Serum copper and ceruloplasmin concentrations in patients with primary breast cancer

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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 tumor markers may be useful supplement for the assessment of diagnosis, stage, and prognosis, and for monitoring response to treatment and early detection of metastases. 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 [1-3].

This study was undertaken in the Department of Biochemistry, at Dokuz Eylül University Medical Faculty, June 1993 and January 1995, a total of 108 patients with primary breast cancer (age range 30-70), 40 patients with benign breast disease (BBD) (aged 18-53), and 26 healthy women (aged 18-52). The 40 benign lesions, all histologically confirmed, were: 18 fibroadenomas, 10 fibrocystic diseases, 4 hyperplasia, 2 papilloma, 2 granulomatosis mastite and 4 other non-malignant pathologies. Patients with malignant pathology and histological confirmation according to the WHO classification were staged using the TNM system of UICC (UICC. TNM classification of malignant tumors. Geneva:MH Harmer, 1979).

Blood samples were obtained by venipuncture before any treatment was given, between 7 and 8 a.m. and after an overnight fast. Standart precautions for trace element determination were taken; samples with signs of hemolysis were discarded.

Copper leves were measured with spectrophotometre by the employing the commercialy kit procedure of Merck Diagnostica. Ceruloplasmin concentrations were determined using the reagent of natrium azide by spectrophotometric method [4].

The obtained tumor marker concentrations were statistically analyzed using the Student's-t test,Wilcoxon test, and Mann & Whitney test. Mann & Whitney test, accepting a "p" value below 5 % ($p< 0.05$) as significant. The diagnostic parameters were evaluated using the following formulas: (TP= number of true positive values;TN= number of true negative values; FP= number of false positive values; FN= number of false negative values):

Sensitivity (%) = (TP/TP + FN) x 100;

Specificity (%) = (TN/TN + FP) x 100.

The cut-off levels used for the evaluation of the diagnostic parameters were: 162.3 µgdl for copper and 41.7 mg/dl for ceruloplasmin.

Table 1 shows serum copper and ceruloplasmin concentrations in cancer patients, BBD, and healthy controls. Table 2 represents the diagnostic ability of copper and ceruloplasmin.

Table 1. Serum copper and ceruloplasmin levels in breast carcinoma, BBD, and controls (total of 174 individuals).

Groups	No of cases	Copper (µg/dl)		Ceruloplasmin (mg/dl)	
Controls	26	135.3	± 13.5	31.3	± 5.2
BBD	40	152.0	± 54.8	39.6	±13.6
Malignant	108	225.1	±196.3[a]	48.3	±15.7[b]
Stage I	33	177.0	±126.6	46.7	±17.2
Stage II	60	259.4	±238.2	48.6	±14.8
Stage III	11	186.2	± 12.8	47.5	±12.8
0 ln+	55	250.1	±238.6	47.0	±15.5
1-3 ln+	28	187.3	±135.6	47.7	±16.0
4-10 ln+	13	212.3	±186.0	50.2	±19.0
> 10 ln+	12	221.2	± 97.8	52.5	±11.5

ln+: Number of positive lymph nodes

[a] $p< 0.001$ as compared to controls and patients with benign lesions.

[b] $p< 0.01$ as compared to controls and benign breast disease.

Table 2. Diagnostic parameters of serum copper and ceruloplasmin in primary breast cancer.

	Sensitivity %	Specificity %
Copper	48	75
Ceruloplasmin	65	75
Copper + ceruloplasmin	80	85

In a study by Schapira & Schapira [5], the ceruloplasmin levels were found to be elevated in 89 % of 103 patients. They also showed that the ceruloplasmin levels of patients with breast carcinoma increased 16-34 weeks before their metastases became clinically overt. These results are discordant with those obtained in our study. 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 tumor growth. Breast cancer cell lines have been found to contain ceruloplasmin mRNA whilst normal breast cells do not express this gene. 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. The observed increase of the ceruloplasmin level in breast cancer patients suspected to be 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 rarerly have been reported in patients with malignancies. Concentrations higher than this should raise the superimposed infection. During infections or inflammatory stress, serum copper concentrations rise because of acute-phase action of interleukin-1. The action interleukin-1 may cause the elevated serum copper (6).

Our study supported that the ceruloplasmin level is often increased in breast cancer patients and suggest that copper + ceruloplasmin determinations can be used as a tumor marker for follow-up of these patients. In a future study, serial determination of copper and ceruloplasmin in patients with malignant lesions.

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Serum copper (SCu), zinc (SZn) and ceruloplasmin (SCP) concentrations were measured in 199 patients with lung cancer and 81 with nonmalignant lung disease. No significant differences were detected between these groups in the mean concentrations or in the SCu:SZn ratio, nor was any correlation found between the histological type or clinical extent of the tumor and the level of SCu, SZn or SCP. SCu and SCP increased significantly in accordance with the symptomatic stages of Feinstein, and in a parallel manner. These measures were also significantly higher in the patients who died within 4 months Serum Ceruloplasmin. Urinary Copper Excretion and Hepatic Copper Concentration. Genetic Testing. Radiolabeled Copper.Â Despite consistently elevated hepatic copper levels in patients with Wilson disease, histochemical staining of liver biopsy specimens for copper is of little diagnostic value. Early in the disease, copper distribution is primarily cytoplasmic and is not readily apparent with rhodamine or rubeanic acid staining. The rate of progression of the liver histology from fatty infiltration to cirrhosis is variable, although it tends to occur by 1 of 2 general processes, either with or without hepatic inflammation.