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Biochemical Status of Vitamin A in Colorectal Cancer

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Summary Serum vitamin A and its carrier proteins, retinol-binding protein and prealbumin, were measured in 41 colorectal cancer patients, 40 patients with benign colorectal disease, and 31 healthy subjects. Serum samples were obtained from the Mayo Clinic (NCI-Serum diagnostic Bank, Rochester, MN). The values for each of the three parameters were significantly lower in colorectal cancer patients than in healthy subjects but were littele different from the values seen in patients with benign disease.

Key Words: colorectal cancer, vitamin A, retinol-binding protein, prealbumin

There is considerable evidence from case-control studies that a low serum level of vitamin A is an important risk factor for the development of a variety of human cancers of epithelial cell origin [1-8]. Several of these studies [1, 4-6, 8] have also indicated that the presence of an established cancer is associated with low serum concentrations of the vitamin A transport proteins, which include retinol-binding protein (RBP) and prealbumin. Furthermore, in our recent study [9] where serum vitamin A and RBP levels were measured in patients with surgically resected cancers of the colon and rectum, those who subsequently had recurrent disease showed lower levels of vitamin A and RBP compared with those who remained free of recurrence. Low RBP levels in plasma have also been reported in patients with recurrence of breast tumors, when compared with the

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levels in breast cancer patients who remained disease-free following mastectomy and adjuvant chemotherapy [10, 11].

We present here the results of a case-control study in which serum vitamin A and its transport proteins were measured in patients with malignant and non-malignant colorectal disease as well as in age- and sex-matched healthy subjects. The biochemical evidence of a low vitamin A level appeared to be a common factor for both benign and malignant colorectal disease.

SUBJECTS AND METHODS

A total of 112 subjects including 41 colorectal cancer patients with distal metastases without liver involvement, 40 patients with benign colorectal disease including polyps, inflammatory bowel disease, and diverticulitis, and 31 healthy subjects were studied. The particulars of these subjects are shown in Table 1. Serum samples from these subjects were obtained from the Mayo Clinic (NCI-Serum Diagnostic Bank), Rochester, MN. The identity of cases and controls was not revealed to us until the data were sent to the Information Management Services (IMS) Data Center, Silver Spring, MD, for analysis.

Vitamin A was determined in the sera by a modification [12] of the fluorometric method of Hansen and Warwick [13]. RBP and prealbumin were determined by the single radial immunodiffusion technique [14] using LC-partigen immunodiffusion plates (Behring Diagnostic, Marburg, FRG). The data were analyzed statistically by Spearman rank correlation, the Kruskal-Wallis test, and the Wilcoxon rank sum.

RESULTS

No significant differences due to sex were found in the median assay values for vitamin A, RBP, or prealbumin in any of the three groups of subjects. However, in the group as a whole, prealbumin was higher in males an this achieved marginal significance ($p<0.05$). The Spearman rank correlations showed that age is not significantly correlated with assay values in any of the three groups of subjects. In the groups combined, prealbumin was significantly correlated with age ($r=-0.22$; $p<0.02$).

The values for the three study parameters in the three groups of subjects are

Table 1. Particulars of the subjects studied.

Subject	Total number	Sex		Age (years) (Mean with median in parenthesis)
		Male	Female	
Colorectal cancer	41	19	22	59.8 (62.0)
Benign colorectal disease	40	11	29	56.0 (57.5)
Healthy	31	13	18	57.0 (59.0)

Table 2. Serum vitamin A, RBP, and prealbumin in patients with colorectal cancer or benign colorectal disease and in healthy subjects.

Measurement	Colorectal cancer ($n=14$)		Benign colorectal ($n=40$)		Healthy subjects ($n=31$)		Overall Kruskal-Wallis test (p-value)	Comparison colorectal vs. normal (p-value)
	Mean	SD	Mean	SD	Mean	SD		
Vitamin A (μg/dl)	83.3	38.7	80.9	29.8	128.9	50.2	0.0001	<0.0001
RBP (mg/dl)	4.28	1.72	3.94	1.27	5.06	1.37	0.003	0.01
Prealbumin (mg/dl)	26.7	9.2	28.6	8.7	34.1	6.3	0.0003	0.0001

Table 3. Correlations between assay measurements.

	Spearman correlation coefficient	p-value
All patients ($n=112$)		
Vitamin A with RBP	0.72	<0.0001
Vitamin A with prealbumin	0.69	<0.0001
RBP with prealbumin	0.87	<0.0001
Colorectal ($n=41$)		
Vitamin A with RBP	0.72	<0.0001
Vitamin A with prealbumin	0.76	<0.0001
RBP with prealbumin	0.86	<0.0001
Benign GI ($n=40$)		
Vitamin A with RBP	0.76	0.0001
Vitamin A with prealbumin	0.74	0.0001
RBP with prealbumin	0.91	0.0001
Normals ($n=31$)		
Vitamin A with RBP	0.49	0.005
Vitamin A with prealbumin	0.36	0.05
RBP with prealbumin	0.77	0.0001

shown in Table 2. Pair-wise comparisons showed that for each study parameter, values for colorectal cancer subjects were significantly lower than those for healthy subjects but were not significantly different from those for the subjects with benign colorectal disease. The correlations between assay measurements were found to be highly significant (Table 3).

DISCUSSION

There have been many case-control studies showing an inverse relationship between cancer incidence and serum concentrations of vitamin A [6, 8, 9, 15, 16]. All of these studies have shown subnormal levels of serum vitamin A in cancer patients compared with the levels of healthy subjects or patients with unspecified

non-malignant disease. These findings are similar to the results obtained in the present study. Not only the serum levels of vitamin A but also of its transport proteins (RBP and prealbumin) were significantly lower in patients with colorectal cancer than in age- and sex-matched healthy subjects. However, no significant differences were apparent when the colorectal cancer patients were compared with a different control group, namely, subjects with benign colorectal disease. These results indicate that depressed levels of the three study parameters are a feature of a diseased state and are not specific to cancer. The results therefore provide no evidence that abnormalities of vitamin A status are directly related to cancer (e.g., by being a precursor or a consequence).

Vitamin A in the serum was measured by the fluorometric procedure of Hansen and Warwick [13], which has been reported to measure not only vitamin A but also phytofluene, a non-vitamin A component [17]. Hence, it may be argued that the validity of the conclusions based on the serum vitamin A levels is questionable. It should, however, be pointed out that serum vitamin A determined in this study was highly correlated with RBP and prealbumin. Thus values derived by simple fluorometry do, at least in part, reflect serum vitamin A. Furthermore, measurement of serum vitamin A alone, even by the most specific method, provides little information on the cause of the low levels because serum vitamin A concentrations are not generally strongly influenced by dietary vitamin A intake [18].

It is noteworthy that the results of the present study resemble a similar study carried out on breast cancer [19]. In that study also cancer patients had lower serum values for the three parameters studied here but the magnitude of the differences were reduced when the cancer patients were compared with patients suffering from benign breast disease. These results underline the importance of the use of appropriate controls; had we used only healthy subjects as the control group, we would have drawn erroneous conclusions.

A low serum vitamin A concentration may occur in true vitamin A deficiency or in conditions in which there is low mobilization from liver stores such as stress [20], infections [21], protein-energy malnutrition [22], and low zinc status [23]. For instance, in patients with protein-energy malnutrition, serum concentrations of both RBP and prealbumin are reduced; while administration of protein without vitamin A causes a rise in serum vitamin A and its carrier proteins levels in these patients [24]. It seems important that the factors affecting vitamin A utilization should be controlled by use of an appropriate 'control' population, especially in case-control studies. For cancer patients, such 'control' subjects should be those with benign disease affecting the same site as in the malignant patients. This is especially important when patients with gastrointestinal cancer are studied.

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