*Acta Medica Okayama*

*Volume* 38, *Issue* 3 1984 *Article* 13

JUNE 1984

# Ceruloplasmin in human malignancies.

Prabir Kishore Chakraborty[*] Aparesh Ghosh[†]

J Roy Chowdhury[‡]

[*]Chittaranjan Natioinal Cancer Research Center,

[†]Chittaranjan Natioinal Cancer Research Center,

[‡]Chittaranjan Natioinal Cancer Research Center,

# Ceruloplasmin in human malignancies.*

Prabir Kishore Chakraborty, Aparesh Ghosh, and J Roy Chowdhury

## Abstract

The ceruloplasmin concentration was determined in 145 cancer patients prior to and after treatment with different radiotherapeutic and chemotherapeutic regimes. The ceruloplasmin concentration was observed to be higher in patients with malignancies than in healthy controls. There was a positive correlation of the values with the clinical condition of the patients. The ceruloplasmin concentration was noted to stop increasing and subsequently fall in patients who responded to therapy, and, in contrast, to remain high or become higher in those who did not respond to therapy. The diagnostic and prognostic value of ceruloplasmin determination is discussed.

**KEYWORDS:** ceruloplasmin, malignant tumors, prognosis

---

*PMID: 6464805 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **38**, (3), 315-320 (1984)

# CERULOPLASMIN IN HUMAN MALIGNANCIES

Prabir Kishore CHAKRABORTY, Aparesh GHOSH and J. Roy CHOWDHURY

*Chittaranjan National Cancer Research Centre, Department of Tumor Biology 37, S.P. Mookerjee Road, Calcutta-700 026, India*

*Received May 4, 1983*

*Abstract.* The ceruloplasmin concentration was determined in 145 cancer patients prior to and after treatment with different radiotherapeutic and chemotherapeutic regimes. The ceruloplasmin concentration was observed to be higher in patients with malignancies than in healthy controls. There was a positive correlation of the values with the clinical condition of the patients. The ceruloplasmin concentration was noted to stop increasing and subsequently fall in patients who responded to therapy, and, in contrast, to remain high or become higher in those who did not respond to therapy. The diagnostic and prognostic value of ceruloplasmin determination is discussed.

*Key words :* ceruloplasmin, malignant tumors, prognosis.

Ceruloplasmin is the major copper protein present in mammalian serum (1). Its elevation along with that of serum copper ($Cu^{2+}$) has been reported by several workers in patients with malignant disease (2-4). An increase in the ceruloplasmin level has also been reported in many viral and inflammatory diseases due to the influence of estrogen, and in pregnancy. A positive correlation between copper and ceruloplasmin concentrations under various pathological conditions has also been confirmed (3). Moreover, the diagnostic and prognostic value of serum copper determination in Hodgkin's disease has been described by different authors (4, 5). The aim of this study was to explore the relation of ceruloplasmin to different types of human malignancies and prognosis.

## MATERIALS AND METHODS

Examinations and tests for ceruloplasmin were carried out in 145 hospitalized patients and outpatients with malignant tumors of different origin at Chittaranjan Cancer Hospital. The patients had solid, primary tumors in various areas including the scalp, urinary bladder, larynx, cervix uteri, cheek, tongue, mouth, liver, lung, stomach, rectum, penis, breast, lymph-node and chorion. In most of the patients the ceruloplasmin concentration was also determined after completion of treatment which included radiotherapy, chemotherapy or both. The patients receiving treatment were grouped according to response as evaluated by clinical examination into responders and non-responders. Except for patients with cancer of the cervix and breast, all other patients were male. For controls, healthy individuals, both male and female, of the same age group were employed.

Blood was collected from the patients and control individuals, and the serum was sepa-

rated and stored in tightly capped tubes at -20 ℃. All glassware used for the experiment was rinsed in 50 % HCl.

The assay of ceruloplasmin activity was performed according to the spectrophotometric procedures of Ravin at 37 ℃, with the pH at 5.4 in the presence of 0.01 M EDTA to prevent non-specific substrate oxidation (5). The statisticall analysis was done using Student's 't' test. Results were considered significant when $p<0.05$.

## RESULTS

Table 1 shows the ceruloplasmin concentrations in normal controls and in patients with different untreated malignancies. The increase from normal was 27 % in scalp cancer, 118 % in carcinoma of the urinary bladder, 64 % in squamous cell carcinoma of the larynx, 27 % in lymphoma, 25 % in chorioadenoma and 38 % in carcinoma of the cervix. The increase was maximum from Stage II to Stage III 28 %).

TABLE 1. SERUM CERULOPLASMIN CONCENTRATION IN NORMAL SUBJECTS AND IN PATIENTS WITH TUMOURS OF DIFFERENT ORIGIN

| Origin of tumor | | Ceruloplasmin concentration (mg/100 ml) |
|---|---|---|
| Control | (26) | 27 ± 2 |
| Scalp | (3) | 33 ± 2** |
| Urinary Bladder | (4) | 58 ± 3** |
| Larynx | (4) | 44 ± 7* |
| Cervix | | |
| Stage I | (10) | 31 ± 3 |
| Stage II | (15) | 32 ± 3 |
| Stage III | (10) | 41 ± 3* |
| Stage IV | (6) | 43 ± 11 |
| Lymphoma | (3) | 34 ± 2** |
| Chorioadenoma | (1) | 33 |

Mean ± S.E.M. The numbers in parentheses indicate the number of patients examined.
*$p<0.05$, **$p<0.01$

Fig. 1 illustrates the ceruloplasmin concentration in controls and in patients suffering from various forms of malignancies before and after treatment. The ceruloplasmin concentration was higher in the tumor bearing patients than in normal controls. The percent increase from the control level in carcinoma of breast was 25, cheek 35, rectum 11, oesophagus 70, tongue 48, penis 36, throat 31, lung 52, mouth 32 and sarcoma of the liver 57. In the treated patients who showed remission (responders), the ceruloplasmin concentration showed a downward trend in most cases. In rectum and cheek cancer, remission did not have any effect on the ceruloplasmin concentration. The best result was observed in

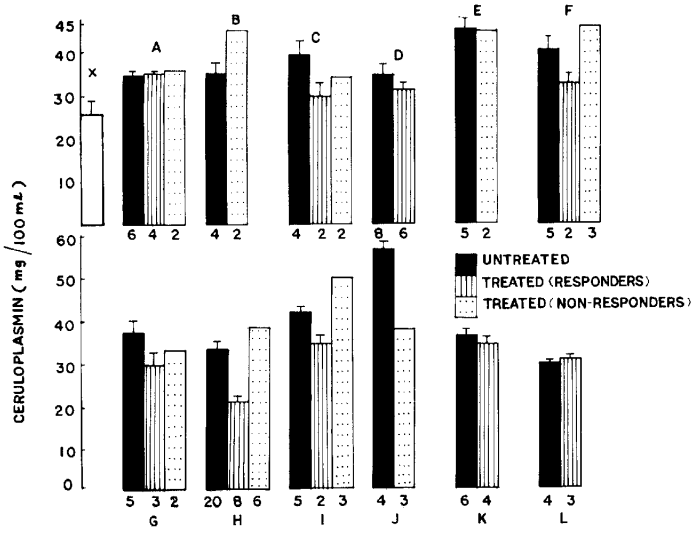
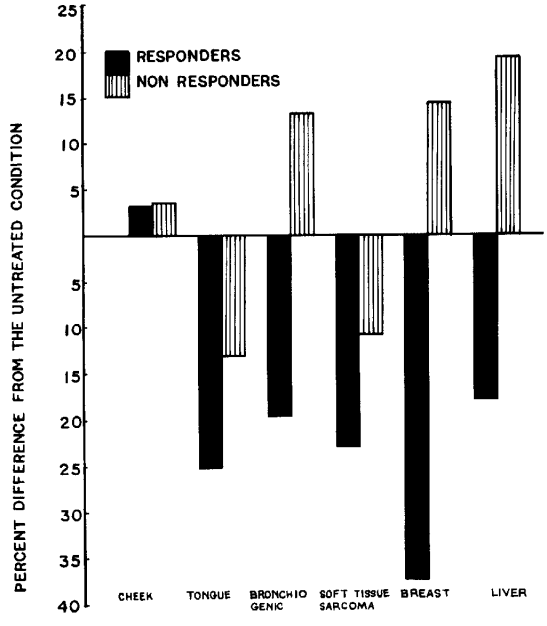



Fig. 1. Ceruloplasmin concentration in serum of normal controls and untreated and treated patients with tumors of various origins. The numerals below the rectangles indicate the numbers of patients examined.

X - control; A - Cheek ($p<0.001$); B - Mouth; C&D - tongue and throat, respectively ($p<0.001$); E - Oesophagus ($p<0.02$); F - Bronchiogenic ($p<0.001$); G - soft tissue sarcoma ($p<0.01$); H - Breast ($p<0.02$); I - liver ($p<0.001$); J - Stomach; K - Penis ($p<0.02$) and L - Rectum ($p<0.01$) (p values for the untreated condition compared with controls).




Fia. 2. Percent differences between ceruloplasmin concentrations in responders and non-responders with six different types of tumors and concentrations in untreated patients.

TABLE 2. SERUM CERULOPLASMIN CONCENRATION IN PATIENTS SHOWING RELAPSE OF THE DISEASE

| Origin of tumor type | Ceruloplasmin concentration (mg/100 ml of serum) |
|---|---|
| **Breast** | |
| a) Advanced (1) | 62 ± |
| b) Relapse (3) | 43 ± 3 |
| Penis (4) | 52 ± 4 |
| Cheek (4) | 38 ± 2* |

Mean ± S.E.M. *$p<0.05$

breast cancer patients in whom the ceruloplasmin level dropped to the control level with the remission of the disease. In general the non-responders showed further elevation of the ceruloplasmin concentration from the untreated condition, after treatment. Among patients with cancer of the tongue, stomach and soft tissue sarcoma, the non-responders had ceruloplasmin concentrations well below those of the untreated patients. The effects of remission and non-remission on the ceruloplasmin concentration are perhaps best understood from Fig. 2, in which we show the percent of decrease and increase in the ceruloplasmin concentration in responders and non-responders with six different malignancies compared to their untreated condition. It is clear from the figure that the ceruloplasmin concentration decreased in all the tumor bearing patients responding to treatment except for those with cheek cancer. We noted a good relation between the ceruloplasmin concentration and the response to treatment for breast cancer. In non-responders, variable results were observed. While most of the cases showed an elevation of the ceruloplasmin concentration, some showed a concentration less than that before treatment.

Table 2 shows the ceruloplasmin concentration in patients showing relapse. The rise in the ceruloplasmin concentration in these patients from the normal control level was great. Considering the concentration of ceruloplasmin in normal controls as one hundred percent, the rise in breast cancer was 132 %, penis cancer 95 % and cheek cancer 42 %. A patient with breast cancer in an advanced stage beyond treatment showed a 42 % rise in the ceruloplasmin concentration, while there was only a 25 % rise in untreated breast cancer patients.

## DISCUSSION

The elevation of ceruloplasmin levels along with copper levels is of significance in Hodgkin's disease (3). In a 10-year study with 241 patients with Hodgkin's disease a significant correlation of serum copper with the stage of disease was observed (6). In the present study, we found a definite relationship between the ceruloplasmin concentration and not only the different types of malignant tumors but also the condition after treatment. We did not find any signifi-

cant difference in the ceruloplasmin concentration between sexes.

In untreated patients the ceruloplasmin concentration was significantly elevated. In patients with cancer of the cervix uteri, the increase in the ceruloplasmin concentration correlated with the increase in the copper content, from Stage I to Stage IV of the disease (7).

In patients after treatment, a positive relation existed between the ceruloplasmin concentration and the tumor. The arresting of the rise and subsequent fall of the ceruloplasmin concentration in responders marked the onset of remission, except in cancer of the cheek and rectum, that remission did not have any effect on the ceruloplasmin concentration in patients with cheek and rectum cancer may be related to their proneness to infection. In non-responders the ceruloplasmin concentration remained constant or became higher with the exception of stomach cancer patients. The difference between remission and relapse in breast cancer patients may contribute to the diagnosis of relapse.

An increase in the ceruloplasmin concentration is also found in patients with infection, but it is less than in untreated patients or those with a relapsed condition. The exact mechanism of ceruloplasmin elevation is not clear. According to one hypothesis, it results from decreased catabolism brought about by resialiation of asialo ceruloplasmin (8). This hypothesis supported by the elevation of serum sialic acid levels observed during malignancy and infection (9). Thus, ceruloplasmin may function as an acute phase protein whose level rises with inflammation and tissue damage (10).

This hematochemical parameter though non-specific, may contribute significantly to the characterization of the tumorous process and to the assessment of the post-treatment condition especially in cases of carcinoma of the cervix and breast. In the former a good relation was found to exist between the ceruloplasmin concentration and different clinical stages of the disease, and in the latter there was differences in the ceruloplasmin levels between untreated, treated and relapsed patients. Together these results indicate that the determination of the ceruloplasmin level may be useful in diagnosis and the determination of the prognosis.

*Acknowledgement.* The authors thank Mr. N. Saha and Mr. P. Baisya for the figures and Mr. P.K. Ghosal for typing the manuscript.

REFERENCES

1. Broman, L.: The function of ceruloplasmin? a moot question. In *Molecular Basis of Some Aspects of Mental Activity.* ed. O. Waless, Academic Press, New York, Vol. 2, pp. 131-146, 1967.
2. Hrgovcic, M., Tessmer, C.F., Minckler, T.M., Nosier, B. and Taylor, G.H.: Serum Copper levels in lymphoma and leukemia. *Cancer* **21**, 743-755, 1968.
3. Larsen, N., Heron, I. and Thorling, E.B.: Elevated serum-Cu in Hodgkin's disease and inhibitory effect of ceruloplasmin on lymphocyte response *in vitro*. *Eur. J. Cancer* **16**, 415-

421, 1980.

4. Koprivova, H., Dienstbier, Z., Samal, M. and Foltynova, V.: Ceruloplasmin in Hodgkin's disease. *Neoplasma* **29**, 333-340, 1982.
5. Ravin, H.A.: An improved coloremetric enzymatic assay of ceruloplasmin. *J. Lab. Clin. Med.* **58**, 161-168, 1961.
6. Thorling, E.B. and Thorling, K.: The clinical usefulness of serum copper determinations in Hodgkin's disease. A retrospective study of 241 patients from 1963-1973. *Cancer* **38**, 225-231, 1976.
7. Chakraborty, P.K. and Chowdhury, J.R.: Level of serum copper in cancer cervix patients prior to and after radiotherapy. Presented in 70th Session of Indian Science Congress, 1983 (Section of Medical and Veterinary Sciences Oncology abstract no. 54).
8. Fisher, G.L. and Shifrine, M.: Hypothesis for the mechanism of elevated serum copper. *Oncology* **35**, 22-25, 1978.
9. Silver, H.K.B., Karim, K.A., Archibold, E.L. and Fernando, A.: Serum sialic acid and sialyl transferase as monitors of tumor burden in malignant melanoma patients. *Cancer Res.* **39**, 5036-5042, 1979.
10. Denko, C.W.: Protective role of ceruloplasmin in inflammation. *Agents Actions* **9**, 333-336, 1979.