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CERULOPLASMIN LEVEL IN WOMEN WITH BREAST DISEASE

Preliminary results

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The average ceruloplasmin levels of 29 patients with active breast cancer and 22 patients in remission were 824 ± 61 mg/l and 630 ± 18 mg/l respectively. The average ceruloplasmin level of 17 patients with benign breast diseases was 555 ± 29 mg/l and of 18 healthy women in a control group 584 ± 17 mg/l. Breast cancer patients not in remission had ceruloplasmin levels which were significantly increased when compared to the other 3 groups. The CA 15-3 levels and ceruloplasmin levels were positively correlated. We propose that ceruloplasmin may be used as a tumour marker in the follow-up of patients with breast cancer.

Specific and highly sensitive biological markers for breast cancer, which can reveal the progress of the disease, are needed (1). Such markers may be synthesized by the tumour cells or produced by normal tissues in response to invasion by cancer cells (2). These markers include a variety of enzymes, hormones and antigens and may be used in conjunction with other tests for determining the state of the disease or response to different therapies (3).

The most recently discovered breast cancer antigen is CA 15-3, which has been identified by reaction with two monoclonal antibodies (4). In clinical studies (5–7), it was found to detect breast carcinoma metastases with higher sensitivity than the most widely used marker carcinoembryonic antigen (CEA). Also serum copper and ceruloplasmin (an acute phase reactant synthesized in the liver) have been reported to be useful markers of disease activity in patients with carcinoma of the breast, lung, gastrointestinal tract, acute leukemias and Hodgkin's and non-Hodgkin's lymphoma (8–10). Ceruloplasmin may also be elevated in non-malignant conditions, such as pregnancy, thyrotoxicosis, cirrhosis, and infections (11).

In the present study, we have attempted to evaluate serum ceruloplasmin as a marker of disease activity in patients with breast cancer and we have also compared it with CA 15-3.

Material and Methods

The study included 17 women with benign breast diseases (BBD), 51 with histologically documented breast carcinoma and 18 apparently healthy female volunteers with a median age of 39 years (range 25–60). All the patients were from the Division of Oncology at the Hacettepe University Hospital. The histological examination of the BBD revealed fibrocystic disease in 5 patients, fibroadenoma in 11, and papilloma in one patient. The median age of this group was 24 years (range 16–51). The median age of the breast cancer patients was 43 years (range 23–63) and 29 out of the 51 patients had metastatic disease or relapse while the remaining 22 were in remission. Twelve of the 22 patients in remission were on adjuvant therapy (CMF or tamoxifen) at the time of the study following radical mastectomy with or without radiotherapy.

None of the patients had laboratory or clinical evidence of infection, primary inflammatory disease, thyrotoxicosis, pregnancy, cirrhosis or proteinuria. Serum ceruloplasmin

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and C-reactive protein (CRP) were measured using radial immunodiffusion (Binding Site, UK) and CA 15-3 by an immunoradiometric assay (Centocor IRMA) (6).

Differences of the means of ceruloplasmin and CA 15-3 levels between groups were analyzed by one-way ANOVA. Posteriori pair-wise comparisons were performed by Student's two-sample independent groups' t-test, with downward adjusted p-values (significance for these comparisons was assigned at $0.05/6 = 0.008$, since the total number of previous comparisons was six) (12). The relationship between ceruloplasmin and CA 15-3 was studied by linear regression analysis (13).

Results

The results of the ceruloplasmin estimates were separated into 4 groups—breast cancer patients in remission, breast cancer patients not in remission, patients with BBD, and healthy volunteers—which are shown in Fig. 1. The average ceruloplasmin level of the 29 patients with active breast cancer disease was 824 ± 27 mg/l (range 525–1 075), while the 22 patients in remission had an average level of 630 ± 18 mg/l (range 525–950). The patients with BBD had an average value of 555 ± 29 mg/l (range 350–750), and the control group's average value was 584 ± 17 mg/l (range 475–700). The patients not in remission were found to have significantly higher levels of ceruloplasmin compared with the other 3 groups ($p = 4.500E\text{-}12$). The difference between the patients in remission, BBD, and the control groups was not statistically significant ($p > 0.008$). The difference between the ceruloplasmin levels of patients with metastatic disease receiving tamoxifen + CMF or tamoxifen alone and those on CMF was not statistically significant ($p > 0.05$). All women in the 4 groups had serum C-reactive protein concentrations within normal limits, i.e. less than 6.0 mg/l. The average CA 15-3 level for the 29 patients not in remission was 88.6 ± 13.9 U/ml (range 20.2–240.0), whilst for the 22 patients in remission the average level was 18.9 ± 1.1 U/ml (range 11.3–34.1). The average CA 15-3 level in 17 patients with BBD was 15.5 ± 1.5 U/ml (range 3.2–26.1), and 16.1 ± 1.0 U/ml (range 10.1–26.0) in the control group. There was a positive correlation between the serum ceruloplasmin and the CA 15-3 levels ($r = 0.57$) in the breast cancer patients (Fig. 2).

Discussion

The diagnosis and classification of human breast cancer is mainly based upon clinical and pathological evaluation of the lesion, which has its difficulties and limitations. The tumour markers may be a useful supplement for the assessment of diagnosis, stage, and prognosis, and for monitoring response to treatment and early detection of metastases (1, 10, 14–16).

In a study by Schapira & Schapira (17), the ceruloplasmin levels were found to be elevated in 89% of 103 patients

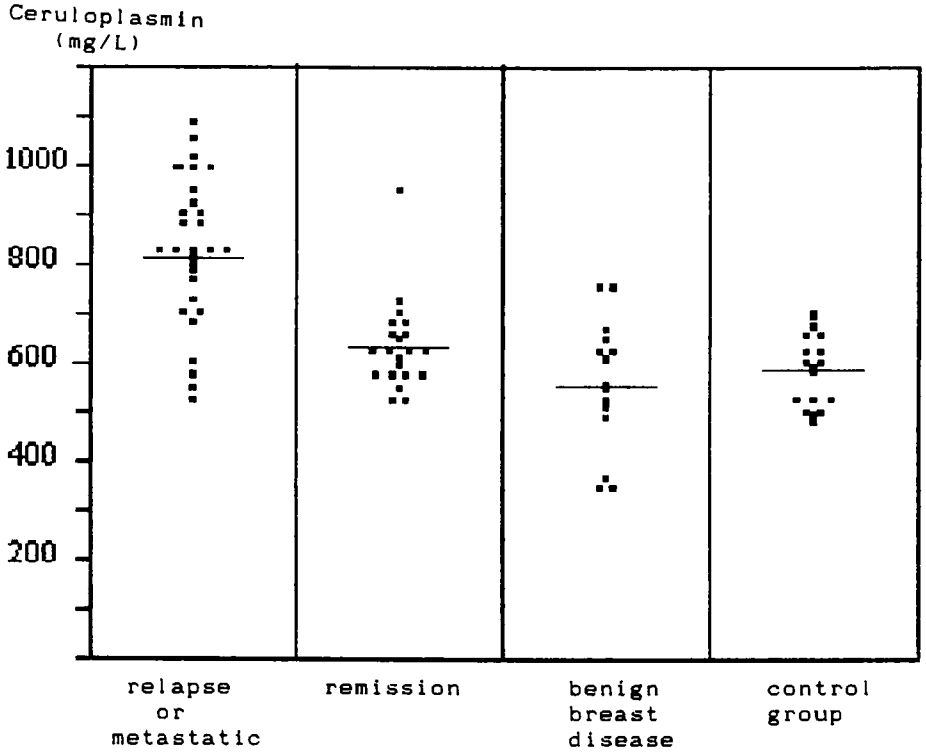

Fig. 1. Distribution of serum ceruloplasmin levels in patients with active breast cancer (relapse or metastases), breast cancer in remission, benign breast disorders, and a control group.

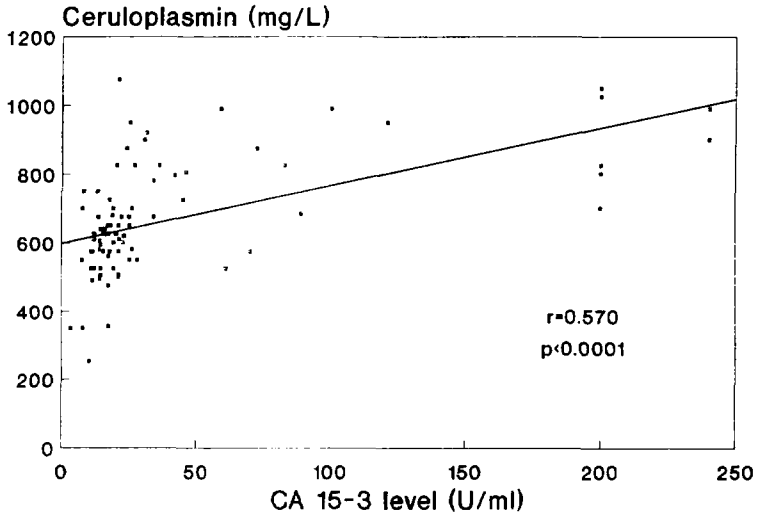

Fig. 2. Relationship between ceruloplasmin and CA 15-3 in breast cancer patients with active disease or in remission.

with breast carcinoma and then fell by 35% as soon as patients responded to treatment. These results are in accordance with those obtained in our study. We have shown that patients with carcinoma of the breast, compared to patients in remission, BBD, and normal healthy volunteers, had higher levels of ceruloplasmin, which correlated with the spread of disease. Schapira & Schapira (17) also showed that the cerulplasmin levels of patients with breast carcinoma increased 16-34 weeks before their metastases became clinically overt.

The possible role of ceruloplasmin in oncogenesis is not clear, but, it has been suggested that it may be involved in angiogenesis and neovascularization at the site of tumour growth. Breast cancer cell lines have been found to contain ceruloplasmin mRNA whilst normal breast cells do not express this gene (18). One may thus speculate that patients with breast carcinoma have increased levels of ceruloplasmin in blood due to an extrahepatic production, proportional to breast cancer cell proliferation.

CA 15-3 levels have been shown to be increased in about 60% of patients with metastases whereas in patients without metastases, only about 30% had increased levels (19). In our hospital, CA 15-3 has been routinely used in the follow-up of breast cancer patients. According to the present study there is a statistical correlation between these two parameters in breast cancer patients.

The observed increase of the ceruloplasmin level in breast cancer patients could be suspected to be a result of acute phase reaction but in our study CRP was within normal limits in all groups, CRP levels exceeding 60 or 80 mg/l rarely have been reported in patients with malignancies (20). Concentrations higher than this should raise the suspicion of superimposed infection.

Our study strongly supports that the ceruloplasmin level is often increased in breast cancer patients and suggests that ceruloplasmin can be used as a tumour marker for follow-up of these patients. In a future study, serial determination of ceruloplasmin and CA 15-3 in patients with malignant lesions of the breast would be useful for evaluating the role of ceruloplasmin as a prognostic predictor.

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