

# Serum Vitamins A and E, $\beta$ -Carotene, and Selenium in Patients with Breast Cancer

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A total of 89 subjects including 30 breast cancer patients with distal metastases, 29 patients with benign breast disease, and 30 healthy subjects were studied. Serum samples from these subjects were obtained from the National Cancer Institute (NCI) Breast Cancer Serum Bank, Bethesda. Serum concentrations of vitamin A and its transport proteins (prealbumin and retinol-binding protein [RBP]),  $\beta$ -carotene, vitamin E, and selenium were determined. For each of these parameters the mean for the breast cancer patients was lower than that of the healthy subjects. The differences between healthy subjects and patients with either breast cancer or benign breast disease were, however, statistically significant only in the case of RBP ( $p < 0.05$ ). In the case of vitamin A and its transport proteins these differences were reduced by comparing the cancer patients with the benign breast disease patients rather than with the healthy controls. This indicates that the low serum levels for those three parameters may be merely a consequence of disease in general rather than a feature of cancer per se.

## INTRODUCTION

The possible protective effects of vitamin A [1-5], vitamin E [6-8],  $\beta$ -carotene [9-11], and selenium [3,12,13] against cancer has attracted much scientific attention. The evidence comes largely from human dietary and serum studies. Unfortunately, such evidence presents serious problems of interpretation. Many of the above studies have shown subnormal levels of serum nutrients in cancer patients. However, numerous factors, such as stress, infections, and protein-energy malnutrition, are known to depress serum nutrient levels, vitamin A in particular [5,14,15]. It is therefore important that such factors be controlled by using an appropriate control population. For cancer patients, the best control subjects are those with nonmalignant disease affecting the same site.

We present here the results of a case-control study in which vitamin A and its transport proteins (RBP and prealbumin),  $\beta$ -carotene (provitamin A), vitamin E, and selenium were measured in sera from patients with malignant and nonmalignant breast disease as well as from age- and sex-matched healthy controls.

## SUBJECTS AND METHODS

### Subjects

A total of 89 subjects including 30 breast cancer patients with distal metastases, 29 patients with benign breast disease, and 30 healthy age-matched control subjects were studied. When the blood samples were taken, the 30 patients with breast cancer were all in an advanced stage of the disease with

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**Table 1. Serum Vitamin A, Vitamin E, and Selenium in Patients with Breast Cancer and Benign Breast Disease and in Healthy Subjects**

Measurement (per dl)	Breast cancer			Benign breast disease			Healthy subjects			Total			F between groups <sup>a</sup>
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	
Vitamin A (µg)	30	68.0	5.3	29	65.8	7.0	30	74.7	6.0	90	69.5	3.5	0.41
RBP (mg)	30	3.92	0.28	29	4.45	0.35	30	5.06	0.39	90	4.48	0.20	3.30 <sup>b</sup>
Prealbumin (mg)	30	26.3	17.8	29	29.3	10.3	30	30.7	13.9	90	28.7	8.4	2.47
β-carotene (µg)	30	0.36	0.07	29	0.57	0.13	30	0.43	0.08	90	0.45	0.06	1.00
Selenium (µg)	19	12.0	10.0	25	11.0	4.0	19	13.0	5.0	63	12.0	4.0	2.51
Vitamin E (mg)	30	0.81	0.08	29	0.91	0.08	28	0.91	0.08	88	0.08	0.05	0.49
Age (yr)	30	55.2	2.4	29	59.3	2.6	30	53.7	2.4	90	56.1	1.4	0.31

<sup>a</sup>Adjusted for age.

<sup>b</sup>p < 0.05.

## Vitamin A in Breast Cancer Patients

distant metastases present. The most frequent sites of metastasis were bone (15 cases), lung (eight cases), and liver (four cases). None of the 30 breast cancer patients were receiving any treatment at least 1 month prior to blood collection. The types of benign breast disease included in this study were essentially fibrosclerosis, cystic mastopathy, inflammatory disease, hypertrophy, and fat necrosis. The histology of these benign disorders included were intraductal papilloma, lipoma, or fibroadenoma. All serum samples (including serum samples from 30 age- and sex-matched healthy controls) were obtained from the National Cancer Institute (NCI Breast Cancer Serum Bank, Bethesda, MD). The identity of cases and controls was not revealed to us until the data were sent to the Division of Cancer Biology and Diagnosis of the NCI.

### Laboratory Analyses

Vitamin A was determined in the sera by a modification [16] of the fluorometric method of Hansen and Warwick [17]. Prealbumin and RBP were determined by the single radial immunodiffusion technique [18] causing LC-partigen immunodiffusion plate (Behring Diagnostics). The serum concentrations of  $\beta$ -carotene [19] and vitamin E [20] were measured using a high-pressure liquid chromatograph (HPLC) with a reverse phase column and an UV detector.

Selenium concentrations in serum were measured by neutron activation analysis [21]. Samples and standards were irradiated in the SLOWPOKE II nuclear reactor at the University of Alberta. Conditions used for the analysis were: 30-s irradiation at a thermal flux of  $10 \times 10^8 \text{ n cm}^{-2} \text{ s}^{-1}$ , 10-s decay, 30-s count. The counting was done using an Ortec Coaxial Ge (Li) detector (relative efficiency of 18.5%, peak to Compton ratio of 53:1, FWHM of 2.1 keV gamma). The selenium concentration was determined by comparing the net counts of the 162-keV gamma emitted by the  $^{77\text{m}}\text{Se}$  ( $T_{1/2} = 17.5 \text{ s}$ ) within the samples and the standards.

### Statistical Analysis

For each measurement the differences between the means for the three groups of subjects were tested for

statistical significance using analysis of covariance with age as the covariate. Pearson's coefficients of correlation were calculated for each pair of measurements.

## RESULTS

Table 1 shows the means and standard deviations of each measurement in the three groups. The mean age of the patients with benign breast disease was somewhat higher (59.3 years) than that of the breast cancer patients (55.2 years) or the healthy controls (53.7 years). These differences did not reach statistical significance, but age was used as a covariate when comparing the serum levels.

The mean for the four patients with liver metastases was lower than that for the remaining breast cancer cases for all six measurements, but the conclusions were not altered by dropping these cases.

For each parameter the mean for the breast cancer patients was lower than that for the healthy subjects. For vitamin A and its transport proteins the magnitude of differences was reduced when the values for the breast cancer patients were compared with that of the patients with benign breast disease. The differences between healthy controls, malignant patients, and patients with benign disease were statistically significant only for the RBP values ( $p < 0.05$ ).

The correlations between the measurements are shown in Table 2. All the significant correlations were in the positive direction. The only strongly significant coefficients ( $p < 0.01$ ) were between prealbumin and three of the other measurements — namely, RBP, selenium, and vitamin E. Less strongly significant associations ( $p < 0.05$ ) were seen between vitamin A and both RBP and  $\beta$ -carotene.

## DISCUSSION

The serum levels of vitamin A, its transport proteins (RBP and prealbumin),  $\beta$ -carotene, selenium, and vitamin E were somewhat lower in patients with breast cancer with distal metastases than in healthy controls. However, only the values of RBP were significant ( $p < 0.05$ ). For vitamin A and its transport proteins the magnitude of the differences

**Table 2.** Correlations Between Serum Vitamin A, Vitamin E, and Selenium in Patients with Breast Cancer and Benign Breast Disease, and in Healthy Subjects

	Vitamin A	RBP	Prealbumin	$\beta$ -carotene	Selenium	Vitamin E	Age
Vitamin A	1	0.19 <sup>a</sup>	0.14	0.20 <sup>a</sup>	0.08	0.09	-0.13
RBP		1	0.51 <sup>b</sup>	0.08	0.22	0.13	0.21 <sup>b</sup>
Prealbumin			1	0.00	0.30 <sup>b</sup>	0.27 <sup>b</sup>	-0.08
$\beta$ -carotene				1	0.03	0.10	0.13
Selenium					1	0.16	-0.19
Vitamin E						1	-0.07

<sup>a</sup>*p* < 0.05.<sup>b</sup>*p* < 0.01.

was reduced when the values of the cancer patients were compared with that of the age-matched female patients with benign breast disease.

Few studies have dealt with serum levels of vitamin A and E,  $\beta$ -carotene, and selenium in patients with breast cancer. In one study of 12 patients, the plasma vitamin A level was markedly lower than that of the healthy subjects while RBP was also somewhat lower [22]. A prospective study indicated that plasma vitamin E and  $\beta$ -carotene levels, though not vitamin A, were lower in those who subsequently developed breast cancer [23]. Other prospective studies indicate that low serum levels of vitamins A and E and of selenium precede the development of various types of cancer [3,23-25]. Similarly, cancer patients were observed to have a lower serum level of vitamin A, prealbumin, and RBP than hospital control patients [5]. Of all the nutrients and related substances,  $\beta$ -carotene is most consistently (and negatively) associated with cancer. This is seen in both diet and blood studies, and in both prospective and retrospective studies [11].

In contrast, the minimal association between most serum micronutrient levels and breast cancer in this study resembles numerous prospective studies involving cancer of sites other than the breast [26-29].

It is noteworthy that in the present study the serum RBP was the only parameter found to be significantly lower in breast cancer patients when compared with the healthy subjects or the patients with benign breast

disease. These results are in agreement with others who found an association between low plasma RBP and recurrence of either breast cancer [30] or colorectal cancer [4] in patients receiving adjuvant chemotherapy. RBP is known to be highly sensitive to an inadequate protein intake, because of its rapid turnover rate and unusually high tryptophan content [31]. Furthermore, several workers have reported that RBP is closely correlated with degree of trauma [14,15]. An important factor is malnutrition. Flaim et al [5] proposed that the depressed vitamin A level seen in cancer patients owes much to their poor nutritional status and consequent low level of vitamin A transport proteins. It is therefore possible that secondary factors rather than cancer itself may have caused the lowered serum levels of RBP in patients bearing metastatic breast cancer. Follow-up studies are needed to establish whether serum RBP has prognostic significance in cancer.

## CONCLUSION

The low level of blood vitamin A and its transport proteins (particularly RBP), often seen in cancer patients, may be a symptom of cancer malnutrition. Case-control studies on cancer patients should utilize appropriate controls, namely patients with either non-malignant or premalignant disease rather than healthy persons.

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