

Plasma Levels of β -Carotene, Lycopene, Canthaxanthin, Retinol, and α - and τ -Tocopherol in Cervical Intraepithelial Neoplasia and Cancer

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ABSTRACT

Epidemiological studies continue to identify an association of dietary antioxidant micronutrients in cancer prevention. A number of case-control and cohort studies have demonstrated a relationship between high intake of foods rich in carotenoids, tocopherols, and vitamin C with a reduced risk of certain human malignancies. The purpose of this study was to investigate the comparative plasma levels of a profile of known dietary antioxidants, namely, β -carotene, lycopene, canthaxanthin, retinol, α -tocopherol, and τ -tocopherol. The target population was women with a histopathological diagnosis of cervical intraepithelial neoplasia (CIN) or cervical cancer and a control group. All women resided in the same catchment area (Bronx Borough, New York City) and were of similar inner-city socioeconomic backgrounds representing a fairly homogenous population group. A cross-sectional sample of 235 women was recruited with informed consent. Plasma nutrient levels were measured by reverse-phase high pressure liquid chromatography under study codes. The mean plasma levels of carotenoids (β -carotene, lycopene, and canthaxanthin), as well as α -tocopherol, were significantly lower in women with CIN and cervical cancer. In contrast, the mean plasma level of τ -tocopherol was higher among patients with CIN, while the mean plasma level of retinol was comparable among the groups. There were significant linear trends for all three carotenoids and quadratic trends for α - and τ -tocopherol with the degree of cervical histopathology. Plasma β -carotene concentrations in cigarette smokers were significantly lower regardless of cervical pathology, whereas plasma lycopene and canthaxanthin levels were significantly lower in smokers with CIN. The findings of a decrease in all plasma antioxidant nutrient levels except τ -tocopherol in women with CIN and cancer suggest a potential role for antioxidant deficiency in the pathogenesis of CIN and carcinoma of the cervix, which requires further investigation.

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INTRODUCTION

The incidence of some human cancers have been reported to be reduced in patients with increased dietary intake of vitamins E and C and β -carotene (1–5). Limited objective information is available in support of epidemiological reports concerning plasma and/or tissue concentrations of essential antioxidant nutrients in women with precancerous and cancerous lesions of the uterine cervix (6–10). The purpose of this study was to investigate the relative plasma concentrations of three potent antioxidant carotenoids: β -carotene, lycopene, canthaxanthin as well as retinol, α -tocopherol, and τ -tocopherol in coded peripheral venous samples using standardized HPLC² technology.

MATERIALS AND METHODS

Subject Population. We studied a cross-sectional sample of 235 nonpregnant patients attending the Family Planning Clinics, Colposcopy Clinics, and/or admitted to the Weiler Hospital of the Albert Einstein College of Medicine (Bronx, NY). The study protocol was approved by the Institutional Review Board, and all subjects were recruited with informed consent. Cases consisted of patients who had abnormal Pap smears and a biopsy-confirmed histopathological diagnosis of CIN I–III or cervical cancer. In addition, nonpregnant women attending regular gynecological clinics for routine care who had three consecutive normal Pap smears, were not using p.o. contraceptives, and had normal menstrual cycles constituted the control group. All study subjects came from the same catchment area (Bronx Borough, New York City) with similar inner-city socioeconomic backgrounds representing a fairly homogenous group. All subjects were on Medicaid or received some form of public assistance. The majority of the study population was African-American (41%) and Hispanic (46%). An epidemiological questionnaire including age, date of last menstrual period, vitamin supplementation, and smoking history was completed by each participant. Recent dietary intake was recorded. Subjects were excluded from the study if they reported a history of current vitamin supplementation.

Venous Blood Samples. A single peripheral venous blood sample (10 ml) was obtained from each participant, including cancer patients, prior to any therapeutic intervention. No dietary restrictions were imposed upon any of the subjects. Coded blood samples, wrapped in aluminum foil, were transported promptly to the laboratory. The plasma was separated and rapidly frozen at -70°C in a light-protected container until assayed. All of the assays were completed within a period of 1 week without any knowledge of the patient's clinical history.

² The abbreviations used are: HPLC, high-pressure liquid chromatography; CIN, cervical intraepithelial neoplasia; Pap, Papanicolaou.

HPLC Analysis of Plasma Micronutrients. Processing of samples was carried out under subdued or gold light. Plasma β -carotene, retinol, and α -tocopherol levels were measured using HPLC attached to a Waters 490E multiwavelength detector, as previously described (6). In brief, samples were extracted by shaking a mixture of 0.3 ml plasma, 0.3 ml ethanol, and 3.0 ml *n*-hexane containing 0.25 g β -hydroxy-toluene/liter. After centrifugation, the entire hexane layer was separated and evaporated under nitrogen stream. The residue was redissolved in 0.3 ml ethanol containing 0.25 g β -hydroxytoluene/liter. For the β -carotene assay, 0.03 ml of freshly extracted samples were injected onto a Ultramax reversed-phase C₁₈ 5 μ column (4.6 mm internal diameter \times 150 mm) and was eluted with acetonitrile:methylene chloride:methanol (75:20:5) at a flow rate of 1.0 ml/min, with monitoring at 450 nm. Lycopene and canthaxanthin levels were simultaneously measured in the same extracted plasma samples with monitoring at 472 nm. For α -tocopherol, τ -tocopherol, and retinol, 0.03 ml of each previously extracted plasma samples were injected onto another C₁₈ column preequilibrated with a mixture of methanol:water (97.5:2.5) and eluted at a flow rate of 1.5 ml/min, monitoring at 292 and 325 nm for respective nutrients. All determinations were carried out in duplicate. Results were calculated using the peak area of the compound over the peak area of the internal standard. The mean interassay coefficient of variation was <8%. The described HPLC system with a four-channel detector allows the separation of many carotenoids in the same run. There was no interference from lutein or zeaxanthin in the detection of canthaxanthin in our system.

Histopathological Diagnoses and Statistical Analysis.

Tissue specimens were submitted to staff pathologists who were blinded to subjects antioxidant status. Statistical analyses for differences between two means were calculated using the two-sample *t* tests, and for comparing multiple groups, one-way ANOVA was applied. The pairwise comparisons were carried out using the Scheffe test, and smoking data were analyzed using the χ^2 test. Measures of the linear, quadratic, and cubic trends for each micronutrient were carried out using a contrast test following the ANOVA using the SAS system.

RESULTS

Of the 235 patients studied, 140 women had abnormal Pap smears and colposcopically directed biopsies. Among these 140 women, 56 were histopathologically diagnosed as CIN I, 40 as CIN II, 29 as CIN III, and 15 had invasive cervical cancer. The control group (*n* = 95) consisted of 58 asymptomatic women attending the regular gynecological clinics for routine care and 37 patients who underwent colposcopy and were biopsied and had no evidence of CIN.

The mean age (\pm SD) and smoking habits of the different groups are shown in Table 1. The age of the study population ranged from 19 to 65 years. Women with cervical cancer were significantly older compared to all other groups (P < 0.05 using Scheffe's test). All smokers reported smoking 4–10 cigarettes a day for at least 6 months. The percentage of smokers was significantly increased (P = 0.045 using χ^2 analysis) in the higher grade CIN groups.

Table 1 Study population with age, smoking habits, and histopathological diagnoses

Subjects	<i>n</i>	Age, yr ^a	% Smoking ^b
Control	95	35.6 \pm 11.4	30.5 (29/95)
CIN (histopathologically graded)	125		
Grade I (<i>n</i> = 56)		31.9 \pm 10.5	26.7 (15/56)
Grade II (<i>n</i> = 40)		30.1 \pm 8.2	52.5 (21/40)
Grade III (<i>n</i> = 29)		33.3 \pm 7.9	44.8 (13/29)
Carcinoma	15	50.2 \pm 14.5 ^c	46.7 (7/15)
Total: 235			

^a Means \pm SDs: ANOVA: $F = 9.817$, $df = 4$, $P < 0.0001$.

^b $\chi^2 = 9.7242$, $df = 4$, $P = 0.0453$.

^c $P < 0.05$ versus all other groups using the Scheffe test.

Table 2 demonstrates that women with CIN and cervical cancer have significantly decreased levels of β -carotene, lycopene, canthaxanthin, and α -tocopherol (P < 0.0001, P < 0.0023, P < 0.0019, and P < 0.0046, respectively, using ANOVA) compared to controls. In contrast, τ -tocopherol levels were significantly increased (P < 0.0202), whereas plasma retinol levels were comparable (P = 0.1517) among the groups.

The measures of linear, quadratic, and cubic trends for each micronutrient are shown in Table 3. There are significant linear trends for β -carotene, lycopene, and canthaxanthin (P < 0.008, P < 0.0244, P < 0.0123, respectively) and quadratic trends for α -tocopherol (P < 0.0221) and τ -tocopherol (P < 0.0046) with the degree of cervical histopathology. No cubic trend was observed with any micronutrient analyzed.

Table 4 compares the effect of smoking on plasma antioxidant nutrients in women with CIN and cervical cancer. Women with different grades of CIN were pooled together to represent one group, and the significance of the differences was evaluated using the two-sample *t* test. Smoking was associated with a significant decrease in plasma β -carotene levels in all groups, whereas plasma lycopene and canthaxanthin levels were significantly lower in CIN groups. In addition, plasma canthaxanthin levels were significantly lower in controls. No significant effect of smoking on plasma levels of retinol or α -tocopherol or τ -tocopherol was observed in either group.

DISCUSSION

Previous reports of plasma carotenoids and cervical cancer have been largely limited to β -carotene (7–9). In this cross-sectional sample of 235 women, we have determined by HPLC a profile of plasma antioxidant nutrient levels consisting of retinol (vitamin A), provitamin A carotenoid (β -carotene), non-provitamin A carotenoids (lycopene and canthaxanthin), as well as α -tocopherol and τ -tocopherol. The notable finding is the detection of a decrease in plasma levels of multiple antioxidant nutrients in association with the histopathological diagnosis of CIN and cervical cancer. The plasma levels of all four lipid-soluble antioxidants (lycopene, canthaxanthin, β -carotene, and α -tocopherol) were significantly decreased. There were significant linear trends for all three carotenoids and quadratic trends for both tocopherols with the degree of cervical histopathology. It is noteworthy that plasma α -tocopherol levels demonstrated a concave upward curve (U-shaped pattern), while τ -tocopherol

Table 2 Plasma β -carotene, lycopene, canthaxanthin, retinol, α -tocopherol, and τ -tocopherol levels in controls and women with CIN and cervical cancer

Micronutrients	Normal ^a	CIN ^a			Cancer ^a	P using ANOVA
		Grade 1	Grade 2	Grade 3		
β -Carotene ($\mu\text{g}/\text{dl}$)	19.9 \pm 16.7 (95)	12.7 \pm 7.7 (56) ^b	11.2 \pm 10.2 (40) ^b	12.3 \pm 6.1 (29)	7.3 \pm 4.5 (15) ^b	0.0001
Lycopene ($\mu\text{g}/\text{dl}$)	53.0 \pm 24.5 (82)	46.2 \pm 22.6 (52)	40.3 \pm 15.0 (37) ^b	41.2 \pm 12.0 (25)	33.7 \pm 12.0 (14)	0.0023
Canthaxanthin ($\mu\text{g}/\text{dl}$)	3.33 \pm 2.5 (83)	2.48 \pm 2.4 (47)	1.83 \pm 1.5 (32) ^b	1.71 \pm 1.1 (20)	1.91 \pm 1.8 (14)	0.0019
Retinol ($\mu\text{g}/\text{dl}$)	65.1 \pm 17.2 (87)	67.6 \pm 15.9 (55)	61.6 \pm 15.4 (40)	68.7 \pm 17.4 (29)	67.1 \pm 11.9 (15)	0.3469
α -Tocopherol (mg/liter)	7.20 \pm 2.6 (88)	5.86 \pm 3.2 (55)	5.17 \pm 2.7 (40) ^b	6.17 \pm 3.6 (29)	6.65 \pm 2.3 (15)	0.0046
τ -Tocopherol (mg/liter)	1.97 \pm 1.8 (49)	3.56 \pm 4.0 (39)	3.81 \pm 3.6 (25)	2.44 \pm 2.6 (25)	1.41 \pm 1.2 (14)	0.0202

^a Means \pm SDs. Numbers in parentheses, number of samples assayed for nutrient levels.

^b $P < 0.05$ versus normal group using the Scheffe test.

Table 3 Tests of linear, quadratic, and cubic trends for the antioxidant micronutrient data in Table 2

Micronutrients	Trend	df	Contrast SS ^a	F	P
β -Carotene	Linear	1	3737.647	11.64	0.0080 ^b
	Quadratic	1	94.229	0.62	0.4310
	Cubic	1	478.060	3.16	0.0769
Lycopene	Linear	1	4082.352	9.45	0.0224 ^b
	Quadratic	1	86.974	0.20	0.6541
	Cubic	1	228.996	0.53	0.4673
Canthaxanthin	Linear	1	30.874	6.40	0.0123 ^b
	Quadratic	1	11.976	2.48	0.1169
	Cubic	1	0.0172	0.00	0.9525
α -Tocopherol	Linear	1	5.1819	0.60	0.4380
	Quadratic	1	45.5858	5.31	0.0221 ^b
	Cubic	1	7.4712	0.87	0.3519
τ -Tocopherol	Linear	1	9.9724	1.12	0.2917
	Quadratic	1	73.6651	8.27	0.0046 ^b
	Cubic	1	8.6113	0.97	0.3271

^a SS, sum of squares.

^b Significant.

levels showed a concave downward curve. Our data concerning α -tocopherol are in agreement with a previous case-control study of women with CIN (9). Plasma retinol levels were within the normal range among the study groups, which is consistent with our earlier report (6). The present findings support an association between decreased antioxidant nutrient levels and CIN and cervical cancer. Whether the present findings are evidence of marginal deficiencies in the dietary intake of each studied antioxidant nutrient or a response to unidentified dietary antioxidant interactions that may be mechanistically involved in the oncogenic process remains to be investigated.

Epidemiological investigations have reported a positive association between cigarette smoking and cervical dysplasia (11) and cervical cancer (12). In the present study, a significant association was observed between smoking and decreased (a) plasma β -carotene levels in all study groups and (b) plasma lycopene and canthaxanthin in CIN groups. However, this association was not evident with respect to retinol, α -tocopherol, and τ -tocopherol. Smokers in the control group had a 23% reduction in plasma β -carotene levels compared to nonsmokers, whereas patients with CIN or cervical cancer had a 32–66% reduction in β -carotene levels. Moreover, smokers with CIN had a 20% and 35% lower plasma lycopene and canthaxanthin levels, respectively, compared to nonsmokers in the same group.

Additional studies are needed to clarify this selective effect of smoking on various antioxidant nutrient concentrations.

β -Carotene, lycopene, canthaxanthin, and α -tocopherol are all biologically active antioxidants. The potent antioxidant properties of these nutrients are postulated to protect DNA against oxidative damage and potentially genotypic mutational events associated with cancer initiation (13, 14). β -Carotene has been studied extensively (15, 16). It is noteworthy, however, that the chain-breaking antioxidant activities of canthaxanthin exceed those of β -carotene as demonstrated by their comparative inhibition of free radical-mediated lipid peroxidation (17). Canthaxanthin is reported to inhibit the formation of UV light-induced skin tumors in mice (18) and neoplastic transformation of murine fibroblast cells (19). In solution, lycopene has been shown to be the most efficient quencher of singlet oxygen (20). The consumption of tomatoes, a rich source of lycopene, has been reported to have a stronger inverse association with lung cancer risk than increased dietary intake of β -carotene (21). Serum levels of lycopene have also been determined to be lower in individuals who develop cancer of the pancreas (22) and bladder (23).

The mechanism(s) underlying antitumor protective effects of carotenoids are thought to involve antioxidant activities (13, 24). β -Carotene is the naturally occurring provitamin A carotenoid. Unlike β -carotene, lycopene and canthaxanthin have no provitamin A activity. The finding in CIN and cervical cancer of a decrease in the plasma levels of both vitamin A and nonvitamin A precursors suggest that any antitumor activity of carotenoids is mediated by mechanisms independent from the established role as retinol precursors. There were some limitations in our present study. Information on potentially confounding variables such as economic status, sexual histories, and long-term dietary habits was not collected. This was deemed to be beyond the scope of this study. Additional research is required to elucidate the synergistic biological functions of β -carotene in conjunction with other non-provitamin A carotenoids in the etiology and possibly the prevention of CIN.

α -Tocopherol is generally considered to be the most potent antioxidant in the vitamin E group and functions as a major peroxy radical scavenger with powerful chain-breaking properties (25). Decreased levels of plasma α -tocopherol in epithelial cancers of reproductive organs exposed to estrogens have been reported (26). α -Tocopherol has been reported to be a potent inhibitor of 3-methylcholanthrene-induced neoplastic transfor-

Table 4 Effects of cigarette smoking on plasma micronutrient levels in controls and women with CIN and cervical cancer

Micronutrient	Smoking status	Normal ^a	CIN ^{a,b}	Cancer ^a
β-Carotene (μg/dl)	Nonsmokers	21.3 ± 8.8 (66)	13.9 ± 8.8 (76)	10.6 ± 1.8 (8)
	Smokers	16.3 ± 10.0 (29)	9.4 ± 6.5 (49)	3.6 ± 3.7 (7)
	<i>P</i> ^c	<0.02	<0.005	<0.001
Lycopene (μg/dl)	Nonsmokers	54.6 ± 23.9 (61)	46.6 ± 18.6 (72)	31.1 ± 8.1 (8)
	Smokers	48.5 ± 26.4 (21)	37.2 ± 16.8 (42)	36.7 ± 13.5 (6)
	<i>P</i>	ns ^d	<0.01	ns
Canthaxanthin (μg/dl)	Nonsmokers	3.90 ± 2.6 (59)	2.45 ± 2.2 (63)	2.15 ± 2.1 (8)
	Smokers	1.90 ± 1.1 (24)	1.58 ± 1.3 (37)	1.58 ± 1.3 (6)
	<i>P</i>	<0.001	<0.05	ns
Retinol (μg/dl)	Nonsmokers	62.8 ± 14.9 (67)	68.8 ± 16.3 (75)	65.7 ± 12.3 (8)
	Smokers	71.6 ± 21.6 (23)	61.6 ± 15.3 (49)	68.8 ± 12.1 (7)
	<i>P</i>	ns	ns	ns
α-Tocopherol (mg/liter)	Nonsmokers	7.22 ± 2.6 (63)	5.90 ± 3.2 (75)	7.34 ± 1.7 (8)
	Smokers	7.12 ± 2.7 (25)	5.41 ± 3.1 (49)	5.86 ± 2.8 (7)
	<i>P</i>	ns	ns	ns
τ-Tocopherol (mg/liter)	Nonsmokers	2.04 ± 1.9 (36)	3.60 ± 4.0 (53)	1.10 ± 0.4 (7)
	Smokers	1.79 ± 1.5 (13)	2.90 ± 2.8 (36)	1.71 ± 1.6 (7)
	<i>P</i>	ns	ns	ns

^a Means ± SDs. Numbers in parentheses, number of samples assayed for nutrient levels.

^b Pooled CIN groups from Table 2.

^c *P* values based on the two-sample *t* tests between smokers and nonsmokers in same group. Smokers are women who have been smoking 4–20 cigarettes/day for last 6 months.

^d ns, not significant (*P* > 0.05).

mation of C3H/10T1/2 cells (27). In contrast to α-tocopherol, there have been few epidemiological studies evaluating any relationship between τ-tocopherol consumption and cancer incidence. It has been reported that serum τ-tocopherol levels were lower in patients with early-stage cervical cancer but higher in patients with late-stage disease compared with controls (9). Our results reveal an increase in plasma levels of τ-tocopherol in patients with CIN and cervical cancer in contrast to other antioxidant levels and demonstrate a concave downward curve with severity of the cervical pathology. The significance of these opposite trends in α- and τ-tocopherol levels in this patient population remains unclear.

Epidemiological studies concerning the role of dietary antioxidants in cancer prevention raise the question as to whether deficiency of antioxidant nutrients, *per se*, may be a contributing etiological factor or whether the cancer and its metabolic consequences are responsible for the depletion of these micronutrients. The present finding of decreased antioxidant nutrient levels in asymptomatic women with CIN as well as patients with invasive cervical cancer suggests that the reduction in antioxidant levels precedes the development of invasion and overt malignancy. As observed in this study, the detectable levels of several carotenoids in human plasma, some in amounts comparable to β-carotene, provide evidence that the biological properties of carotenoids are not limited to β-carotene. The physiological role of non-provitamin A carotenoids, namely, lycopene and canthaxanthin, in reproduction and carcinogenesis is largely unknown. The current data suggest that dietary and consequently plasma deficiencies of carotenoids, individually or interactively, may be a risk factor for CIN and cervical cancer. Identifying the presence and concentrations of individual carotenoids and tocopherols in human plasma and various tissues is a first requirement to assess the biological activity of individual antioxidants and their potential role in cellular proliferation and

neoplastic transformation. Future research is needed in this area to investigate the potential role of antioxidant nutrient supplementation in the prevention of CIN and cervical cancer.

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