

Serum Lipoprotein Levels in Patients with Cancer

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SUMMARY

Serum lipoproteins were quantitated in 122 patients with malignant tumors and in 186 normal subjects. The various serum components measured included α_1 -lipoproteins, β -lipoproteins, total lipids, phospholipids, triglycerides, cholesterol, and esterified fatty acids. α_1 -Lipoproteins, phospholipids, and cholesterol were markedly decreased in cancer patients when compared with age- and sex-matched normal subjects. α_1 -Lipoproteins were decreased in cancer patients regardless of whether the cancer was local or extensive or whether treatment was surgery, irradiation, or cytotoxic chemotherapy. Estrogen treatment, however, did cause an elevation of lipoproteins.

INTRODUCTION

Phospholipids have been reported to be decreased in patients with certain types of malignant tumors. Decreased α_1 -lipoprotein levels were reported in patients with advanced breast cancer (1, 2) and gynecological malignant tumors (5). Heretofore, there has been no systematic study of lipoproteins in patients with other types of cancer. This study was undertaken to examine systematically the levels of serum lipoprotein and lipids in a large number of cancer patients and to compare them with normal control subjects.

MATERIALS AND METHODS

Patients. Serum was obtained from 186 normal subjects and 122 patients with malignant tumors. The samples were obtained after a 12-hr fast. A detailed questionnaire concerning the type of cancer, proof of cancer, and other parameters was obtained for 86 cancer patients from the referring physician. Seventy-three of the cancer patients were seen personally by one of the authors (U.E.N.), including the 36 patients on whom a detailed questionnaire was not available.

All cases were histologically or cytologically proven malignant tumors, with the exception of 1 gastric cancer case. Six cases within the group, "uterus and ovaries," were preinvasive carcinoma and therefore represented early-diagnosed cancers. In all other cases, diagnosis was established at least 6 months before the serum for lipoprotein analysis was obtained. For 86 patients, data on whether the cancer was local or metastatic were available by either autopsy or clinical evidence. The patients with metastatic disease (41

of 86) did not differ from the patients with localized cancer with regard to age, sex, or nutritional state.

Inanition was not a factor in the great majority of cases in this study. Serum protein levels in 81 of 88 patients (including the 86 patients mentioned above) were between 5 and 8 g/100 ml (6.6 ± 0.9). However, the albumin:globulin ratio was decreased to 0.83 ± 0.28 , reflecting a relative increase of globulins. The 34 patients who did not have serum protein determinations were personally seen by the author (U.E.N.) and were clinically described as of good overall nutritional status.

Fifteen of 86 patients received cytotoxic chemotherapy (alkylating agents). Five patients with breast cancer and 3 patients with prostate neoplasm received estrogen therapy (ethinyl-estradiol and diethylidioxystilbendiphosphate, respectively). Sixty-three of 96 patients received either X-ray, surgery, or symptomatic treatment.

Quantitative Determination of Lipoproteins. A number of problems are associated with the quantitative assay of serum lipoproteins. Various methods for their analysis have been reviewed recently (9), and since then new methods have been developed (11). We have chosen the single radial immunodiffusion method (14), as recommended by Hatch and Lees (9).

The antiserum against the α_1 -lipoprotein used was produced in rabbits and purchased from Behringwerke, Marburg/Lahn, Germany. It was tested in our laboratory for specificity against pooled plasma by double diffusion and immunoelectrophoresis. The antibody-containing agar was prepared according to published methods (8, 14). The β -lipoprotein quantitation was performed with immunodiffusion plates obtained from Behringwerke.

Standard preparations of lipoproteins were not commercially obtainable, and we therefore pooled the sera of 96 young blood donors without apparent disease. This pool was used as a standard for 100% α_1 - and 100% β -lipoprotein. A reference curve was established by serially diluting this pool, with 0.15 M NaCl as a diluent. With every serum tested for α_1 - and β -lipoproteins, serial dilutions of the standard pool were used as controls, and sera as well as controls were done in duplicate. The mean values of the horizontal and vertical measurements of the 2 precipitation rings were plotted on semilogarithmic paper and compared with the standard curve of the reference pool. The 3 dilutions of the control sera and the sera examined were plotted on the standard reference curve.

Quantitation of serum proteins was done by the biuret method. Separation of serum protein fractions was carried out by cellulose-acetate electrophoresis followed by densitometric quantitation, according to routine laboratory procedures.

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Table 1
Mean ± S.D. of variables in different age groups

Age group	% of standard pool		TL (mg/100 ml)	EFA (mg/100 ml)	PhL (mg/100 ml)	Chol (mg/100 ml)	TG (mg/100 ml)
	β-LP ^a	α ₁ -LP					
Below 30 years							
Healthy controls	108 ± 29 (33) ^b	123 ± 24 (33)	745 ± 122 (33)	316 ± 53 (33)	149 ± 30 (33)	198 ± 26 (33)	102 ± 39 (32)
Cancer	108 ± 23 (3)	95 ± 18 (3)	720 ± 70 (3)	318 ± 50 (3)	115 ± 4 (2)	193 ± 49 (3)	105 ± 52 (3)
30–39 years							
Healthy controls	114 ± 39 (20)	119 ± 31 (20)	767 ± 126 (19)	339 ± 71 (19)	170 ± 42 (19)	212 ± 40 (19)	118 ± 65 (19)
Cancer	116 ± 20 (3)	91 ± 30 (3)	923 ± 261 (3)	423 ± 159 (3)	142 ± 40 (3)	204 ± 43 (3)	285 ± 137 (3)
40–49 years							
Healthy controls	106 ± 27 (19)	139 ± 34 (19)	828 ± 134 (19)	327 ± 59 (18)	188 ± 25 (19)	227 ± 42 (19)	113 ± 40 (19)
Cancer	133 ± 36 (12)	89 ± 32 (12)	819 ± 224 (11)	363 ± 72 (11)	157 ± 46 (11)	212 ± 73 (11)	131 ± 38 (11)
50–59 years							
Healthy controls	130 ± 34 (28)	139 ± 30 (28)	975 ± 137 (12)	400 ± 91 (12)	205 ± 46 (12)	256 ± 37 (12)	162 ± 72 (12)
Cancer	121 ± 38 (25)	97 ± 41 (25)	718 ± 178 (21)	313 ± 52 (21)	136 ± 38 (21)	196 ± 49 (21)	126 ± 48 (21)
60–69 years							
Healthy controls	118 ± 27 (28)	137 ± 28 (28)	919 ± 171 (7)	381 ± 127 (7)	177 ± 44 (7)	234 ± 40 (7)	162 ± 75 (7)
Cancer	129 ± 44 (40)	98 ± 39 (40)	828 ± 276 (37)	357 ± 155 (37)	146 ± 37 (36)	205 ± 54 (36)	153 ± 82 (37)
70–79 years							
Healthy controls	153 ± 35 (26)	137 ± 27 (26)	982 ± 187 (7)	305 ± 46 (6)	200 ± 56 (7)	258 ± 41 (7)	123 ± 24 (7)
Cancer	122 ± 42 (31)	87 ± 41 (31)	716 ± 210 (24)	318 ± 93 (23)	137 ± 38 (23)	185 ± 46 (24)	134 ± 53 (24)
80–89 years							
Healthy controls	131 ± 29 (26)	140 ± 24 (26)	818 ± 104 (5)	336 ± 62 (5)	216 ± 26 (5)	221 ± 23 (5)	124 ± 43 (5)
Cancer	118 ± 51 (8)	95 ± 43 (8)	691 ± 308 (6)	311 ± 78 (6)	114 ± 34 (6)	176 ± 48 (6)	132 ± 66 (6)
90–99 years							
Healthy controls	110 ± 20 (6)	133 ± 29 (6)					
Cancer							

^a The abbreviations used in this table are: β-LP, β-lipoprotein; α₁-LP, α₁-lipoprotein; TL, total lipids; EFA, esterified fatty acids; PhL, phospholipids; Chol, cholesterol; TG, triglycerides.
^b No. in parentheses, no. of cases.

Estimation of lipids was done according to published methods (3, 6, 12, 15, 17, 19, 20).

Computer Analysis. The data from 100 patients with malignant tumors and from 100 donors without apparent disease were evaluated with a program for regression and correlation on a Bull γ 30-S computer and were subjected to a discriminant analysis (4).

RESULTS

Serum Lipoproteins and Lipids in Normal Subjects and in Cancer Patients. The mean values for serum lipoproteins and lipids in normal subjects and in cancer patients are represented in Table 1. A comparison of the values within the different age groups between cancer patients and healthy control subjects reveals consistent decreases of α₁-lipoproteins, phospholipids, and cholesterol. The same comparison is made in Charts 1 and 2 for α₁-lipoproteins and β-lipoproteins, respectively. Chart 1 shows different peak maxima for cancer patients and healthy controls, whereas in Chart 2 no significant difference is seen. The α₁- and β-lipoprotein levels in the 2 groups are compared on the basis of age in Charts 3 and 4, respectively. We see that the difference between the groups cannot be attributed to age.

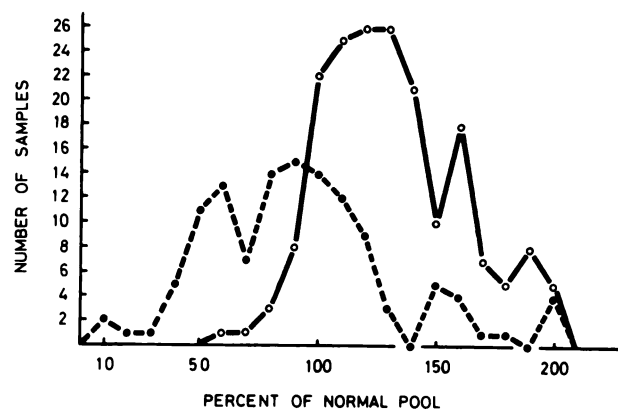


Chart 1. Single values of α₁-lipoprotein in healthy controls and in cancer patients showing different peaks. ○, 186 healthy subjects; ●, 122 patients with tumors.

Serum Lipoproteins According to Type and Site of the Cancer. The single values for α₁-lipoproteins according to type and site of the malignant tumor are shown in Chart 5. With the exception of (estrogen-treated) breast carcinoma, the majority of patients have levels less than 120%. The most marked

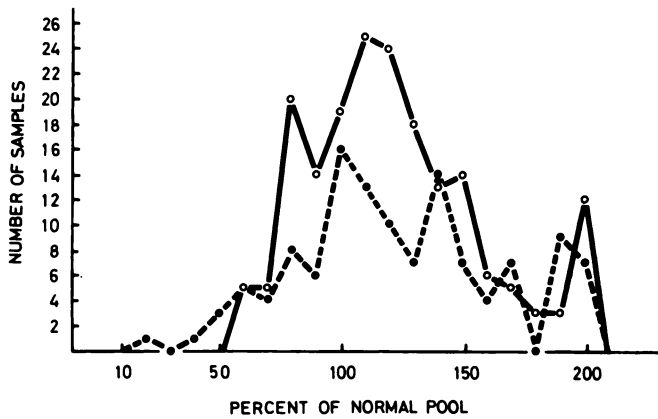


Chart 2. Single values of β -lipoprotein in healthy controls and in cancer patients. Maximum peaks in the same region. \circ , 186 normal subjects; \bullet , 122 patients with tumor.

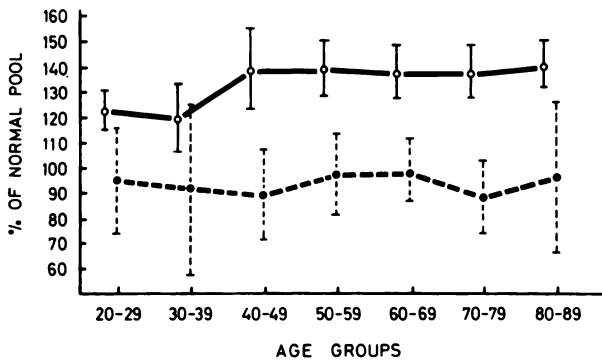


Chart 3. Mean values and 95% confidence intervals of α_1 -lipoprotein in healthy controls and in cancer patients are compared according to the age of the donor. All age groups reveal clear-cut differences. \circ , 186 normal subjects; \bullet , 122 patients with tumor.

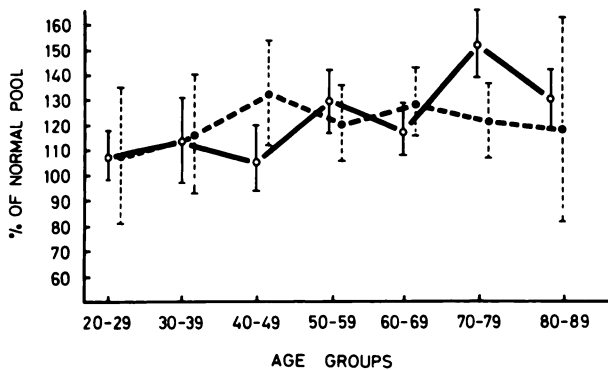


Chart 4. Mean values and 95% confidence intervals of β -lipoproteins in healthy controls and cancer patients are compared according to the age of the donor. No consistent difference is observed. \circ , 186 normal subjects; \bullet , 122 patients with tumor.

decrease in the α_1 -lipoprotein levels is encountered in tumors affecting the digestive system and in gynecological cancer.

Serum Lipoprotein Levels According to the Extent of the Tumor and Treatment. The difference between patients with metastasis and patients with local malignant tumors was

statistically not significant ($p > 0.1$) (Table 2). The subjects receiving cytostatic treatment did not differ from those who received symptomatic therapy, X-ray, or surgery. The group with estrogen therapy (5 breast cancer cases and 3 prostate neoplasms) shows significantly elevated mean values.

Discriminance Analysis of Subject Groups according to Lipoprotein Levels and Lipid Determinations. By means of the discriminance analysis, the computer takes into account all variables and calculates a discrimination index, X , which coordinates all characteristics. The X values have been used in a frequency distribution curve (Chart 6) for patients with malignant tumors and for donors without apparent disease, with the 4 best separating variables which are α_1 -lipoproteins, phospholipids, β -lipoproteins, and triglycerides. If the assumption is made that the discrimination index of zero marks the borderline between cancer patients and normal blood donors, then only 20 misclassified sera (7 in the malignant group and 13 in the healthy controls) became undiscriminant.

In order to strengthen this assumption, we may add that a seemingly incorrect classification in the normal controls is due to sera with extremely high α_1 -lipoprotein levels. In the group with the malignant tumors, this incorrect classification could be attributed to different classes of tumors.

The function $X = 0.00317 (\beta\text{-lipoproteins}) + 0.00239 (\alpha_1\text{-lipoproteins}) + 0.005529 (\text{phospholipids}) - 0.002111 (\text{triglycerides})$ allows the attribution of any serum sample to the normal or tumor group.

Taking as an example for β -lipoprotein a value of 125%; for α_1 -lipoprotein, 115%; for phospholipids, 157 mg/100 ml; and for triglycerides, 233 mg/100 ml, a discrimination index of $X = 0.268$ would result. This positive number is evidence against the presence of a malignant tumor, the probability of a seemingly incorrect classification being about 10%.

DISCUSSION

α_1 -Lipoproteins, phospholipids, and cholesterol have been found to be diminished in patients with malignant tumors. Triglycerides, esterified fatty acids, and β -lipoproteins were not decreased.

These findings confirm the results of de Alvarez and Goodell (5), who studied α_1 -lipoproteins in patients with gynecological cancer, and Barclay *et al.* (1, 2), who showed decreased α_1 -lipoprotein levels in breast carcinoma. We have extended these observations to many other malignant tumor types. Recently, Suga and Tamura (18) reported that α_1 -globulins were increased in gastric cancer. However, their study did not analyze the lipoprotein moiety of the α -globulin, and their results may be consistent with ours.

The estrogen therapy caused an increase in α_1 -lipoprotein values. This increase is more important in the patients with breast cancer than in those with prostate cancer. This increase of lipoproteins is consistent with the estrogen-induced increases in serum α_1 - and phospholipid-lipoprotein in 276 males reported by Stamler *et al.* (16). The possibility that hormones produced by certain malignant tumors depress or increase lipid levels should also be considered, but in none of

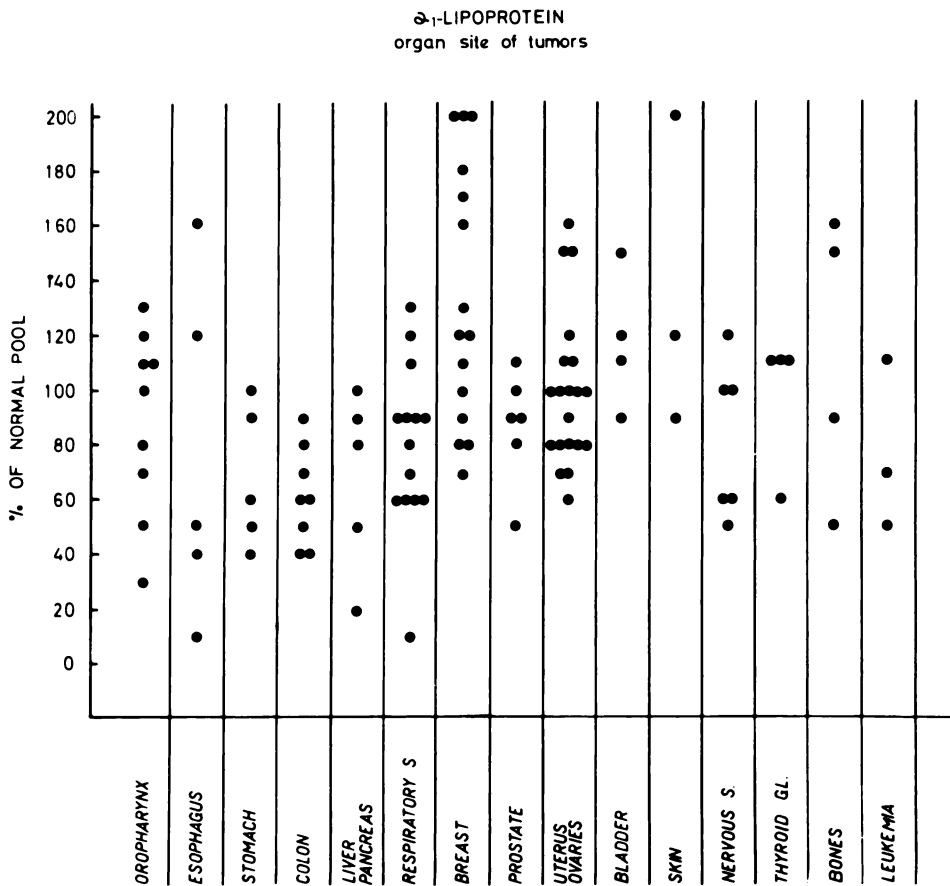


Chart 5. Single values of α_1 -lipoprotein are measured in patients with various malignant tumors and are grouped according to the organ site of the tumor.

Table 2
 α_1 -Lipoprotein levels in cancer patients according to the extent of tumor spread and mode of treatment

Group examined	No. of cases	α_1 -lipoprotein (% of standard pool)	Serum protein levels (g/100 ml)
Primary tumors only	45	89 \pm 5 ^a	6.3 \pm 0.3
Metastasizing cancer	41	97 \pm 6	6.5 \pm 0.3
Cytotoxic therapy	15	88 \pm 4	6.4 \pm 0.5
Symptomatic, X-ray, or surgical treatment	63	91 \pm 5	6.4 \pm 0.4
Estrogen therapy	8	151 \pm 7	6.9 \pm 0.2

^a Mean \pm S.E.

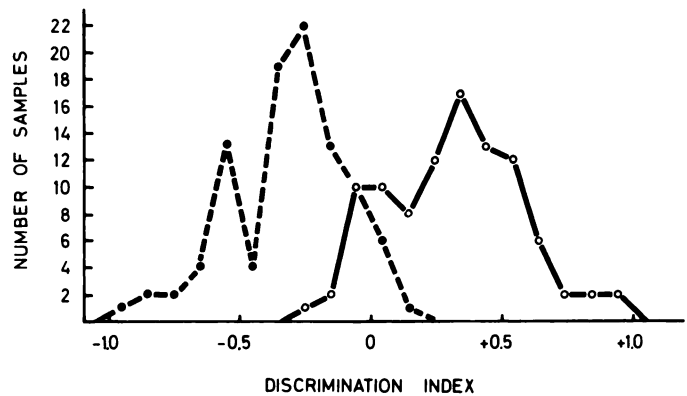


Chart 6. Discriminance analysis of healthy controls and cancer patients as obtained with α_1 -lipoprotein, phospholipids, β -lipoprotein, and triglycerides. \circ , 97 normal subjects; \bullet , 97 patients with tumor.

the 122 cases examined did the case history provide evidence for paraneoplastic hormone activity.

Although the metastatic and nonmetastatic groups are comparable in nutritional state by clinical and/or serum protein levels (Table 2), no significant difference in the overall decrease of lipoprotein values was noted when these groups were compared with cancer patients as a whole. The age and sex distribution in these groups was such that these factors could not explain the results.

The pathogenesis of the decreased lipoprotein values in patients with cancer is not known. The possibilities for decreased α_1 -lipoprotein and cholesterol levels include decreased synthesis or increased catabolism. The decrease

noted with phospholipids may perhaps be caused by decreased levels of α_1 -lipoproteins known to transport phospholipids, and the cholesterol depression may be on the same basis, at least in part (7). Theoretically, synthesis of lipoproteins and cholesterol by the liver could be inhibited by tumor metabolites. Liver metastases cannot explain the depression in most of our patients (only 9 out of 86 had liver metastasis). The possibility of an increased catabolism accounting for decreased lipoproteins cannot be excluded. Especially with gastrointestinal neoplasms, a protein loss through the intestine

is a possibility. Antibodies to lipoproteins have also been detected (W. Riesen, G. Nosedá, and U. E. Nydegger, unpublished). It is conceivable that this could lead to accelerated immune elimination of the antigen-antibody complex.

Further speculations concerning the increased lipoprotein and cholesterol loss should also include the observation of Haven *et al.* (10) about the properties of tumors to draw on the host for phospholipids. Finally, Lüscher *et al.* (13) have suggested that α_1 -lipoproteins may have a protective effect against the development of malignant neoplasia, so that decreased lipoproteins may in fact precede the development of cancer. However, no increased incidence of cancer has been reported in patients with congenital absence of α_1 -lipoproteins (Tangier disease) to support this concept.

This study suggests that there exists in patients suffering from cancer a decrease in α_1 -lipoproteins, phospholipids, and cholesterol which seems to be independent of age, sex, state of nutrition, treatment, and organ site of the cancer. In addition, early-diagnosed cancer, such as the preinvasive carcinoma of the cervix, shows the same decrease. A decreased level of serum α_1 -lipoproteins therefore not only reflects the neoplastic state in general, it perhaps may be especially useful in the early detection of cancers.

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