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Polymorphisms in hOGG1 and XRCC1 and Risk of Prostate Cancer: Effects Modified by Plasma Antioxidants

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Abstract

Background—Accumulating evidence indicates that oxidative stress plays a role in prostate carcinogenesis. This study thus investigated whether polymorphisms in genes involved in the repair of oxidative DNA damage modulate and/or interact with antioxidants to influence prostate cancer risk in a population-based case-control study in Central Arkansas.

Methods—Cases (n=193) were men, ages 40–80 years, diagnosed with prostate cancer in three major hospitals in 1998–2003, and controls (n=197) were matched to cases by age, race, and county of residence.

Results—After adjustment for confounders, subjects who were heterozygous or homozygous for the variant allele of the *hOGG1* Ser326Cys polymorphism appeared to experience a lower risk of prostate cancer than those who were homozygous for the wild-type allele [OR (95%CI): 0.72 (0.46–1.10)]. Conversely, a significant increased risk was observed for individuals who carried one or two copies of the variant allele of the *XRCC1* Arg399Gln polymorphism, compared with those who only harbored the wild-type allele [OR (95%CI): 1.56 (1.01–2.45)]. The above associations were generally more pronounced among subjects with low plasma carotenoids or α-tocopherol (<median). Among subjects who had low plasma levels of β-cryptoxanthin (<73 μg/l), possession of at least one copy of the *XRCC1* 399Gln allele conferred an over two-fold elevated risk [OR (95%CI): 2.64 (1.40–5.07)].

Conclusions—Our study offers preliminary but intriguing data suggesting that variability in the capacity of repairing oxidative DNA damage influences susceptibility to prostate cancer and that these effects are modified by antioxidants.

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Keywords

Polymorphism; DNA repair gene; antioxidants; oxidative stress; prostate cancer

INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide.[1] Although the etiology of this disease remains largely unclear, several lines of evidence suggest that oxidative stress plays a role in prostate carcinogenesis. First, the expression of major antioxidant enzymes (*e.g.*, Mn-superoxide dismutase, catalase, and glutathione peroxidase) was lower in prostate tumors than in adjacent healthy tissues.[2,3] Two prostate cancer cell lines are defective in repairing oxidative DNA damage. Furthermore, some epidemiological studies have showed that antioxidants reduce prostate cancer risk.[4] Inflammation enhances oxidative stress because inflammatory cells release oxygen- and nitrogen-reactive species under inflammation conditions.[5] Inflammation is common in prostate biopsies and surgical specimens.[5] In addition, prostatitis is associated with an increased risk of prostate cancer.[6]

Carotenoids in the human diet are primarily derived from yellow, orange, and red vegetables and fruits.[7,8] Common carotenoids include α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, zeaxanthin, and α-tocopherol.[7] These natural pigments possess antioxidant properties. A habitual low intake of carotenoids may induce oxidative stress and thus increase prostate cancer risk.

Sustained oxidative stress induces oxidative DNA damage, a major form of which is 8-hydroxy-2-deoxyguanine (8-OH-dG).[9,10] 8-OH-dG is highly mutagenic and, if not repaired on DNA replication, can cause in GC to TA transversions in several oncogenes and tumor suppressor genes and in turn lead to carcinogenesis.[9,10] Oxidative DNA damage is repaired by the base-excision repair pathway.[11] Two major players in this pathway are human oxoguanine glycosylase 1 (hOGG1) and X-ray repair cross-complementing group 1 (XRCC1).[11] Abundantly expressed in the prostate, hOGG1 catalyzes the excision and removal of 8-OH-dG.[9] A C/G polymorphism in the exon 6 of the *hOGG1* results in an amino acid substitution from serine to cysteine in codon 326 (Ser326Cys) (rs1052133).[9] After a damaged base is removed by hOGG1, XRCC1 acts as a scaffold to bring together a complex of DNA repair enzymes (*e.g.*, polymerase-α, DNA ligase III) in the subsequent restoration of the site.[11] A G/A polymorphism in the exon 10 of the *XRCC1* gene has been identified, leading to a substitution of glutamine for arginine in codon 399 (Arg399Gln) (rs25487).[12] Some experimental studies suggested that the two single nucleotide polymorphisms (SNPs) described above have functional impact.[13–15]

It is reasonable to hypothesize that these genetic variants may influence the occurrence of prostate cancer. It can be further hypothesized that persons who have a reduced inherited ability to repair oxidatively damaged DNA bases are more susceptible to low dietary intake of antioxidants and are thus more likely to develop prostate cancer. To date, several studies [9,16–18] have examined the effect of these two SNPs, yielding mixed results, and none of these studies have evaluated interactions between these variants and plasma antioxidants in relation to prostate cancer. Therefore, the present study aimed to investigate these questions in a study of Caucasian and African-American men in Arkansas.

MATERIALS AND METHODS

Study Population

A population-based case-control study was conducted from 1998 to 2003 in Arkansas to explore the role of diet and metabolic polymorphisms in prostate cancer etiology.[8,19] A total of 618 cases and 403 controls were enrolled in the study. The present study made a preliminary analysis of 193 cases and 197 controls that were randomly selected from all the subjects recruited in the parent study.

The design and methodology of the case-control study of prostate cancer in Arkansas have been described in detail elsewhere.8,[19] Briefly, patients with primary, incident, histologically-confirmed prostate cancer, ages 40–80 years, were recruited within 3 months of diagnosis. Cases were ascertained from three major hospitals in central Arkansas:the University Hospital of the University of Arkansas for Medical Sciences in Little Rock, the Central Arkansas Veterans Health Care System (CAVHCS) in Little Rock, and the Jefferson Regional Medical Center in Pine Bluff. Controls were randomly selected from the population that gave rise to cases. Specifically, controls were identified from the Arkansas State Drivers' License records, Centers for Medicare and Medicaid records, and a mass-mailing database, which accounted for 19%, 13%, and 68% of the controls recruited, respectively. The mass-mailing database contained contact information for approximately 89% of Arkansas residents. Controls were frequency matched to cases by age (±5 years), race, and county of residence. The response rate was 69% for cases and 56% for controls. Subjects were excluded from the study if they had a history of cancer (other than nonmelanoma skin cancer), uncontrolled cardiovascular diseases, hepatic dysfunction, or renal dysfunction.[19]

The study protocol was approved by the appropriate institutional review boards, and informed consent was obtained from all subjects. During the interview at the home of participants or any other place of their preference, subjects were asked to respond to a questionnaire eliciting information on demographics, family cancer history, occupational history, physical activity, use of tobacco and alcohol, and diet.

Laboratory Measurement

A 30-ml blood sample was drawn in tubes containing citric acid at the end of the interview. Blood samples were packed on ice and delivered to the CAVHCS hospital and processed within 2 hours of collection. Lymphocytes were isolated from blood for DNA extraction. Separated plasma specimens were aliquoted into 0.5 ml-straws of a sealed capillary tube straw system (CryoBioSystems, Paris, France) and stored in liquid nitrogen tanks at −196°C until analysis.

Genotyping—DNA was extracted from lymphocytes using a commercial kit (Qiagen Inc., Valencia, CA). Polymorphisms of interest were genotyped at BioServe Biotechnologies Ltd. (Beltsville, MD) by high-throughput chip-based matrix-assisted laser desorption time-of-flight mass spectrometry (Sequenom, Inc., San Diego, CA).[19] All laboratory personnel were blinded to case-control status, and a 10% of the tested samples were randomly replicated and were 100% concordant.

Plasma Carotenoids—Plasma concentrations of α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin, and α-tocopherol were measured using high-performance liquid chromatography at the Biomarker Analysis and Lipoprotein Research Laboratories of Harvard School of Public Health. The method, internal and external quality control measures, and between-run and within-run coefficients of variation for the determination of these antioxidants have been described in detail elsewhere.[8,20] Because lutein and zeaxanthin co-elute on the chromatogram, the two were grouped and provided as lutein/zeaxanthin.

Statistical Analysis

Prior to data analysis, genotyping data were examined for possible genotyping errors by testing deviation from the Hardy-Weinberg equilibrium among controls. Odds ratios (OR) and 95% confidence intervals (CI) for prostate cancer risk in relation to genotypes of the selected polymorphisms were estimated by unconditional logistic regression analysis. In the regression models, individuals who were homozygous for the wild-type allele were treated as the reference group to calculate ORs for those who were heterozygous or homozygous for the variant allele. Heterozygous and homozygous variant genotypes were combined in all analyses due to the relatively small sample size of the present study. To evaluate the independent effects of each of the polymorphisms of interest on prostate cancer risk, the following variables were adjusted in the multivariate models: age, race, body mass index (weight in kg/height in m^2), education (three levels), and smoking status (never and ever).

To investigate whether plasma levels of carotenoids and α-tocopherol modified the effects of the genetic variants examined on prostate cancer risk, an interaction term between each of the selected polymorphisms (divided into two genotype groups) with each of the measured antioxidants (classified into < and ≥ median) was introduced into the above multivariable models. The statistical significance of each of the interaction terms constructed was evaluated by the likelihood ratio test. Given the biological plausibility of interactions between base excision repair genes and antioxidants, stratified analyses by low and high plasma concentrations of the antioxidants examined (defined as < and ≥ median) were performed for the associations between selected polymorphisms and prostate cancer risk regardless of whether the multiplicative interaction terms examined in the full models were statistically significant. All statistical analyses were performed with the SAS software (version 9.1; SAS Institute, Inc., Cary, NC). A p value of < 0.05 (two-sided) was considered statistically significant.

RESULTS

Table 1 shows that cases were somewhat older, leaner, less educated, and more likely to smoke than controls. Table 2 displays the risk of prostate cancer in relation to the genotypes of polymorphisms of interest. The observed genotype frequencies of the two polymorphisms examined among controls were statistically consistent with the Hardy-Weinberg equilibrium. After adjustment for age, race, body mass index, education, and smoking status, subjects who were heterozygous or homozygous for the variant allele (326Cys) of *hOGG1* appeared to experience a lower risk of prostate cancer than those who were homozygous for the wild-type allele (326Ser) [OR (95% CI): 0.72 (0.46–1.10)]. Conversely, a statistically significant increased risk was observed for individuals who carried one or two copies of the variant allele (399Gln) of *XRCC1*, compared with those who only harbored the wild-type allele (399Arg) [OR (95% CI): 1.56 (1.01–2.45)]. A significant gene-gene interaction was detected [OR (95% CI): 2.03 (1.12–3.67) (Ser/Ser of hOGG1 and Arg/Gln and Gln/Gln of XRCC1 vs. Ser/Cys and Cys/Cys of hOGG1 and Arg/Arg of XRCC1)] (data not shown).

The results of stratified analysis of the above associations by plasma levels of antioxidants (< and ≥ median) were shown in Table 3 for the *hOGG1* Ser326Cys polymorphism and in Table 4 for the *XRCC1* Arg399Gln polymorphism. The protective effect of the *hOGG1* 326Cys allele on prostate cancer was more pronounced for subjects with the low plasma levels of all measured carotenoids, except lutein/zeaxanthin. ORs for the low-level groups attained statistical significance for β-cryptoxanthin, lycopene, and α-carotene. A 62% reduction in risk was found for individuals who had one or two copies of the 326Cys allele and low plasma levels of α-tocopherol [OR (95% CI): 0.38 (0.20–0.73)], but the favorable effect of this allele was absent for those with high levels of α-tocopherol. Similarly, the promoting effect of the *XRCC1* 399Gln allele was more striking among subjects who had low levels of all the antioxidants

considered. ORs ranged from 1.82 (α-tocopherol) to 2.64 (β-cryptoxanthin) for heterozygotes or homozygotes of the 399 Gln allele with low levels of the six antioxidants examined but were statistically significant only for lutein/zeaxanthin, β-cryptoxanthin, and lycopene.

We also evaluated whether the effects of the genetic variants under study on prostate cancer risk varied by race and Gleason score. Our stratified analysis revealed that the inverse association between the Cys allele of the *hOGG1* Ser326Cys polymorphism and the risk of prostate cancer was stronger among men who were African-American [OR (95% CI): 0.49 (0.25–0.94)] or were diagnosed with a less differentiated tumor (Gleason score ≥7) [OR (95% CI): 0.55 (0.29–1.01)] (data not shown). No effect modification of race and Gleason score was found for the *XRCC1* Arg399Gln polymorphism in relation to prostate cancer. We did not examine interactions between SNPs, plasma antioxidants, and race or Gleason score because of insufficient statistical power for such a three-way interaction analysis.

DISCUSSION

In this study, we demonstrated that the variant allele of the *XRCC1* Arg399Gln polymorphism was associated with an increased risk of prostate cancer, whereas the variant allele of the *hOGG1* Ser326Cys polymorphism appeared to reduce risk. Furthermore, the effects of these mutations were generally more remarkable among subjects with low plasma concentrations of antioxidants.

Although experimental studies suggest that the genetic polymorphisms examined in this study have functional significance and thus modulate prostate cancer risk, several epidemiologic studies[9,10,12,16–18,21,22] have investigated these associations. The potential protective effect of the Cys allele of the *hOGG1* Ser326Cys polymorphism observed in our study was also found in a study in Baltimore, Maryland9 and in a study in Toronto, Canada.[16] It should be pointed out that the variant allele (Cys) was used as the reference in the logistic regression analysis in the Baltimore study.[9] However, an opposite result was reported from a small hospital-based case-control study in Tampa, Florida, which showed that the Cys allele was associated with a statistically significant elevated risk of prostate cancer.10 To date, six studies12,17,[18,21–23] have examined the association between *XRCC1* Arg399Gln polymorphism and prostate cancer risk and the findings obtained were inconsistent. The two of these studies17,[22] revealed a statistically significant increased risk associated with the mutant allele (Gln), which was concordant with the results of the present study. This deleterious effect, however, was not replicated in the other four studies.12,18,21,23 The discrepant findings from previous case-control studies may be partly due to their differences in study design (population-based vs. hospital-based), allele frequencies of the populations studied, and adjustment for confounders.

It is necessary to investigate the phenotypic significance of genetic polymorphisms for understanding the biological plausibility for the associations between these molecular variants and cancer of interest. Several studies have examined the functionality of the two SNPs (*hOGG1* Ser326Cys and *XRCC1* Arg399Gln) considered in the present study. In 1998, Kohno *et al*.[13] demonstrated that the 326Cys protein was approximately 7-fold less capable of repairing 8-OH-dG than the 326Ser protein in an *in vitroE. coli* complementation activity assay. A decreased ability to repair oxidative DNA damage makes one more predisposed to prostate cancer. It thus appears that this functional study does not support our risk estimates for this polymorphism. However, two subsequent functional studies[24,25] indicate that it is still inconclusive whether this sequence variant really alters hOGG1 activity. One study [24] found no significant difference in the activity of hOGG1 to repair 8-OH-dG formed from exposure of DNA to γ-irradiation between two glutathione *S*-transferase (GST)-hOGG1 fusion proteins (*i.e.,* GST-hOGG1-326Ser and GST-hOGG1-326Cys). Furthermore, another study[25] revealed that hOGG1 activity in cultured human lymphocytes did not depend on this molecular variant.

Our observation that the variant allele of the *XRCC1* Arg399Gln polymorphism significantly increased prostate cancer risk is consistent with the results of functional studies.[14,15] This polymorphism involves an amino acid change at an evolutionarily conserved region and thus could alter the function of *XRCC1*. DNA adducts, sister chromatin exchange, and somatic glycophorin A are commonly used as biomarkers of DNA damage.[14,15] Experimental studies have shown that the 399 Gln allele was significantly associated with higher levels of aflatoxin B1-DNA adducts in placental tissue, polyphenol DNA adducts in mononuclear cells, sister chromatin exchange in lymphocytes, and somatic glycophorin A mutation in erythrocytes.[14, 15] These studies indicate that subjects who carry the variant allele of the *XRCC1* Arg399Gln polymorphism have a reduced capacity of repairing DNA damage and, in turn, an enhanced predisposition to prostate cancer.

Although it is biologically plausible that DNA-repairing genes interact with antioxidants to modulate prostate cancer risk, only one small study (77 cases and 174 controls)[26] has investigated this important question. A reduced risk associated with high dietary intake of lycopene was only observed in subjects with the Arg/Arg genotype of the *XRCC1* Arg399Gln polymorphism.[26]*hOGG1* was not considered in that study. Our study showed that the protective effect of the *hOGG1* 326Cys allele and the promoting effect of the *XRCC1* 399Gln were generally more evident or only existed in individuals with low levels of plasma carotenoids or vitamin E. Although the exact biological mechanisms underlying these interactions are not clear, our findings suggest that the two selected variants in *hOGG1* and *XRCC1* exert stronger influence on prostate cancer risk when oxidative stress challenge is present. Many, but not all, epidemiologic studies have shown that antioxidants protect against prostate cancer.[4] The discrepant results on the relation between antioxidants and prostate cancer may be partly ascribed to the failure to evaluate the interactions of antioxidants with genes involved in the repair of oxidative DNA damage in the majority of previous studies.

We found that a reduced risk of prostate cancer associated with the variant allele of the *hOGG1* Ser326Cys polymorphism was greater in African Americans or patients with a less differentiated (or more aggressive) tumor (Gleason score ≥7). African Americans are more likely to develop a more aggressive prostate tumor than Caucasians.[27] It merits further investigation whether racial difference in the protective effect of this genetic variant is real or is confounded by some unmeasured risk factors, for example, intake of carcinogenic heterocyclic amines from meats cooked at high temperature, a common cooking practice in Arkansas.[28,29]

The present study has some advantages. It was among the first to investigate the interactions of variants in genes repairing oxidative DNA damage with antioxidants in relation to prostate cancer. We measured plasma carotenoids and vitamin E, which was free from recall bias, an error often present in dietary assessment using food frequency questionnaire.[7] Roughly equal numbers of African and Caucasian Americans were drawn from the parent study, which allowed us to examine the effects of the selected genetic polymorphisms by race. As the etiology of slow- and fast-growing prostate tumors may be different,[30] we also evaluated the effects of genetic variants by Gleason score and revealed that the potential beneficial effect of the mutant allele of the selected polymorphism in *hOGG1* on prostate cancer was more prominent in African Americans or patients with more aggressive tumor.

Our study is subject to several weaknesses. Selection bias may be a concern when controls are recruited from the Medicare and Medicaid recipients because they may differ from the general population in some socioeconomic factors. In this study, only 13% of the controls were enrolled from this source. Genotyping error should be considered in any genetic association studies. However, consistency with the Hardy-Weinberg equilibrium among control subjects and concordance of the genotyping of 10% replicated samples randomly selected from all tested

samples suggest that genotyping error, if any, would be likely small in the present study. It is possible that cases might have changed their dietary habits after they were diagnosed or treated with prostate cancer. Therefore, plasma levels of carotenoids and α-tocopherol might not well reflect their usual intake of these nutrients in these persons. Although our plasma specimens were stored at −196°C, plasma antioxidants were measured 3–8 years after blood collection. Changes in concentrations of these biomarkers during this period should not be substantial because one study[31] showed that serum levels of β-carotene, retinol, and α-tocopherol were stable for at least 15 years of storage at −70°C. One-time measurement of plasma levels of corotenoids and α-tocopherol might have introduced a misclassification error due to within-person variability of these chemical compounds, which tended to result in attenuated risk estimates. Polymorphisms in other DNA repair genes (*e.g., APE1* Asp148Glu, *XPD* Lys751Gln) have been linked to prostate cancer[21,22] but were not considered in the present study. Another weakness of the present study is its relatively small sample size. Hence, it cannot be entirely ruled out that some of our findings, especially those from stratified analysis, might be obtained by chance alone.

In summary, the present study offers preliminary but intriguing data suggesting that sequence variants in two major genes involved in the repair of oxidative DNA damage modulate prostate cancer risk and that these effects are generally more pronounced in subjects with low plasma levels of antioxidants. Although our findings need to be replicated in large epidemiologic studies, they underscore the importance and necessity of investigating gene-nutrient interactions in the study of prostate cancer etiology and contribute to an improved understanding of the causes, detection, and prevention of this malignancy.

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Table 1

Characteristics of cases and controls in a population-based case-control study of prostate cancer in Arkansas, 1998–2003

Characteristic	Cases (n=193)	Controls (n=197)
Age (years)[a]	64.4 (9.0)	59.4 (10.5)
Race		
Caucasian	53.4%	48.2%
African-American	46.6%	51.8%
BMI (kg/m^2)[a]	28.1 (4.6)	29.0 (5.7)
Education		
Some high school or lower	33.7%	18.8%
High school graduate or some college	48.7%	55.3%
College graduate or higher	17.6%	25.9%
Smoking		
Never smokers	31.6%	35.0%
Ever smokers	68.4%	65.0%
Gleason score		
< 7	61.7%	
≥ 7	38.3%	

[a] Values given are mean (SD).

Table 2

Risk of prostate cancer in relation to SNPs in genes involved in oxidative DNA repair in a population-based case-control study of prostate cancer in Arkansas, 1998–2003

	Cases (n=193)		Controls (n=197)			
Genotype	**Number**	**%**	**Number**	**%**	**OR (95% CI)[a]**	***P* value**
hOGG1 (Ser326Cys)						
Ser/Ser	126	66.0	118	60.2	1.00[b]	
Ser/Cys or Cys/Cys	65	34.0	78	39.8	0.72 (0.46, 1.10)	0.13
Allele frequency of *Cys*		18.1		21.7		
XRCC1 (Arg399Gln)						
Arg/Arg	102	53.7	127	65.1	1.00[b]	
Arg/Gln or Gln/Gln	88	46.3	68	34.9	1.56 (1.01, 2.45)	0.049
Allele frequency of *Gln*		26.8		18.2		

Ser, Serine; Cys, Cytosine; Arg, Arginine; Gln, Glutamine.

[a] Adjusted for age, race, body mass index, education, and smoking status.

[b] Reference.

Table 3

Risk of prostate cancer in relation to the *hOGG1* Ser326Cys polymorphism, stratified by plasma levels of antioxidants, in a population-based case-control study of prostate cancer in Arkansas, 1998–2003

	Ser/Ser		Ser/Cys or Cys/Cys			
Antioxidant[a]	**Cases/Controls**	**OR[b]**	**Cases/Controls**	**OR (95% CI)[c]**	***P* value**	$P_{interaction}$
Lutein/zeaxanthin						
Low	73/60	1.00	36/38	0.73 (0.40, 1.33)	0.30	
High	53/58	1.00	29/40	0.70 (0.37, 1.33)	0.28	0.88
β-cryptoxanthin						
Low	74/53	1.00	38/45	0.50 (0.27, 0.92)	0.027	
High	52/65	1.00	27/33	0.93 (0.48, 1.78)	0.82	0.19
Lycopene						
Low	70/52	1.00	39/47	0.46 (0.24, 0.85)	0.014	
High	56/66	1.00	26/31	0.96 (0.49, 1.84)	0.89	0.11
α-carotene						
Low	66/58	1.00	32/40	0.52 (0.27, 0.99)	0.052	
High	60/60	1.00	33/38	0.87 (0.47, 1.59)	0.65	0.38
β-carotene						
Low	54/57	1.00	25/40	0.58 (0.30, 1.16)	0.12	
High	72/61	1.00	40/38	0.85 (0.47, 1.52)	0.58	0.48
α-tocopherol						
Low	65/50	1.00	27/47	0.38 (0.20, 0.73)	0.004	
High	61/68	1.00	38/31	1.26 (0.68, 2.34)	0.46	0.01

Ser, Serine; Cys, Cytosine.

[a] Low: <median; high: ≥median. Median plasma levels of lutein/zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, β-carotene, and α-tocopherol (μg/l) were 155, 73, 275, 19, 99, and 9202, respectively.

[b] Reference.

[c] Adjusted for age, race, body mass index, education, and smoking status.

Table 4

Risk of prostate cancer in relation to the *XRCC1* Arg399Gln polymorphism, stratified by plasma levels of antioxidants, in a population-based case-control study of prostate cancer in Arkansas, 1998–2003

	Arg/Arg		Arg/Gln or Gln/Gln			
Antioxidant[a]	**Cases/Controls**	**OR[b]**	**Cases/Controls**	**OR (95% CI)[c]**	***P* value**	$P_{interaction}$
Lutein/zeaxanthin						
Low	54/66	1.00	55/31	2.15 (1.17, 4.01)	0.015	
High	48/61	1.00	33/37	1.17 (0.60, 2.29)	0.66	0.14
β-cryptoxanthin						
Low	54/70	1.00	58/27	2.64 (1.40, 5.07)	0.003	
High	48/57	1.00	30/41	0.92 (0.48, 1.78)	0.81	0.03
Lycopene						
Low	58/69	1.00	50/29	2.05 (1.07, 3.98)	0.032	
High	44/58	1.00	38/39	1.24 (0.66, 2.34)	0.50	0.41
α-carotene						
Low	53/68	1.00	45/29	1.87 (0.97, 3.67)	0.063	
High	49/59	1.00	43/39	1.33 (0.72, 2.47)	0.36	0.56
β-carotene						
Low	42/69	1.00	37/28	1.92 (0.96, 3.88)	0.066	
High	60/58	1.00	51/40	1.28 (0.71, 2.31)	0.41	0.52
α-tocopherol						
Low	50/68	1.00	42/29	1.82 (0.95, 3.54)	0.072	
High	52/59	1.00	46/39	1.40 (0.76, 2.60)	0.28	0.40

Arg, Arginine; Gln, Glutamine.

[a] Low: <median; high: ≥median. Median plasma levels of lutein/zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, β-carotene, and α-tocopherol (μg/l) were 155, 73, 275, 19, 99, and 9202, respectively.

[b] Reference.

[c] Adjusted for age, race, body mass index, education, and smoking status.