Mean level	SD	Median level	Range
Treated patients	0/42 (0%)	6.5	2.4	5.0	5–11.9
Untreated patients[+]	8/55 (14.5%)*	11.8**	15.0	5.8	5–77.9

[+] Treatment defined as hormonal or chemotherapy applied in the 3 months preceding the test
* P=0.009
** P=0.05

Table 3. PRL and CA 15-3 mean serum level and positivity rate according to the state of disease in breast cancer patients.

No.of patients	Mean (SD) PRL level (ng/ml)	No. (%) of patients with PRL >20 ng/ml	Mean (SD) CA 15-3 level (units/ml)	No. (%) of patients with CA 15-3 >35 units/ml
No evidence of disease (n=60)	10.2 (14.0)	6 (10%)	18.2 (8.5)	3 (5%)
Active disease (n=39)	8.2 (6)	2 (5.2%)	144.7 (179.1)*	24 (61.5%)*

* P<0.001

patients who received either hormonal or chemotherapy in the preceding 3 months, as compared to PRL levels in patients who did not receive therapy (6.53 vs. 11.76 ng/ml, P=0.05) [Table 2].

A stratified analysis of PRL level according to state of disease [Table 3] revealed that mean PRL levels were similar in patients with no evidence of disease and patients with active disease, whereas CA 15-3 level was significantly higher in patients with active disease compared to patients with no evidence of disease. PRL positivity rate was similar in patients with no evidence of disease as compared to patients with active disease, in contrast to CA 15-3 for which positivity rate was significantly higher in patients with active disease compared to patients with no evidence of disease.

Discussion

Accumulated evidence suggests that PRL is an important factor in the growth and regulation of normal and malignant cancer cells [1,3]. Previous studies have described an abrupt decrease in PRL level following hormonal or chemotherapy in patients with breast cancer [11–14]. Bianco et al. [11] documented a significant decrease in PRL levels following adjuvant CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and tamoxifen in 120 women with stage I-II operable breast cancer. Willis et al. [14] evaluated PRL levels in postmenopausal women with recurrent breast cancer who were treated with tamoxifen. They found that PRL levels were increased in 18 of 44 patients (41%), and 13 of these patients did not respond to treatment. Treatment did not change the mean PRL level when this was within the normal range, but it significantly reduced PRL levels in hyperprolactinemic patients within 2 weeks in those who responded well to therapy (P<0.01) and by 6 weeks in those who showed no remission (P<0.05). Similar results were observed by other authors [12,13].

The next logical step in the evaluation of PRL in breast cancer patients was to assess its role as a tumor marker. Bhatavdekar and team [7] showed a correlation between serial prolactin level changes and the state of disease in 144 patients with advanced breast cancer. A later study demonstrated that increased PRL levels provided an independent predictor of short-term prognosis in 69 patients with advanced breast cancer [8].

A group led by Holtkamp [10] measured PRL level in 149 patients with metastatic breast cancer and 221 patients with no evidence of disease. None of the 221 patients with breast cancer at remission had PRL>30.8 ng/ml in repeated measures. In those with metastatic disease, PRL>30.8 ng/ml was found in 142 of 1,690 determinations (8%). Patients with PRL>30.8 ng/ml had a shortened survival after mastectomy than patients who never had PRL>30.8 ng/ml (154 and 89 months, respectively, P=0.01).

In their study of 135 patients with advanced breast cancer, Dowsett's team [9] observed that more patients had PRL>15.4 ng/ml in the group that developed progressive disease than those who stayed in remission or had a stable disease. The median survival for patients with PRL>15.4 ng/ml was 5.3 months compared to 10.0 months for patients with PRL<15.4.

In the current study, we found that 8 of 55 breast cancer patients (14.5%) had increased PRL levels, which concurs with results reported by other authors [11–14]. However, mean PRL levels and positivity rates were not correlated to disease state, a finding that did not concur with other studies [7–10]. It is possible that the disconcordance in results between the studies is attributable to different patient subsets. We evaluated PRL serum level in patients with early disease as well as in those with advanced disease. In the studies in which PRL levels were correlated with disease state, the patients comprised mainly those with advanced breast cancer [11–14]. Interestingly, contradictory observations on the association between hyperprolactinemia and disease activity in systemic lupus erythematosus were reported [4–6].

Interpreting the results in this study depends on the confidence with which a single PRL estimate represents the PRL status of the patient. It was suggested that high PRL levels may occur due to changes in diurnal rhythm, pulsatile release, or stress at venpuncture. However, it was later demonstrated that venpuncture rarely if ever induces PRL release, and that frequent sampling does not improve the value of a single PRL measurement [9]. Thus, the results obtained in the present report may be viewed with confidence.

We conclude that PRL levels are decreased following hormonal or chemotherapy in some patients with breast cancer and that there is no correlation between PRL serum level and the state of disease, in conrast to CA 15-3 serum level. Further studies are needed to clarify the meaning of increased PRL levels in patients with breast cancer.

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Old mismanagement is no excuse for the continuance of it.

Albert, German-born husband of Queen Victoria (1851)