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Plasma carotenoids and tocopherols in relation to prostate-specific antigen (PSA) levels among men with biochemical recurrence of prostate cancer

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ABSTRACT

Background: Although men presenting with clinically localized prostate cancer (PrCA) often are treated with radical prostatectomy or radiation therapy with curative intent, about 25–40% develop biochemically recurrent PrCA within 5 years of treatment, which has no known cure. Studies suggest that carotenoid and tocopherol intake may be associated with PrCA risk and progression. We examined plasma carotenoid and tocopherol levels in relation to prostate-specific antigen (PSA) levels among men with PSA-defined biochemical recurrence of PrCA.

Methods: Data analyzed were from a 6-month diet, physical activity and stress-reduction intervention trial conducted in South Carolina among biochemically recurrent PrCA patients ($n=39$). Plasma carotenoids and tocopherol levels were measured using high-performance liquid chromatography (HPLC). Linear regression was used to estimate least-square means comparing PSA levels of men with high versus low carotenoid/tocopherol levels, adjusting for covariates.

Results: After adjusting for baseline PSA level, plasma *cis*-lutein/zeaxanthin level at 3 months was related inversely to PSA level at 3 months ($P=0.0008$), while α-tocopherol ($P=0.01$), β-cryptoxanthin ($P=0.01$), and all-*trans*-lycopene ($P=0.004$) levels at 3 months were related inversely to PSA levels at 6-months. Percent increase in α-tocopherol and *trans*-β-carotene levels from baseline to month 3 were associated with lower PSA levels at 3 and 6 months. Percent increase in β-cryptoxanthin, *cis*-lutein/zeaxanthin and all-*trans*-lycopene were associated with lower PSA levels at 6 months only.

Conclusions: Certain plasma carotenoids and tocopherols were related inversely to PSA levels at various timepoints, suggesting that greater intake of foods containing these micronutrients might be beneficial to men with PSA-defined PrCA recurrence.

1. Introduction

Prostate cancer (PrCA) is the most frequently diagnosed visceral tumor and the second most lethal malignancy among men in the United States [1]. The majority (≈94%) of these men diagnosed with PrCA present with clinically localized disease; and they are often treated with radical prostatectomy or radiation as primary therapy [2,3]. Unfortunately, about 25–40% of these men develop biochemical evidence of recurrent disease within five years of these definitive therapies [4–7]. Biochemical recurrence of PrCA denotes rising serum prostate-specific antigen (PSA) level on three or more successive tests after achieving post-treatment nadir

Abbreviations: ACSM, American College of Sports Medicine; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHAMPS, Community Health Activities Model Program for Seniors; CI, confidence interval; HPLC, high-performance liquid chromatography; IRB, institutional review boards; METs, metabolic equivalents; PrCA, prostate cancer; PSA, prostate-specific antigen; SC, South Carolina; SD, standard deviation.

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(lowest detectible PSA level) [8]. PSA-defined PrCA recurrence following definitive therapy is often an early sign of metastasis, and precedes pathological and radiographic evidence of metastasis by several years [9,10]; in some instances by an average of eight years [9]. Thus, the detection of biochemical recurrence of PrCA provides ample time for intervention to alter the disease course.

There is currently no known cure for biochemically recurrent PrCA [11]. This disease state is often managed with surgical or medical androgen ablation to delay the time to metastasis and to prolong survival [11,12]. Though initially successful, androgen ablation ultimately fails in controlling the disease progression as most patients develop hormone-refractory PrCA within two years, preceded by a continuous rise in PSA [13,14]. Androgen ablation also has been associated with severe side effects [11,13]. Thus, there is continued interest in the search for adjuvant and neoadjuvant therapies for the management of biochemical PrCA relapse [15]. Epidemiologic data from migrant studies indicate that in addition to age, race/ethnicity and a positive family history, diet plays an important role in PrCA [16,17]. Greater intake of cruciferous vegetables, fruits, and specific dietary nutrients such as lycopene, soy isoflavones and polyphenols have been associated with modest reduction in PrCA risk, while energy imbalance and increased consumption of fat, meat, calcium and dairy products have been associated with increased risk of PrCA [18–21].

Few studies have investigated whether the progression of biochemically recurrent PrCA can be altered using plant-based, dietary intervention [15,22–27]. Most of these intervention trials incorporated supporting interventions such as stress reduction [22,24–26] and physical activity [15] to reinforce dietary modifications. Five of the studies reported potential inhibitory effect of the intervention on PrCA progression [22–26], while two reported null results [15,27]. Because these trials involved different combinations of diet, stress reduction and physical activity, it is difficult to determine to what degree these factors were responsible for the beneficial effects reported. Other studies have investigated the effects of dietary modifications alone among men with biochemical recurrence (reviewed in Refs. [19,28,29]); however, the diet used in these studies had multiple components, such as higher levels of fruits, vegetables, legumes, and whole grain intake while decreasing meat and dairy intake, which makes it difficult to examine the independent effects of specific food components. Additional work is needed to evaluate the role of specific foods and nutrients. Of particular interest are biomarkers of antioxidant intake, which have been inversely associated with PrCA risk in some studies [30,31] and therefore may have an inverse relation with the progression of biochemically recurrent PrCA [28].

Our team previously reported results of a pilot intervention trial conducted in South Carolina that investigated whether a plant-based, dietary intervention integrated with physical activity and stress reduction could alter the progression of PrCA in men with biochemical recurrence after definitive therapy [15]. In the current report, we expand on that work by examining whether plasma carotenoids (including all major carotenoids) and tocopherols (α- and γ-tocopherol) were associated with serum PSA levels, used as a marker of PrCA progression, in these patients.

2. Materials and methods

2.1. Study population

Details of the study design and methods have been published [15]. Briefly, participants were men with histologically confirmed, organ-confined, adenocarcinoma of the prostate, who had been treated with radical prostatectomy, radiation, or both as primary therapy and had experienced a minimum of three successive rises in serum PSA level of at least 1.5 ng/ml above the post-treatment nadir level (which was usually at or close to zero) with each assayed at 2- to 3-month intervals. Prospective participants were included in the study if they: (1) were free of any other malignancy in the previous 5 years (with the exception of non-malignant skin cancer); (2) spoke English as a first language; (3) were able to read at a sixth-grade level; (4) were of sound mind, memory, and understanding; (4) had not been taking thyroid medication, steroids, antibiotics, or diuretics; and (5) were willing to be randomized to intervention or control (with an option to obtain the intervention at the end of the study). The participants were required to enter the study with their spouse or another partner of choice to provide support for compliance with the study protocol. Participant ineligibility was determined by: (1) having received post-operative hormonal therapy for treatment of PrCA; (2) having a current diagnosis or symptoms of active ulcerative colitis or cardiovascular, pulmonary, Crohn's or metabolic disease; (3) have experienced weight loss of five or more pounds within the previous 3 months; (4) plan to use hormone supplements, fish oil, or other ω-3 fatty acids-based supplements; or (5) having a diagnosis of post-traumatic stress disorder (PTSD). All participants provided written informed consent prior to enrollment. The research protocol of the parent study was reviewed and approved by the Institutional Review Boards (IRBs) of the University of South Carolina (USC) and Palmetto Health. The current analysis also was approved by the USC IRB.

All participants were recruited from major urological practices located in seven counties of the Midlands Region of SC (i.e., Richland, Lexington, Orangeburg, Kershaw, Sumter, Fairfield, and Newberry). The majority of participants were from Richland (67%) and Lexington (9%) counties, which are the two most densely populated counties in the greater Columbia area. The intervention was conducted at locations near the recruitment sites under the auspices of the primary investigator (JRH).

2.2. Study design

Participants were randomly assigned to the intervention or control group blocked by age (±5 years) and race (African American/European American). Participant involvement spanned 6 months, consisting of an initial 3-month period of active intervention followed by monthly booster sessions for the following 3 months. The intervention consisted of dietary modifications, physical activity, and mindfulness-based stress reduction training. The 3-month active phase of the intervention involved individual diet and physical activity counseling and goal-setting sessions, as well as twelve weekly group meetings that included cooking classes and shared model meals. In addition, participants were given weekly assignments on how to shop for and cook study-compliant meals, attain physical activity goals, and practice meditation for stress management. The diet aspect of the intervention emphasized increased intake of plant-based foods such as whole grains, fruits, vegetables, and legumes (particularly soybeans and soybean products) along with decreased intake of meat and dairy products. The physical activity aspect involved working with participants to identify activities that they enjoyed and reinforcing those activities to promote physical fitness and overall well-being, with the goal that each participant attains the Centers for Disease Control and Prevention and American College of Sports Medicine (CDC/ACSM) recommendations of ≥30 min of moderate intensity physical activity for ≥5 days/week [32]. Because comprehensive dietary change can be difficult to maintain, participants were taught to meditate in a way that inculcates mindfulness about decisions concerning food choices in order to promote their sense of control over the change in diet and culinary habits [33]. Partner support was integrated to provide an

encouraging environment for the process of change. Following the 3-month active phase, monthly booster sessions were held in a supportive group environment for another 3 months. This phase of the intervention included frequent telephone calls to each participant and their spouse/partner to check wellness, and to provide encouragement to sustain the intervention.

Participants in the control group underwent the same general assessment as those in the intervention group and, through the consent process, were made aware of the general nature of the intervention. No attempt was made to restrict their access to psychosocial support or any other educational resources available to PrCA patients in the community. These participants, along with their spouse/partner, were given the opportunity to undertake the intervention at the end of the 6-month study period at no cost to them. Further details can be found elsewhere [15].

2.3. Data collection and phlebotomy

Data on clinical and pathologic attributes of PrCA were abstracted from participants' medical records obtained from referring urologist. At baseline, participants responded to questionnaires that solicited information on demographics and health-related behaviors, including age, race, education, marital status, employment and smoking status. Data on diet, physical activity, and anthropometry were obtained at each of the three study checkpoints: baseline, 3 months, and 6 months. Dietary assessment was performed using 24-hour dietary recalls on three randomly selected days that included two weekdays and one weekend day; a method found to be least prone to measurement error [34,35]. Physical activity was assessed using the CHAMPS questionnaire [36] and expressed as metabolic equivalent (MET) value based on description of the activity as referenced in the *Compendium of Physical Activities* [37], with one MET being equivalent to resting metabolic rate. Total METs of physical activity were estimated for each participant as the sum of METs from light, moderate, and vigorous physical activity per week. Anthropometric measurements included standing height (cm) and weight (kg), waist-to-hip ratio, and bioelectric impedance measures of percent body fat and lean body mass. Body mass index (BMI) was subsequently calculated as: weight (kg)/height $(m)^2$.

Table 1
Baseline characteristics of study subjects and changes in PSA levels.

	All subjects ($n = 39$) Mean ± SD	Intervention ($n = 22$) Mean ± SD	Control ($n = 17$) Mean ± SD	P^*
Age (years)	70 ± 8	69 ± 9	71 ± 7	0.51
BMI (kg/m^2)	29.75 ± 5.21	29.49 ± 4.86	30.09 ± 5.77	0.73
Energy (kcal/day)	1683.90 ± 414.24	1741.24 ± 367.52	1609.68 ± 468.92	0.33
Physical activity (total METs/week)	44.60 ± 35.51	52.02 ± 41.29	35.43 ± 24.96	0.13
	n (%)	*n* (%)	*n* (%)	
Race				
White/European American	28 (72)	17 (77)	11 (65)	0.48
Black/African American	11 (28)	5 (23)	6 (32)	
Education				
High school graduate or less	8 (20)	4 (18)	4 (23)	0.70
High school and some college	12 (31)	8 (36)	4 (23)	
College graduate	19 (49)	10 (45)	9 (53)	
Marital status				
Married or with partner	31 (79)	16 (73)	15 (88)	0.43
Widowed, divorced, or single	8 (21)	6 (27)	2 (12)	
Employment				
Yes, full time	7 (18)	3 (14)	4 (23)	0.68
Yes, part time	4 (10)	2 (9)	2 (12)	
No	28 (72)	17 (77)	11 (65)	
Smoking status				
Never	14 (37)	8 (36)	7 (41)	0.80
Former	21 (53)	11 (50)	9 (53)	
Current	4 (10)	3 (14)	1 (6)	
Tumor grade (Gleason score)				
Well differentiated (<5)	1 (3)	1 (5)	0 (0)	0.95
Moderately differentiated (5–6)	9 (23)	5 (23)	4 (24)	
Poorly differentiated (≥7)	20 (51)	12 (54)	8 (47)	
Missing	9 (23)	4 (18)	5 (29)	
Type of treatment				
Prostatectomy	6 (15)	3 (14)	3 (18)	0.99
Prostatectomy and radiation	18 (46)	10 (45)	8 (47)	
Radiation only	15 (39)	9 (41)	6 (35)	
PSA levels, mean (range) (ng/ml)[a]				
Baseline	3.91 (0.10–52.00)	3.24 (0.10–37.90)	4.78 (0.10–52.00)	0.61
At 3-months	5.01 (0.10–68.30)	4.37 (0.10–44.70)	5.85 (0.10–68.30)	0.70
At 6-months	4.72 (0.10–67.20)	4.26 (0.10–54.40)	5.27 (0.10–67.20)	0.80

PSA, prostate-specific antigen; SD, standard deviation; METs, metabolic equivalent task per week from physical activity.
[*] *P* value comparing intervention and control groups using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables.
[a] Data represents actual PSA values, not logarithm transformed values.

Each participant provided a 5 ml vial of blood from venipuncture obtained by a trained phlebotomist at each of the three study timepoints. The samples were fractionated by centrifuge, frozen at –80 °C within 1 h of collection, and transported on ice within 1 week via overnight courier to Quest® Laboratories for analysis. PSA was measured in serum at baseline, at 3 months and at 6 months. Carotenoids and tocopherols were measured in plasma using high-performance liquid chromatography (HPLC) [38]. Because of limited availability of samples, data on carotenoids and tocopherols were measured at baseline and at 3 months only. The following carotenoids and tocopherols were measured: α- and γ-tocopherol, α-carotene, *cis*- and *trans*-β-carotene, lutein, zeaxanthin, *cis*-lutein/zeaxanthin, α- and β-cryptoxanthin, *cis*- and all-*trans*-lycopene.

2.4. Statistical methods

Overall, 54 men with a history of localized PrCA and rising PSA levels after definitive treatment with radical prostatectomy, radiation or both were successfully randomized to intervention ($n = 29$) and control ($n = 25$). Of these participants, seven were lost to follow-up (intervention, $n = 3$; control, $n = 4$) [15]. Of the remaining 47 participants, data on plasma carotenoid and tocopherol levels were available for 39 participants at baseline and 35 participants at 3 months.

Differences in baseline characteristics were assessed using Student's *t*-test to compare means of continuous variables and Fisher's exact test for categorical variables. Means and standard deviations (SDs) of plasma carotenoids and tocopherols at baseline and at 3 months also were calculated and compared by intervention group. Because carotenoids and tocopherols are transported in the blood by lipoproteins [39], we corrected for circulating lipid levels by dividing each carotenoid and tocopherol (μg/ml) by total plasma cholesterol level (mg/dl). These variables were subsequently categorized into binary groups in comparison to the median due to nonlinear distribution patterns as assessed by the generalized additive model procedure in SAS® (PROC GAM). A total antioxidant score was computed as a measure of overall antioxidant status following the method described by Li et al. [40]. In estimating the antioxidant score, the carotenoid and tocopherol variables (i.e., α- and γ-tocopherol, α-carotene, *cis*- and *trans*-β-carotene, α- and β-cryptoxanthin, lutein, zeaxanthin, and *cis*- and all-*trans*-lycopene) were first categorized into quartiles and scores assigned to each quartile in multiples of 3 (i.e., 3–12, from low to high). The scores were summed for each participant across all carotenoids and tocopherols, then categorized into binary groups (<median versus ≥ median).

The associations between plasma carotenoids and tocopherol levels and serum PSA levels were examined in three sets of analyses. First, we considered how baseline carotenoid and tocopherol levels are related to baseline PSA level. Second, we explored whether carotenoid and tocopherol levels at 3 months are related to PSA levels at 3 months and at 6 months, adjusting for baseline PSA level, as baseline PSA is related to subsequent PSA values [41]. Finally, we examined percent change in carotenoid and tocopherol levels (from baseline to 3 months) in relation to PSA levels at 3 months and at 6 months, adjusting for baseline PSA values. The sign for the percent change values was reversed [i.e., (3-month value − baseline)/baseline] to ensure that a positive value represented an increase in plasma carotenoid and tocopherol levels. These "percent change" variables also were categorized into binary (increase versus decrease) as well as tertile [decrease, minimal increase (1–20%), or substantial increase (>20%)] groups. Linear regression was used for all of the analyses to estimate least squares means and *P* values for testing the difference between group means, modeling PSA values as a continuous variable. Natural log transformation was performed on the positively skewed PSA data in order to achieve normality; results were back transformed for presentation.

Analyses were performed in minimally adjusted (i.e., "crude model" that adjusted only for age, race and randomized group), and in multivariable-adjusted models. Covariates chosen for inclusion in the multivariable-adjusted models were age, race, education, marital status, employment, smoking status, Gleason score, BMI, physical activity, energy intake and randomized group, and modeled as continuous or categorical variables as presented in Table 1. These variables were selected based on evaluation of confounding effect (≥10% change in effect estimates) in conjunction with the backward elimination model selection procedure. Additional variables considered but not included in the final analyses were the type of PrCA treatment received; body fat mass; fruit, vegetables, fiber and dairy intake; and total dietary fat and omega-3 fatty acids intake. All statistical tests were two-sided with *P* value <0.05 considered statistically significant. All analyses were performed using SAS® version 9.3.

3. Results

Differences in the distribution of baseline characteristics and PSA levels at all three timepoints are presented in Table 1. The

Table 2
Means and standard deviations of plasma carotenoid and tocopherol levels at baseline and at 3-months post-intervention.

Plasma carotenoids and tocopherols (mg/ml)	Baseline				Post-intervention (at 3-months)			
	All subjects ($n = 39$) Mean ± SD	Intervention ($n = 22$) Mean ± SD	Control ($n = 17$) Mean ± SD	*P**	All subjects ($n = 35$) Mean ± SD	Intervention ($n = 20$) Mean ± SD	Control ($n = 15$) Mean ± SD	*P**
α-Tocopherol	14.91 ± 5.15	15.23 ± 5.56	14.51 ± 4.71	0.67	14.35 ± 5.17	14.64 ± 5.48	13.96 ± 4.87	0.71
γ-Tocopherol	1.70 ± 1.01	1.67 ± 1.01	1.73 ± 1.04	0.86	1.65 ± 0.99	1.60 ± 0.89	1.70 ± 1.13	0.78
α-Carotene	0.04 ± 0.03	0.04 ± 0.03	0.05 ± 0.03	0.6	0.05 ± 0.04	0.04 ± 0.03	0.05 ± 0.05	0.64
cis-β-Carotene	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.07	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.32
trans-β-Carotene	0.20 ± 0.13	0.18 ± 0.12	0.24 ± 0.15	0.17	0.20 ± 0.14	0.20 ± 0.16	0.21 ± 0.12	0.83
α-Cryptoxanthin	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.77	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.86
β-Cryptoxanthin	0.11 ± 0.08	0.11 ± 0.09	0.10 ± 0.07	0.71	0.10 ± 0.07	0.10 ± 0.08	0.09 ± 0.06	0.87
Lutein	0.11 ± 0.06	0.10 ± 0.06	0.12 ± 0.07	0.4	0.12 ± 0.07	0.12 ± 0.07	0.12 ± 0.08	0.92
Zeaxanthin	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.02	0.3	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.47
cis-Lutein/zeaxanthin	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.59	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.07
cis-Lycopene	0.18 ± 0.13	0.18 ± 0.11	0.18 ± 0.15	0.94	0.17 ± 0.11	0.19 ± 0.10	0.15 ± 0.13	0.26
trans-Lycopene	0.19 ± 0.12	0.20 ± 0.11	0.19 ± 0.14	0.8z1	0.19 ± 0.11	0.22 ± 0.10	0.16 ± 0.12	0.12

SD, standard deviation.
* *P* value comparing intervention and control groups based on Student's *t*-test.

mean age of the study sample was 70 years (SD = 8), with mean BMI of 29.75 kg/m^2 (SD = 5.21), and included 28 (72%) European Americans and 11 (28%) African Americans. Fifteen percent of the participants underwent radical prostatectomy, 39% had radiation only, and 46% had both radiation and prostatectomy prior to enrollment in the study. We compared tumor characteristics and intervention group by type of treatment received prior to recruitment into the study and noted no differences by treatment type (Supplemental Table 1). Mean serum PSA levels were 3.91, 5.01, and 4.72 ng/ml at baseline, at 3 months, and at 6 months, respectively. None of the baseline characteristics, including education, marital status, employment, smoking status, and tumor grade, differed significantly by intervention status. The plasma carotenoid and tocopherol concentrations did not vary significantly between the intervention and control groups at baseline or at 3 months (Table 2). Analysis of baseline data also did not show any significant difference in mean PSA levels between participants with high versus low carotenoid/tocopherol levels or total antioxidant score (Table 3).

Table 4 presents results for associations of plasma carotenoids and tocopherols at 3 months in relation to serum PSA levels at 3 months and 6 months, after adjusting for baseline PSA level in addition to age, race, education, marital status, employment, smoking status, Gleason score, BMI, physical activity and randomization status. Participants with higher carotenoid and tocopherol levels at 3 months tended to have lower PSA levels at 3 months as compared to those with lower carotenoid and tocopherol levels, though the association with PSA at 3 months after adjustment for covariates was statistically significant only for cis-lutein/zeaxanthin ($P = 0.008$). The 3-month carotenoid and tocopherol levels appeared to be more strongly associated with serum PSA levels at 6 months, as participants with high plasma levels of α-tocopherol ($P = 0.01$), β-cryptoxanthin ($P = 0.01$), all-*trans*-lycopene ($P = 0.004$), and total antioxidant score ($P = 0.003$) showed significantly lower mean PSA levels at 6 months than those with low levels of these micronutrient antioxidants. We further examined whether percent change in carotenoid and tocopherol levels from baseline to month 3 was associated with PSA levels at 3 months and at 6 months, adjusting for baseline PSA level (Table 5). These results showed that participants who experienced an increase in carotenoid and tocopherol levels generally had lower mean PSA levels at 3 months compared to those who had a decrease in carotenoid and tocopherol levels. The evidence of an inverse relation with serum PSA at 3 months was particularly strong for α-tocopherol ($P = 0.0007$). Although significantly lower mean PSA levels were observed for higher levels of all-*trans*-β-carotene and α-cryptoxanthin in relation to PSA level at 3-months, significant findings in the tertile categories were confined to participants who had a minimal increase in their plasma levels (i.e., up to 20% increase). In the analysis of 6-month PSA values, percent increase in carotenoid/tocopherol level was related inversely to mean PSA level for α-tocopherol, *trans*-β-carotene, β-cryptoxanthin, *cis*-lutein/zeaxanthin, *trans*-lycopene, and total antioxidant score. Results from this analysis were very similar to those observed using a linear mixed models approach (Supplemental Table 1).

4. Discussion

In this study, we examined the relations between plasma carotenoid and tocopherol levels, and serum PSA levels among men with biochemical recurrence of PrCA who were enrolled in a

Table 3
Baseline PSA levels by baseline carotenoid and tocopherol levels.

Plasma tocopherols and carotenoids at baseline[c]		*n*		Crude model[a]		Adjusted model[b]	
				Mean (95% CI)[d]	*P*[*]	Mean (95% CI)[d]	*P*[*]
α-Tocopherol	Low	19	C = 9, I = 10	0.80 (0.39–1.62)	0.35	0.53 (0.25–1.16)	0.4
	High	20	C = 8, I = 12	1.34 (0.57–3.14)		0.79 (0.30–2.07)	
γ-Tocopherol	Low	20	C = 8, I = 12	1.40 (0.59–3.30)	0.3	0.71 (0.29–1.71)	0.5
	High	19	C = 9, I = 10	0.78 (0.38–1.58)		0.52 (0.23–1.20)	
α-Carotene	Low	19	C = 8, I = 11	1.10 (0.52–2.34)	0.67	0.49 (0.20–1.19)	0.45
	High	20	C = 9, I = 11	0.88 (0.42–1.88)		0.70 (0.30–1.63)	
Cis-β-carotene	Low	20	C = 5, I = 15	0.77 (0.35–1.67)	0.37	0.67 (0.26–1.70)	0.71
	High	19	C = 12, I = 7	1.27 (0.58–2.78)		0.55 (0.23–1.31)	
Trans-β-carotene	Low	20	C = 7, I = 13	0.91 (0.42–1.95)	0.75	0.50 (0.21–1.18)	0.44
	High	19	C = 10, I = 9	1.07 (0.49–2.34)		0.72 (0.30–1.74)	
α-Cryptoxanthin	Low	21	C = 7, I = 14	0.94 (0.44–2.00)	0.86	0.87 (0.35–2.19)	0.2
	High	18	C = 10, I = 8	1.03 (0.48–2.22)		0.46 (0.20–1.05)	
β-Cryptoxanthin	Low	20	C = 10, I = 10	0.92 (0.45–1.89)	0.76	0.56 (0.23–1.35)	0.8
	High	19	C = 7, I = 12	1.08 (0.49–2.37)		0.66 (0.23–1.89)	
Lutein	Low	19	C = 8, I = 11	0.91 (0.40–2.06)	0.79	0.70 (0.29–1.68)	0.52
	High	20	C = 9, I = 11	1.05 (0.51–2.14)		0.51 (0.22–1.22)	
Zeaxanthin	Low	18	C = 6, I = 12	0.96 (0.43–2.16)	0.93	0.53 (0.20–1.43)	0.74
	High	21	C = 11, I = 10	1.01 (0.49–2.05)		0.63 (0.29–1.37)	
Cis-lutein/zeaxanthin	Low	21	C = 9, I = 12	0.94 (0.46–1.91)	0.82	0.61 (0.28–1.34)	0.9
	High	18	C = 8, I = 10	1.05 (0.47–2.38)		0.58 (0.23–1.42)	
Cis-lycopene	Low	21	C = 8, I = 13	1.39 (0.60–3.22)	0.3	0.46 (0.14–1.54)	0.48
	High	18	C = 9, I = 9	0.72 (0.28–1.87)		0.30 (0.11–0.85)	
Trans-lycopene	Low	20	C = 8, I = 12	1.27 (0.35–2.07)	0.5	0.42 (0.16–1.07)	0.14
	High	19	C = 9, I = 10	0.85 (0.54–3.03)		0.22 (0.09–0.56)	
Antioxidant score[e]	Low	20	C = 8, I = 12	1.16 (0.55–2.42)	0.51	0.77 (0.32–1.85)	0.31
	High	19	C = 9, I = 10	0.82 (0.38–1.79)		0.45 (0.19–1.12)	

PSA, prostate-specific antigen; CI, confidence interval; C, Control group; I, intervention group.
[*] *P* values from regression model comparing mean difference between low and high tocopherol/carotenoid categories.
[a] Adjusted for age, race and randomized group.
[b] Adjusted for age, race, education, marital status, employment status, smoking status, Gleason score, body mass index, total metabolic equivalent (MET) per week of physical activity, energy intake, and randomized group.
[c] Categorized by median splits as less than median (low) versus greater than or equal to median (high).
[d] Data are reported as least square means.
[e] Antioxidant score; low : 57–83, high: 84–123.

Table 4
Associations of carotenoid and tocopherol levels at 3-months in relation to PSA levels at 3- and 6-months, adjusting for baseline PSA level.

Plasma tocopherols and carotenoids at 3 months[b]		*n*		PSA levels at 3 months[a]				PSA levels at 6 months[a]			
				Crude model[c]		Adjusted model[d]		Crude model[c]		Adjusted model[d]	
				Means (95% CI)	P^*	Means (95% CI)	P^*	Means (95% CI)	P^*	Means (95% CI)	P^*
α-Tocopherol	Low	18	C = 9, I = 9	0.98 (0.74–1.29)	0.09	0.62 (0.45–0.85)	0.1	1.00 (0.45–2.21)	0.11	0.76 (0.28–2.01)	**0.01**
	High	17	C = 6, I = 11	0.68 (0.49–0.94)		0.42 (0.27–0.65)		0.38 (0.16–0.93)		0.13 (0.03–0.48)	
γ-Tocopherol	Low	17	C = 8, I = 9	0.70 (0.50–0.98)	0.16	0.56 (0.39–0.83)	0.82	0.75 (0.32–1.72)	0.62	0.64 (0.16–2.59)	0.45
	High	18	C = 7, I = 11	0.97 (0.73–1.28)		0.53 (0.33–0.83)		0.55 (0.21–1.39)		0.33 (0.10–1.08)	
α-Carotene	Low	18	C = 7, I = 11	1.00 (0.76–1.33)	0.07	0.65 (0.45–0.93)	0.13	1.04 (0.45–2.40)	0.12	0.88 (0.26–2.95)	0.08
	High	17	C = 8, I = 9	0.69 (0.50–0.93)		0.44 (0.30–0.66)		0.42 (0.19–0.95)		0.23 (0.07–0.73)	
Cis-β-carotene	Low	17	C = 5, I = 12	1.04 (0.77–1.41)	0.05	0.66 (0.45–0.96)	0.16	0.74 (0.32–1.68)	0.65	0.51 (0.18–1.50)	0.52
	High	18	C = 10, I = 8	0.69 (0.52–0.92)		0.49 (0.34–0.68)		0.56 (0.23–1.39)		0.33 (0.10–1.15)	
Trans-β-carotene	Low	18	C = 8, I = 10	1.03 (0.78–1.35)	0.03	0.63 (0.43–0.92)	0.25	0.85 (0.37–1.95)	0.36	0.46 (0.12–1.70)	0.87
	High	17	C = 7, I = 10	0.66 (0.49–0.90)		0.50 (0.35–0.70)		0.49 (0.21–1.17)		0.41 (0.14–1.23)	
α-Cryptoxanthin	Low	18	C = 8, I = 10	0.97 (0.73–1.30)	0.15	0.57 (0.41–0.80)	0.65	0.67 (0.29–1.57)	0.9	0.69 (0.15–3.22)	0.46
	High	17	C = 7, I = 10	0.72 (0.54–0.97)		0.50 (0.30–0.83)		0.63 (0.26–1.50)		0.36 (0.12–1.04)	
β-Cryptoxanthin	Low	17	C = 7, I = 10	0.99 (0.74–1.32)	0.13	0.56 (0.39–0.83)	0.82	0.69 (0.27–1.44)	0.86	0.97 (0.33–2.86)	**0.01**
	High	18	C = 8, I = 10	0.72 (0.54–0.97)		0.53 (0.36–0.78)		0.62 (0.29–1.63)		0.17 (0.05–0.53)	
Lutein	Low	17	C = 8, I = 9	1.01 (0.75–1.36)	0.09	0.61 (0.41–0.93)	0.45	0.80 (0.33–1.91)	0.53	0.77 (0.22–2.65)	0.17
	High	18	C = 7, I = 11	0.71 (0.54–0.95)		0.51 (0.35–0.73)		0.55 (0.24–1.26)		0.28 (0.09–0.86)	
Zeaxanthin	Low	17	C = 5, I = 12	0.92 (0.66–1.29)	0.48	0.60 (0.43–0.82)	0.17	0.56 (0.23–1.37)	0.63	0.59 (0.15–2.30)	0.55
	High	18	C = 10, I = 8	0.79 (0.59–1.05)		0.44 (0.29–0.68)		0.76 (0.32–1.78)		0.38 (0.13–1.08)	
Cis-lutein/zeaxanthin	Low	18	C = 11, I = 7	1.02 (0.77–1.35)	0.05	0.75 (0.52–1.07)	**0.008**	1.05 (0.46–2.35)	0.09	0.76 (0.23–2.50)	0.16
	High	17	C = 4, I = 13	0.67 (0.49–0.92)		0.45 (0.33–0.62)		0.37 (0.15–0.91)		0.31 (0.11–0.86)	
Cis-lycopene	Low	17	C = 10, I = 7	0.97 (0.72–1.30)	0.2	0.61 (0.43–0.88)	0.29	0.77 (0.34–1.75)	0.54	0.73 (0.25–2.15)	0.08
	High	18	C = 5, I = 13	0.72 (0.52–0.99)		0.49 (0.34–0.71)		0.52 (0.20–1.36)		0.43 (0.07–0.73)	
All-*trans*-lycopene	Low	17	C = 10, I = 7	0.90 (0.66–1.22)	0.57	0.58 (0.40–0.82)	0.6	0.77 (0.34–1.75)	0.54	0.89 (0.33–2.37)	**0.004**
	High	18	C = 5, I = 13	0.78 (0.56–1.10)		0.51 (0.33–0.78)		0.51 (0.18–1.42)		0.10 (0.03–0.37)	
Antioxidant score[e]	Low	17	C = 7, I = 10	1.03 (0.77–1.37)	0.05	0.62 (0.44–0.87)	0.18	0.84 (0.36–1.96)	0.38	0.86 (0.32–2.25)	**0.003**
	High	18	C = 8, I = 10	0.69 (0.52–0.92)		0.47 (0.32–0.68)		0.51 (0.22–1.17)		0.14 (0.04–0.44)	

PSA, prostate-specific antigen; CI, confidence interval; C, control groups; I, intervention group.
[*] *P* values from regression model comparing mean difference between low and high tocopherol/carotenoid categories.
[a] Data are reported as least square means.
[b] Categorized by median splits as less than median (low) versus greater than or equal to median (high).
[c] Adjusted for age, race randomized group and baseline PSA level.
[d] Adjusted for age, race, education, marital status, employment status, smoking status, Gleason score, body mass index, total metabolic equivalent (MET) per week of physical activity, energy intake, randomized group and baseline PSA level.
[e] Antioxidant score; low : 45–80, high: 81–111.

6-month diet and lifestyle intervention trial conducted in South Carolina. In analysis of baseline data, no significant differences in mean PSA levels were observed between participants with high versus low carotenoid or tocopherol levels. We further explored whether carotenoid and tocopherol levels at 3 months (during the study intervention period) were associated with PSA levels at 3 months and at 6 months, adjusting for baseline PSA values. Results from this analysis showed that participants with higher *cis*-lutein/zeaxanthin level at 3 months had statistically lower mean PSA level at 3 months. Additionally, participants with higher plasma levels of α-tocopherol, β-cryptoxanthin, all-*trans*-lycopene, and higher antioxidant score at 3 months, had significantly lower mean PSA level at 6 months. Finally, we examined whether percent change in plasma carotenoid and tocopherol levels from baseline to month 3 were inversely related to PSA levels at 3 months and at 6 months, independent of baseline PSA values. These results showed significantly lower mean PSA values at 3 months and at 6 months for participants with an increase in α-tocopherol and *trans*-β-carotene levels compared to who had a decrease in the levels of these nutrients. In addition, those with an increase in β-cryptoxanthin, *cis*-lutein/zeaxanthin, all-*trans*-lycopene and antioxidant score had significantly lower mean PSA values at 6 months. Overall, higher plasma levels of certain carotenoids and tocopherols were associated with lower PSA level at various time points, with most pronounced effects in the 6-month data; suggesting that it may take a few months before a clinical benefit on PSA is observed from dietary intervention aiming to increase consumption of certain carotenoids and tocopherols.

The idea of using dietary agents as an alternate therapy or as a neoadjuvant to delay the use of more traditional therapy such as androgen ablation is a prospect that would be appealing to most patients because of the severe side effects associated with traditional therapy [11,12]. While it is possible that intake of certain carotenoids and tocopherols may influence serum PSA levels, it also is plausible that these nutrients could alter PSA levels without affecting cancer progression. Interestingly, declines in PSA have been found to correlate with inhibition of the androgen-sensitive LNCaP prostate tumor cell growth in animal models [42], findings consistent with those from tissue culture studies using human prostate carcinoma cell lines [23,43]. Secretion of PSA by prostate epithelial cells, and the hormone-dependent LNCaP tumor cell growth are both modulated by androgens [44,45]. Physiological levels of antioxidants such as lycopene and α-tocopherol are shown to be capable of down-regulating androgen activity [46–48]. Thus, suppression of androgen activity could be an underlying mechanism for the potential effect of certain carotenoids and tocopherols on PSA, and possibly, PrCA progression. Other mechanisms involving antioxidative and anti-inflammatory activities also have been proposed [49,50].

No study has yet examined serologic markers of carotenoid or tocopherol intake in relation to PSA levels among men with biochemically recurrent PrCA. The literature on the relationship between dietary and supplemental sources of carotenoids and tocopherols and PSA levels among men with biochemical PrCA relapse is sparse (reviewed in Refs. [19,28,29]). The majority of the available data emanates from intervention trials examining the potential benefits of lycopene.

Table 5
Percent change in carotenoid and tocopherol levels from baseline to 3-months in relation to PSA levels at 3- and 6-months, adjusting for baseline PSA level.

Change in plasma tocopherols and carotenoids from baseline to 3 months		Means (95% CI)									
				PSA level at 3 months[a]				PSA level at 6 months[a]			
		n		Crude model[b]		Adjusted model[c]		Crude model[b]		Adjusted model[c]	
					*P**		*P**		*P**		*P**
α-Tocopherol	Decrease	13	C = 6, I = 7	1.13 (0.80–1.59)	Ref	0.84 (0.58–1.21)	Ref	0.82 (0.63–1.06)	Ref	0.89 (0.72–1.10)	Ref
	Increase	21	C = 9, I = 12	0.73 (0.56–0.95)	0.04	0.47 (0.36–0.62)	**0.0007**	0.63 (0.52–0.77)	0.11	0.51 (0.44–0.60)	<0.0001
	Decrease	13	C = 6, I = 7	1.13 (0.53–1.03)	Ref	0.88 (0.61–1.26)	Ref	0.81 (0.63–1.05)	Ref	0.92 (0.74–1.13)	Ref
	Minimal increase (1–20%)	14	C = 7, I = 7	0.74 (0.53–1.03)	0.08	0.54 (0.37–0.77)	**0.008**	0.66 (0.52-0.84)	0.25	0.55 (0.45–0.67)	<**0.0001**
	Substantial increase (>20%)	7	C = 2, I = 5	0.71 (0.45–1.12)	0.1	0.40 (0.26–0.61)	**0.004**	0.57 (0.40-0.80)	0.09	0.45 (0.35–0.58)	<**0.0001**
γ-Tocopherol	Decrease	17	C = 7, I = 10	0.96 (0.69–1.32)	Ref	0.56 (0.39–0.80)	Ref	0.70 (0.55–0.90)	Ref	0.62 (0.48–0.79)	Ref
	Increase	17	C = 8, I = 9	0.77 (0.56–1.05)	0.34	0.52 (0.36–0.76)	0.73	0.68 (0.55–0.85)	0.87	0.54 (0.42–0.71)	0.38
	Decrease	17	C = 7, I = 10	0.95 (0.69–1.31)	Ref	0.56 (0.39–0.80)	Ref	0.70 (0.55–0.89)	Ref	0.62 (0.48–0.79)	Ref
	Minimal increase (1–20%)	8	C = 4, I = 4	0.70 (0.45–1.08)	0.25	0.50 (0.32–0.77)	0.64	0.61 (0.45–0.84)	0.2	0.50 (0.37–0.68)	0.2
	Substantial increase (>20%)	9	C = 4, I = 5	0.84 (0.56–1.28)	0.66	0.55 (0.33–0.89)	0.93	0.75 (0.56–1.00)	0.19	0.60 (0.44–0.84)	0.91
α-Carotene	Decrease	29	C = 13, I = 16	0.85 (0.67–1.09)	Ref	0.52 (0.38–0.71)	Ref	0.71 (0.60–0.84)	Ref	0.59 (0.47–0.73)	Ref
	Increase	5	C = 2, I = 3	0.88 (0.47–1.64)	0.92	0.67 (0.33–1.36)	0.5	0.52 (0.32–0.85)	0.23	0.55 (0.33–0.94)	0.82
	Decrease	29	C = 13, I = 16	0.85 (0.67–1.09)	Ref	0.53 (0.38–0.73)	Ref	0.72 (0.61–0.85)	Ref	0.62 (0.50–0.76)	Ref
	Minimal increase (1–20%)	3	C = 1, I = 2	0.91 (0.30–2.26)	0.39	0.79 (0.32–1.90)	0.38	0.67 (0.37–1.24)	0.32	0.82 (0.44–1.54)	0.35
	Substantial increase (>20%)	2	C = 1, I = 1	0.83 (0.44–1.90)	0.53	0.54 (0.19–1.51)	0.98	0.37 (0.19–0.74)	0.36	0.34 (0.17–0.67)	0.11
Cis-β-carotene	Decrease	19	C = 9, I = 10	0.97 (0.75–1.03)	Ref	0.92 (0.48–0.99)	Ref	0.84 (0.69–1.02)	Ref	0.74 (0.61–0.88)	Ref
	Increase	15	C = 6, I = 9	0.76 (0.50–0.96)	0.29	0.79 (0.33–0.87)	0.52	0.73 (0.44–0.87)	0.39	0.68 (0.34–0.82)	0.84
	Decrease	19	C = 9, I = 10	0.97 (0.75–1.03)	Ref	0.90 (0.51–0.93)	Ref	0.84 (0.70–1.02)	Ref	0.75 (0.63–0.90)	Ref
	Minimal increase (1–20%)	7	C = 4, I = 3	0.67 (0.41–1.09)	0.16	0.68 (0.15–0.86)	0.65	0.79 (0.42–0.89)	0.56	0.71 (0.36–0.89)	0.28
	Substantial increase (>20%)	8	C = 2, I = 6	0.81 (0.46–1.07)	0.28	0.87 (0.53–0.98)	0.94	0.66 (0.39–0.78)	0.15	0.63 (0.29–0.86)	0.63
Trans-β-carotene	Decrease	19	C = 10, I = 9	1.08 (0.82–1.42)	Ref	0.72 (0.51–1.04)	Ref	0.88 (0.74–1.04)	Ref	0.84 (0.69–1.03)	Ref
	Increase	15	C = 5, I = 10	0.63 (0.47–0.86)	0.009	0.44 (0.32–0.60)	**0.01**	0.49 (0.41–0.60)	<0.0001	0.45 (0.38–0.54)	<**0.0001**
	Decrease	19	C = 10, I = 9	1.08 (0.82–1.42)	Ref	0.71 (0.51–0.99)	Ref	0.89 (0.75–1.04)	Ref	0.84 (0.69–1.03)	Ref
	Minimal increase (1–20%)	9	C = 5, I = 4	0.63 (0.43–0.92)	0.02	0.34 (0.23–0.49)	**0.0005**	0.55 (0.43–0.72)	0.002	0.46 (0.37–0.58)	<**0.0001**
	Substantial increase (>20%)	6	C = 0, I = 6	0.65 (0.40–1.08)	0.08	0.67 (0.42–1.06)	0.85	0.43 (0.32–0.58)	<0.0001	0.44 (0.34–0.57)	<**0.0001**
α-Cryptoxanthin	Decrease	10	C = 6, I = 4	1.00 (0.68–1.48)	Ref	0.73 (0.44–1.20)	Ref	0.76 (0.56–1.02)	Ref	0.90 (0.64–1.27)	Ref
	Increase	24	C = 9, I = 15	0.79 (0.60–1.04)	0.33	0.51 (0.38–0.69)	0.16	0.67 (0.55–0.81)	0.48	0.77 (0.46–0.67)	0.39
	Decrease	10	C = 6, I = 4	1.01 (0.68–1.48)	Ref	0.73 (0.45–1.18)	Ref	0.76 (0.56–1.02)	Ref	0.90 (0.65–1.26)	Ref
	Minimal increase (1–20%)	5	C = 2, I = 3	0.64 (0.37–1.10)	0.18	0.37 (0.23–0.61)	**0.03**	0.66 (0.45–0.96)	0.56	0.69 (0.48–0.92)	0.43
	Substantial increase (>20%)	19	C = 7, I = 12	0.84 (0.62–1.15)	0.49	0.60 (0.42–0.85)	0.45	0.67 (0.53–0.84)	0.51	0.64 (0.41–0.64)	0.18
β-Cryptoxanthin	Decrease	18	C = 9, I = 9	0.85 (0.63–1.16)	Ref	0.62 (0.43–0.89)	Ref	0.62 (0.50–0.79)	ref	0.66 (0.52–0.84)	Ref
	Increase	16	C = 6, I = 10	0.86 (0.61–1.20)	0.97	0.47 (0.32–0.67)	0.18	0.77 (0.61–0.97)	0.21	0.49 (0.37–0.65)	0.07
	Decrease	18	C = 9, I = 9	0.84 (0.62–1.14)	Ref	0.62 (0.43–0.89)	Ref	0.61 (0.49–0.76)	Ref	0.67 (0.53–0.83)	Ref
	Minimal increase (1–20%)	7	C = 3, I = 4	1.00 (0.61–1.64)	0.57	0.45 (0.26–0.79)	0.29	1.01 (0.74–1.38)	0.21	0.70 (0.47–1.04)	0.82
	Substantial increase (>20%)	9	C = 3, I = 6	0.77 (0.50–1.18)	0.71	0.47 (0.31–0.72)	0.25	0.63 (0.48–0.82)	0.89	0.44 (0.33–0.58)	**0.009**

Lutein	Decrease	15	C = 8, I = 7	0.81 (0.59–1.12)	Ref	0.47 (0.32–0.69)	Ref	0.76 (0.60–0.96)	Ref	0.60 (0.46–0.80)	Ref
	Increase	19	C = 7, I = 12	0.90 (0.66–1.24)	0.65	0.59 (0.42–0.83)	0.29	0.63 (0.51–0.79)	0.27	0.68 (0.45–0.73)	0.74
	Decrease	15	C = 8, I = 7	0.82 (0.60–1.12)	Ref	0.47 (0.32–0.69)	Ref	0.76 (0.61–0.96)	Ref	0.61 (0.45–0.81)	Ref
	Minimal increase (1–20%)	6	C = 4, I = 2	0.65 (0.47–2.31)	0.22	0.64 (0.35–1.18)	0.37	0.78 (0.48–1.25)	0.95	0.75 (0.35–0.98)	0.75
	Substantial increase (>20%)	13	C = 3, I = 10	0.77 (0.54–1.10)	0.8	0.58 (0.40–0.83)	0.33	0.60 (0.47–0.77)	0.16	0.63 (0.44–0.86)	0.77
Zeaxanthin	Decrease	22	C = 8, I = 14	0.82 (0.62–1.08)	Ref	0.48 (0.35–0.67)	Ref	0.61 (0.50–0.74)	Ref	0.57 (0.45–0.70)	Ref
	Increase	12	C = 7, I = 5	0.94 (0.64–1.37)	0.55	0.53 (0.46–0.99)	0.1	0.65 (0.49–1.09)	0.33	0.63 (0.48–0.89)	0.29
	Decrease	22	C = 8, I = 14	0.80 (0.61–1.05)	Ref	0.47 (0.35–0.63)	Ref	0.61 (0.50–0.74)	Ref	0.55 (0.44–0.68)	Ref
	Minimal increase (1–20%)	7	C = 5, I = 2	1.16 (0.71–1.87)	0.2	0.54 (0.40–1.00)	0.21	0.66 (0.58–1.29)	0.25	0.77 (0.54–1.16)	0.65
	Substantial increase (>20%)	5	C = 2, I = 3	0.71 (0.41–1.23)	0.68	0.48 (0.29–0.77)	0.97	0.64 (0.53–1.09)	0.29	0.54 (0.37–0.80)	0.86
Cis-lutein/zeaxanthin	Decrease	11	C = 8, I = 3	0.81 (0.54–1.22)	Ref	0.63 (0.39–1.00)		0.84 (0.63–1.11)	Ref	0.80 (0.60–1.07)	
	Increase	23	C = 7, I = 16	0.88 (0.66–1.16)	0.76	0.51 (0.38–0.71)	0.42	0.63 (0.52–0.77)	0.11	0.52 (0.42–0.64)	**0.003**
	Decrease	11	C = 8, I = 3	0.81 (0.54–1.22)	Ref	0.63 (0.39–1.01)	Ref	0.84 (0.64–1.11)	Ref	0.78 (0.60–1.02)	Ref
	Minimal increase (1–20%)	8	C = 3, I = 5	0.83 (0.53–1.29)	0.94	0.51 (0.33–0.79)	0.48	0.72 (0.52–0.98)	0.46	0.64 (0.49–0.83)	0.26
	Substantial increase (>20%)	15	C = 4, I = 11	0.90 (0.64–1.28)	0.68	0.52 (0.36–0.74)	0.45	0.59 (0.47–0.75)	0.06	0.47 (0.38–0.57)	**0.0004**
Cis-lycopene	Decrease	14	C = 7, I = 7	0.77 (0.53–1.11)	Ref	0.55 (0.37–0.81)	Ref	0.77 (0.59–1.00)	Ref	0.73 (0.57–0.94)	Ref
	Increase	19	C = 7, I = 12	0.93 (0.70–1.25)	0.4	0.54 (0.37–0.79)	0.97	0.68 (0.55–0.85)	0.49	0.67 (0.39–0.86)	0.19
	Decrease	14	C = 7, I=7	0.76 (0.54–1.07)	Ref	0.77 (0.44–1.36)	Ref	0.76 (0.59–0.99)	Ref	0.78 (0.65–0.98)	Ref
	Minimal increase (1-20%)	8	C = 3, I = 5	0.73 (0.61–1.11)	0.87	0.59 (0.40–0.87)	0.4	0.83 (0.60–1.14)	0.68	0.72 (0.56–1.01)	0.69
	Substantial increase (> 20%)	11	C = 4, I = 7	0.70 (0.49–1.00)	0.75	0.48 (0.33–0.71)	0.34	0.59 (0.45–0.78)	0.17	0.64 (0.34–0.82)	0.28
Trans-lycopene	Decrease	14	C = 8, I = 6	0.79 (0.55–1.11)	Ref	0.55 (0.37–0.83)	Ref	0.73 (0.57–0.93)	Ref	0.69 (0.53–0.91)	Ref
	Increase	20	C = 7, I = 13	0.91 (0.68–1.21)	0.52	0.53 (0.38–0.75)	0.89	0.67 (0.54–0.83)	0.59	0.53 (0.42–0.66)	0.07
	Decrease	14	C = 8, I = 6	0.80 (0.57–1.12)	Ref	0.56 (0.37–0.83)	Ref	0.73 (0.57–0.93)	Ref	0.69 (0.55–0.87)	Ref
	Minimal increase (1–20%)	7	C = 2, I = 5	1.23 (0.76–1.99)	0.14	0.64 (0.39–1.06)	0.61	0.76 (0.53–1.10)	0.85	0.73 (0.55–0.97)	0.72
	Substantial increase (>20%)	13	C = 5, I = 8	0.79 (0.56–1.10)	0.95	0.50 (0.34–0.72)	0.63	0.63 (0.49–0.81)	0.39	0.45 (0.36–0.56)	**0.002**
Antioxidant score[d]	Decrease	14	C = 8, I = 6	0.87 (0.55–0.35)	Ref	0.64 (0.40–1.02)	Ref	0.81 (0.59–1.10)	Ref	0.93 (0.72–1.21)	Ref
	Increase	19	C = 9, I = 10	0.85 (0.66–1.11)	0.96	0.51 (0.37–0.70)	0.37	0.65 (0.54–0.79)	0.26	0.50 (0.42–0.60)	<**0.0001**
	Decrease	14	C = 8, I = 6	0.85 (0.55–1.31)	Ref	0.65 (0.42–1.01)	Ref	0.81 (0.59–1.10)	Ref	0.92 (0.72–1.16)	Ref
	Minimal increase (1–20%)	8	C = 4, I = 4	1.07 (0.73–1.59)	0.43	0.73 (0.47–1.14)	0.69	0.64 (0.47–0.87)	0.31	0.62 (0.50–0.78)	0.01
	Substantial increase (>20%)	11	C = 5, I = 6	0.71 (0.50–1.00)	0.53	0.43 (0.30–0.60)	0.1	0.66 (0.52–0.84)	0.3	0.44 (0.37–0.53)	<**0.0001**

PSA, prostate-specific antigen; CI, confidence interval; C, control group; I, intervention group.

[*] *P* values from regression models comparing mean difference between decrease in tocopherol/carotenoid categories with an increase, minimal increase or substantial increase, respectively.

[a] Data are reported as least square means and confidence intervals.

[b] Adjusted for age, race, randomized group and baseline PSA level.

[c] Adjusted for age, race, education, marital status, employment status, smoking status, Gleason score, body mass index, total metabolic equivalent (MET) per week of physical activity, energy intake, randomized group and baseline PSA level.

[d] Antioxidant score; low : 45–80, high: 81–111.

In a study involving 71 men with biochemical recurrence who were randomized to intervention with supplemental lycopene alone (15 mg) or together with soy isoflavone capsules (40 mg) taken twice daily for 6 months, no decline in serum PSA level was observed in either group [51]. In that same study, however, the rate of PSA rise decreased in 95% of patients in the lycopene-only group and 67% of those in the lycopene plus soy isoflavones group [51]. In another study in which 36 men with biochemical recurrence of PrCA were given varying doses of lycopene (15, 30, 45, 60, 90 and 120 mg/day) for one year, no change in serum PSA was observed across all the six dose groups [52]. In a related study, Chen et al. [49] investigated the effects of lycopene on cancer progression among 32 patients with incident PrCA treated with tomato sauce-based diet containing 30 mg of lycopene per day for 3 weeks before their scheduled prostatectomy. The results showed significant reduction in serum PSA levels as well as declines in markers of oxidative DNA damage measured in leukocytes and prostate tissue, when comparing pre- and post-intervention measurements [49].

Ansari and Gupta [53] evaluated the effect of lycopene and orchiectomy versus lycopene alone in 54 patients with metastatic PrCA, and found significantly lower PSA levels in the lycopene-only group after 6 months of follow-up. Others have reported a decline in PSA velocity and prolonged PSA doubling time among men treated with supplemental lycopene [54]. Among studies conducted in disease-free men, one found an inverse association between serum α-carotene levels and percent free PSA level (OR = 0.49, 95% CI: 0.32–0.76), but not total PSA, and no inverse association was found for other carotenoids [55]. Another study found no association between tocopherol intake and serum PSA level or PSA velocity [56]. Systematic reviews of the literature suggest that lycopene intake may decrease serum PSA levels in men with benign prostatic hyperplasia and in men with PrCA [57,58]. The variability in these findings may be related to the source of the nutrients (e.g., supplement versus diet for lycopene) or the possibility that these nutrients may have varying effects according to the natural history of PrCA.

The results of the current study show that after controlling for baseline PSA values, certain plasma carotenoids and tocopherols as well as combined antioxidant score were associated with low mean PSA values at various timepoints. Because the intervention of the parent study encouraged increased intake of foods that are rich sources of carotenoids and tocopherols, it is conceivable that the plasma carotenoids and tocopherol showing significant associations may have served as surrogates for a pattern of food consumption, particularly fruits and vegetables, which contain other beneficial dietary factors. Of note, the parent study did not find a beneficial effect of the diet and lifestyle intervention on serum PSA level [15], although at 3 months, increases in fruit and vegetable intakes were similar between the intervention and control groups. Challenges associated with conducting an intervention trial of lifestyle modification, such as an insufficient contrast between the intervention and control groups due to treatment contamination or suboptimal compliance [59] may partially explain the finding from that analysis. The current findings merit further investigation and may be better understood by considering temporal relationship between plasma carotenoid and tocopherol levels, and change in PSA levels. Thus, larger studies with longer follow-up are warranted.

Limitations of the current study include the small sample size, which limits statistical power, short duration, and the lack of plasma carotenoid and tocopherol data at 6 months, which prohibited evaluation of temporal associations. Due to the exploratory nature of these analyses, adjustment for multiple comparisons was not attempted [60]. This may have increased the probability of chance findings. Because humans consume foods containing many nutrients, there also is the possibility that the study results may reflect interactions between nutrients, rather than the effect of a single nutrient per se [61]. Alternatively, some of the findings may be reflecting an overall healthy lifestyle that might confer favorable prognosis after PrCA recurrence [23]. Restricting the study to a subgroup of PrCA patients with strictly defined disease attributes precludes generalizability of the findings to the larger population of men with PrCA. However, because the study participants had already undergone radical prostatectomy or radiation, or both, for the treatment of organ-confined disease, biochemical recurrence of PrCA as defined in this study most likely reflects progressive disease, rather than residual normal tissue spared during prostatectomy or left from radiation. Other strengths of the study include the use of biomarkers of nutrient intake, which are free of recall bias; an error that is common in dietary assessment using food frequency questionnaire [62]. To our knowledge, this is the first study to examine biomarkers of carotenoids and tocopherols in relation to PSA levels among men with biochemical recurrence of PrCA. Several potential confounders including BMI, smoking, physical activity, tumor grade and race were controlled for in the analysis. The findings from this study add to the limited data on potentially beneficial dietary factors for the management of biochemically recurrent PrCA.

5. Conclusion

This study offers preliminary evidence that higher plasma levels of α-tocopherol, β-cryptoxanthin, *trans*-β-carotene, cis-lutein/zeaxanthin, and all-*trans*-lycopene are associated with lower PSA levels among men with biochemically defined PrCA recurrence. A higher antioxidant score, used as a measure of total antioxidant exposure, also was associated with lower PSA levels at various timepoints. These findings suggest that increased intake of these micronutrients, which are found in many fruits and vegetables, may slow the progression of PSA among men with biochemical recurrence of PrCA. Considering the small sample size and short duration, additional research in larger cohorts with longer follow-up is warranted.

6. Authorship contribution

All authors made substantial contribution to the conception, design, acquisition of data or analysis. The lead author was responsible for drafting of the article, and all co-authors were involved in revising it critically for important intellectual content and approved the final revised version for submission to *Cancer Epidemiology*.

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8. Disclosure statement

The authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2015.06.008.

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