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Dietary, but Not Supplemental, Intakes of Carotenoids and Vitamin C Are Associated with Decreased Odds of Lower Urinary Tract Symptoms in Men[1,2]

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Abstract

Lower urinary tract symptoms (LUTS) in men may be related to micronutrients involved in prevention of oxidative damage or cell growth and differentiation. We tested the hypothesis that carotenoid, vitamin A, and vitamin C intake were inversely associated with total LUTS, voiding, and storage symptoms. We conducted a cross-sectional multivariate analysis of 1466 men aged 30–79 y in the Boston Area Community Health survey (2002–2005), a population-based random sample survey. Data were collected by in-person interview and validated FFQ. Moderate-to-severe LUTS were defined using the American Urological Symptom Index and analyzed using multivariate logistic regression. Overall, men consuming greater dietary lycopene, β-carotene, total carotenoid, or vitamin A had ~40–50% decreased odds of LUTS compared with the lowest intake quartiles (e.g. β-carotene and storage symptoms, OR = 0.56, 95% CI = 0.39, 0.82; P-trend = 0.02). Interactions were observed between dietary iron and vitamin C or β-cryptoxanthin, whereby inverse associations with LUTS, particularly voiding symptoms, occurred only among men with moderate-to-high iron intake (P-interaction = 0.001). High-dose supplemental and total vitamin C were positively associated with LUTS (e.g. supplemental vitamin C $\geq$ 250 mg/d, OR = 1.83, 95% CI = 1.21, 2.77; P-trend = 0.02). An interaction between β-carotene and smoking status (P-interaction = 0.004) indicated greater odds of LUTS with higher β-carotene intake among current smokers. Results suggest that modifying consumption of carotenoids and vitamin C may influence LUTS in men. J. Nutr. 141: 267–273, 2011.

Introduction

Lower urinary tract symptoms (LUTS)[7] are a common problem in men and are associated with both decreased quality of life and high economic costs (1–3). LUTS include problems with voiding (e.g. intermittency, weak urinary stream) and storage (e.g. urgency, frequency), both of which are often symptoms of benign prostatic hyperplasia (BPH), particularly among older men. Pathophysiological mechanisms leading to LUTS may include inflammation, oxidative damage, and sympathetic nervous system tone (4–6). Accumulating evidence suggests that modifiable lifestyle factors, including physical activity, obesity, and diet, may influence these mechanisms for the development of LUTS (3,7–10).

An important role for diet in the development of LUTS is plausible, and epidemiological studies have found associations between LUTS and dietary macronutrients such as protein and fat (11–13). Certain micronutrients, particularly carotenoids and vitamin C, could influence LUTS by their abilities to prevent cellular damage by inhibiting oxidation and also influence cell growth and differentiation (14,15). However, findings that high-dose antioxidant supplements are associated with adverse health outcomes indicate that their role in disease prevention and treatment is complex (16–19). In addition, high intake of vitamin C alters the composition of urine and may affect the urothelium, thereby potentially contributing fairly immediately to the development of urinary symptoms such as urgency (15,20,21).

Limited evidence exists regarding vitamins C and A and carotenoids in their association with LUTS. Previous case-control studies were small and focused on older men and surgically

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[7] Abbreviations used: AUASI, American Urological Association Symptom Index; BACH, Boston Area Community Health; BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptom.

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treated BPH, generally finding inverse associations with consumption of fruits and vegetables rich in β-carotene, lutein, or vitamin C (22–24). A cross-sectional study of older men from the NHANES-III found lower serum concentrations of lycopene in men with LUTS compared with controls, but no associations were observed for other carotenoids (25). Two prospective epidemiological studies of micronutrients and BPH have been conducted. Among men in the placebo arm of the Prostate Cancer Prevention Trial, there was a suggestive inverse association between dietary lycopene intake and incident BPH, but no significant associations with carotenoids or vitamin C (11). The Health Professionals' Follow-up Study found inverse associations between dietary sources of β-carotene, lutein/zeaxanthin, or vitamin C and BPH, but not vitamin C from supplements (26). Both study populations consisted primarily of white men, sampled from specific populations rather than general community-based probability samples, and studied for clinical BPH. Thus, whether their findings hold true for moderate-to-severe LUTS that is nonspecific to BPH among broader age and racial/ethnic populations remains uncertain. Furthermore, prior studies have not examined dietary associations by symptom subtype, which could help elucidate underlying mechanisms. Our objective was to test the hypothesis that inverse associations exist between intakes of carotenoids, vitamin A, and vitamin C and moderate-to-severe LUTS among a diverse population-based sample of men.

Materials and Methods

The Boston Area Community Health (BACH) survey used a multistage random sample design to recruit 2301 men aged 30–79 y of 3 racial/ethnic groups from Boston, MA from 2002 to 2005. Details on BACH's methods have been previously published (27). Information about urologic symptoms, comorbidities, lifestyle, and anthropometrics was obtained by in-person interviews. Participants completed the English or Spanish language SWAN 01/02 version of the 1995 Block FFQ, which was designed for use in multiethnic populations to capture usual diet over the past year and has been validated in various settings with moderate-to-high validity and reliability (28–31). Participants provided written informed consent. The study was approved by the New England Research Institutes' Institutional Review Board.

Analytic sample. The final sample size for this analysis was 1466 men. Men were excluded if they did not complete the FFQ (n = 430), reported an implausible daily energy intake (outside 600–4200 kcal/d), omitted ≥60 of the 103 dietary questions (n = 296), or had surgery on the prostate or bladder (n = 79). Compared with the larger BACH sample, the resulting analytic sample had significantly more white men (44.0 vs. 36.3%) and fewer Hispanic (28.1 vs. 33.3%) or black men (27.9 vs. 30.4%) but was similar in age, physical activity, and LUTS prevalence.

LUTS measurement. During the in-home interview, LUTS was assessed by a validated, 7-item scale, the American Urologic Association Symptom Index (AUASI) (32–34). The AUASI identifies the presence of total moderate-to-severe LUTS by a symptom score ≥ 8. We also evaluated continuous symptom score (ranging from 0 to 35) as a secondary outcome. Voiding symptoms are identified by a score ≥ 5 (of total possible 20) based on responses to 4 AUASI questions regarding incomplete bladder emptying, intermittency, weak urinary stream, and hesitancy. Storage symptoms are identified by a score ≥ 4 (of possible 15) on 3 storage symptom questions assessing frequency, urgency, and nocturia. In secondary analyses, to facilitate comparison of our results to studies of BPH (11,26), we examined the outcome of high-moderate to severe LUTS, defined by an AUASI score ≥15 for total LUTS, ≥ 12 for voiding symptoms, and ≥ 9 for storage symptoms.

Data analysis. Dietary nutrient intakes were adjusted for total energy intake using residuals (35). Participants were grouped into quartiles of daily intake of each nutrient, with the lowest quartile as the reference. To minimize the influence of outliers, linear relationships and trends were assessed using the median values of deciles of intake as a continuous variable (36).

Logistic regression was used to estimate the odds of LUTS vs. no/low LUTS. In preliminary analyses, associations between LUTS status and potential covariates were examined using chi-square tests. Multivariate regression models were created by manually adding/removing potential confounders and retaining those that remained significant ($P \leq 0.10$) or affected estimates > 10%. Relevant sociodemographic, lifestyle, and medical characteristics that were included in final models are listed in the Table 2 footnotes. Factors that were considered but not included in any final models were BMI; socioeconomic status; alcohol intake; dietary cholesterol intake; use of multivitamins, vitamin D supplements, tricyclic antidepressants, diuretics, or a bladder catheter; duration of supplements use; and history of stroke, Parkinson's disease, or cancer. We evaluated effect modification by PUFA intake, which was found to be positively associated with storage symptoms (12), but there were no significant interactions (data not shown). We examined interactions between vitamin C and iron, because it has been shown that vitamin C may exert altered antioxidant capacity in the presence of transition metal ions (37), and a prior study of serum concentrations suggested effect modification by iron for LUTS (25). Racial/ethnic differences were examined in stratified analysis. We used multiple imputation to impute plausible values for missing covariate data. Statistical tests for the nutrients of interest were conducted at the α = 0.05 significance level. Statistical analyses were conducted in SAS v.9.2 or SUDAAN v.10.0.

Results

Moderate-to-severe LUTS were present in 19.2% of the 1466 men in this analysis. Storage symptoms were present in 431 men (29.4%) and voiding symptoms were present in 186 men (12.7%). The most common storage symptom was frequent urination (62.5% of LUTS cases). Common voiding symptoms among men with LUTS were a sensation of incomplete emptying (27.5%) and intermittent urinary stream (25.7%). Overall, men with LUTS were older, less physically active, had larger waist circumferences, and were more likely to have comorbid medical conditions (**Table 1**).

Higher dietary intake levels of carotenoids and vitamin C were associated with older age, current use of vitamin supplements, and race/ethnicity. Among black men, dietary β-carotene and lutein intakes were substantially higher compared with Hispanics or whites, whereas white men had the highest vitamin C intakes. Men with higher dietary vitamin C intake were also less likely to have depression symptoms or diabetes or smoke.

Associations between dietary nutrient intakes and LUTS from the primary analysis are presented in **Table 2**. Among the carotenoids, β-carotene and lycopene had inverse associations with LUTS, indicating 40–50% decreased odds of LUTS with higher intake levels. Lycopene was most strongly associated with total LUTS. Dietary β-carotene, total carotenoids, and vitamin A had significant inverse linear trends with the continuous AUASI symptom scores and consistent inverse associations with presence of moderate-to-severe storage symptoms. Dietary vitamin C was inversely associated with total (P-trend = 0.04) and voiding (P-trend = 0.056) symptom scores, but results were not consistent across quartiles of intake. In secondary analyses, a higher cut-point for LUTS (AUASI score ≥ 15, high-moderate/severe symptoms: 77 cases, 1186 noncases, excluding 203 men scoring 8–14) resulted in similar estimates of associations with wider CI.

Analyses of supplemental intakes of β-carotene or vitamin C and LUTS showed that high doses were significantly positively associated with LUTS (**Table 3**). For β-carotene supplements,

TABLE 1 Characteristics of men by presence of moderate-to-severe LUTS (BACH Survey, 2002–2005)[1]

	LUTS[2]	No/Low LUTS
n	281	1185
Total symptom score	12.8 ± 0.3	2.2 ± 0.1
Voiding symptoms present,[3] %	61.1	1.2
Storage symptoms present,[4] %	90.4	14.9
Age, y	55.3 ± 0.7	48.0 ± 0.4
Race/ethnicity, %		
Black	29.7	27.5
Hispanic	21.5	29.7
White	48.8	42.9
Cigarette smoking pack-years,[5] %		
0	34.6	44.3
<2.5	13.7	13.8
2.5–9.9	9.6	13.8
10–19.9	12.8	11.0
≥20	29.2	17.0
Waist circumference, cm	101.2 ± 1.0	96.2 ± 0.4
Physical activity,[6] %		
Low	37.8	27.8
Medium	41.8	46.7
High	20.4	25.5
Medical history, %		
Arthritis or rheumatism	35.7	14.9
Asthma	18.9	12.8
Cardiac disease	22.8	7.5
Depression symptoms	32.2	11.3
Diabetes	24.3	8.7
Use of vitamin supplements, %	45.0	34.2
Use of α-blockers or 5-α-reductase inhibitors, %	5.7	3.2

[1] Values are percent or means ± SEM, $n = 1466$. The groups differed in all variables, $P \leq 0.01$ (chi-square or *t-test*).
[2] Moderate-to-severe LUTS status, as defined using the AUASI score ≥ 8 (of total possible 35).
[3] Moderate-to-severe voiding symptoms were identified by AUASI score ≥ 5 (of total possible 20) based on responses to 4 AUASI questions regarding incomplete bladder emptying, intermittency, weak urinary stream, and hesitancy.
[4] Moderate-to-severe storage symptoms were identified by a score ≥ 4 (of possible 15) on 3 storage symptom questions assessing frequency, urgency, and nocturia.
[5] Pack-years of cigarette smoking was calculated as (number of cigarettes smoked per day × number of years smoked)/20. Never smokers were defined as men who reported never smoking more than 100 cigarettes in their lifetime.
[6] Physical activity was measured by means of the validated Physical Activity Scale for the Elderly (38); scores were classified as follows: < 100 = low, 100–249 = medium, ⩾ 250 = high.

men in the highest dose category (≥3000 μg/d) were 80% more likely to report moderate-to-severe LUTS (P-trend = 0.025). The association was considerably stronger among current smokers (OR = 3.00; 95% CI = 1.12, 8.05; $P = 0.003$) and null among nonsmokers, with a significant interaction (P-interaction = 0.004) between smoking and total (diet plus supplement) β-carotene. Vitamin C and β-carotene supplement use were correlated ($r = 0.55$), yet even among men who took <100 mg/d vitamin C, β-carotene supplement use remained positively associated (P-trend = 0.03), as was vitamin C supplement use (P-trend = 0.02) among men taking <3000 μg β-carotene. Unlike β-carotene, there was no interaction between vitamin C intake and smoking status for LUTS. In secondary analyses of high-moderate/severe symptoms, the positive association for high-dose vitamin C supplements and LUTS was greater in magnitude (OR = 2.34; 95% CI = 1.20, 4.55; P-trend < 0.001). Total vitamin C intake (dietary + supplemental) above 250 mg/d was also positively associated with LUTS [Q4 (260–3000 mg/d) vs. Q1 (<79 mg/d) multivariate OR = 1.73, 95% CI = 1.00, 2.98; P-trend = 0.02].

No racial/ethnic differences were found for associations between dietary lycopene or vitamin C, nor supplemental vitamin C or β-carotene, and LUTS. However, differences by race/ethnicity were observed for dietary β-carotene (P-interaction = 0.002), total carotenoids (P-interaction = 0.02), and vitamin A (P-interaction = 0.004); associations were strong among Hispanic men, small-to-moderate among white men, and null among black men.

Interactions with iron intake. Because prior research has suggested that vitamin C has altered antioxidant capacity in the presence of catalytically active metal ions such as iron (37,39–41) and that iron overload may cause oxidative stress (42), we evaluated whether the association between vitamin C and LUTS was modified by iron intake. Significant interactions were found between dietary iron and vitamin C for LUTS, particularly voiding symptoms (**Table 4**). Among men who consumed relatively high amounts of iron from diet (above median 13.3 mg/d), an increase of 100 mg/d dietary vitamin C was associated with 40–50% reductions in LUTS, voiding, or storage symptoms. The inverse association strengthened as iron intake level increased (e.g. dietary iron upper quintile, vitamin C 100 mg/d, and voiding symptoms OR = 0.31; 95% CI = 0.14, 0.71; $P = 0.005$). Among men with low iron intakes, there was no association between dietary vitamin C and LUTS. Conversely, iron intake was positively associated with LUTS only among men below the median of dietary vitamin C intake (P-trend = 0.05). In contrast to findings regarding dietary intakes, the association between supplemental vitamin C and LUTS was not appreciably affected by iron intake.

Because these findings suggest a specific antioxidant pathway for dietary vitamin C, we explored whether carotenoids had similar interactions with iron. All carotenoids, with the exception of lycopene (P-interaction = 0.87), had significant interactions with iron for outcomes of total LUTS or voiding symptoms, but not storage symptoms. The strongest of these was for β-cryptoxanthin (e.g. total LUTS P-interaction = 0.03, voiding symptoms P-interaction = 0.001), which is commonly consumed from orange juice and highly correlated with dietary vitamin C.

Discussion

In this population-based cross-sectional study, greater dietary intakes of β-carotene, lycopene, total carotenoids, or vitamin A were inversely associated with the likelihood of LUTS in men depending on symptom subtype. Dietary vitamin C and β-cryptoxanthin were associated with 40–50% reductions in odds of LUTS, particularly voiding symptoms, among men with relatively high iron intake but not among men consuming low levels of iron, suggesting antioxidant mechanisms of action. In contrast, high-dose supplemental or total vitamin C was positively associated with LUTS, and supplemental β-carotene was positively associated with LUTS among current smokers.

Prior studies of carotenoids and vitamin C in relation to LUTS have been limited to older men with BPH and related symptoms or small studies of men with surgically treated BPH. Results have been inconsistent, some showing strong inverse associations between dietary carotenoids and vitamin C (24,26) and others showing no significant associations (11,22). Our objectives were to examine plausible antioxidant associations

TABLE 2 Association of dietary carotenoids, vitamin A, and vitamin C with LUTS in 1466 men (BACH Survey, 2002–2005)[1]

Nutrient	Quartile of dietary intake[2]				*P*-trend	Continuous AUASI score *P*-trend
	1	2	3	4		
			OR (95% CI)			
β-Carotene, *μg/d*	775	1474	2454	4780		
Total LUTS	1.00	0.64* (0.42, 0.99)	0.62* (0.41, 0.95)	0.75 (0.49, 1.14)	0.31	0.06
Voiding symptoms	1.00	0.75 (0.46, 1.22)	1.01 (0.62, 1.63)	0.73 (0.44, 1.22)	0.19	0.06
Storage symptoms	1.00	0.64** (0.44, 0.92)	0.53*** (0.37, 0.77)	0.56** (0.39, 0.82)	0.02	0.05
Lycopene, *μg/d*	285	677	1199	2248		
Total LUTS	1.00	0.72 (0.47, 1.08)	0.67 (0.43, 1.02)	0.61* (0.39, 0.95)	0.04	0.22
Voiding symptoms	1.00	0.79 (0.48, 1.29)	0.93 (0.57, 1.52)	0.93 (0.57, 1.51)	0.83	0.72
Storage symptoms	1.00	0.69 (0.48, 1.01)	0.72 (0.49, 1.05)	0.63* (0.43, 0.94)	0.06	0.32
α-Carotene, *μg/d*	50	131	239	458		
Total LUTS	1.00	0.74 (0.50, 1.12)	0.79 (0.53, 1.20)	0.73 (0.49, 1.10)	0.37	0.15
Voiding symptoms	1.00	1.01 (0.63, 1.62)	0.87 (0.53, 1.42)	0.91 (0.55, 1.51)	0.78	0.82
Storage symptoms	1.00	0.81 (0.57, 1.15)	0.82 (0.58, 1.17)	0.83 (0.58, 1.19)	0.19	0.12
Lutein, *μg/d*	386	874	1527	3897		
Total LUTS	1.00	0.85 (0.55, 1.32)	0.98 (0.65, 1.48)	0.85 (0.56, 1.29)	0.90	0.77
Voiding symptoms	1.00	1.00 (0.60, 1.66)	1.13 (0.69, 1.84)	1.23 (0.75, 2.04)	0.84	0.81
Storage symptoms	1.00	0.87 (0.60, 1.26)	0.97 (0.68, 1.40)	0.78 (0.54, 1.13)	0.59	0.75
β-Cryptoxanthin, *μg/d*	30.0	81.2	145	263		
Total LUTS	1.00	0.78 (0.52, 1.17)	0.97 (0.64, 1.46)	0.87 (0.58, 1.33)	0.23	0.09
Voiding symptoms	1.00	0.67 (0.42, 1.07)	0.78 (0.49, 1.25)	0.77 (0.49, 1.21)	0.46	0.09
Storage symptoms	1.00	0.71 (0.50, 1.02)	1.08 (0.75, 1.55)	0.95 (0.66, 1.37)	0.99	0.28
Total carotenoids, *μg/d*	921	1657	2616	4670		
Total LUTS	1.00	0.72 (0.47, 1.10)	0.81 (0.54, 1.21)	0.72 (0.47, 1.10)	0.24	0.01
Voiding symptoms	1.00	0.85 (0.53, 1.36)	0.95 (0.58, 1.54)	0.71 (0.43, 1.20)	0.15	0.03
Storage symptoms	1.00	0.66* (0.46, 0.95)	0.67* (0.47, 0.95)	0.62** (0.43, 0.89)	0.02	0.07
Vitamin A,[3] *IU/d*	3023	4714	6660	10,926		
Total LUTS	1.00	0.93 (0.61, 1.42)	0.81 (0.54, 1.23)	0.84 (0.55, 1.29)	0.26	0.01
Voiding symptoms	1.00	1.11 (0.69, 1.79)	0.95 (0.59, 1.56)	0.96 (0.57, 1.62)	0.23	0.04
Storage symptoms	1.00	0.64* (0.45, 0.92)	0.63** (0.44, 0.90)	0.53*** (0.36, 0.77)	0.008	0.04
Vitamin C, *mg/d*	44.6	78.0	126.3	219.3		
Total LUTS	1.00	0.83 (0.55, 1.25)	0.61* (0.40, 0.92)	0.74 (0.47, 1.08)	0.98	0.04
Voiding symptoms	1.00	0.86 (0.54, 1.37)	0.60* (0.36, 0.99)	0.82 (0.52, 1.30)	0.34	0.06
Storage symptoms	1.00	0.90 (0.63, 1.30)	0.85 (0.59, 1.21)	0.86 (0.60, 1.24)	0.48	0.40

[1] Values are OR (95% CI) for LUTS vs. no/low LUTS. Asterisks denote significant OR: *$P \leq 0.05$; **$P \leq 0.01$; ***$P \geq 0.001$.
[2] Values are the median intakes of the nutrients by men in a given quartile of intake. All multivariate models were controlled for age (5-y age groups), race/ethnicity, waist circumference (quintiles), cigarette smoking (pack-year categories), total energy intake (quintiles), depression symptoms, cardiac disease, diabetes, use of α-blockers or 5-α-reductase inhibitors, and supplemental intake of the relevant nutrient (β-carotene, vitamin A, or vitamin C). Models for voiding symptoms additionally controlled for protein intake and multiple sclerosis. Models for storage symptoms were additionally controlled for total fluid intake (quintiles), PUFA intake, sodium intake, arthritis, multiple sclerosis, physical activity (low, medium, or high), and use of antispasmodic or anticholinergic medication. Tests for trends with the continuous AUASI score were conducted using generalized linear multivariate models.
[3] To obtain an approximation of micrograms retinol equivalents from IU, multiply by 0.17.

for a larger spectrum of LUTS nonspecific to BPH among men in broader age and racial/ethnic groups. Our results for moderate-to-severe total LUTS were consistent with some studies of BPH regarding dietary sources of β-carotene or vitamin C (24,26). Unlike studies of BPH, we also observed inverse trends between lycopene intake and LUTS. However, this finding is compatible with an NHANES-III study showing serum lycopene concentration was significantly reduced among men with LUTS (25), as well as suggested inverse trends between tomato juice consumption and BPH in the Health Professionals Follow-up Study (26). Furthermore, a small, randomized, controlled trial of 15 mg/d lycopene supplementation in men with BPH found that lycopene prevented prostate enlargement and improved LUTS over 6 mo follow-up (43).

Lycopene may influence LUTS through several different hypothesized mechanisms. Of carotenoids, lycopene has been identified as the most efficient singlet-oxygen quencher (14) and has the highest presence in prostate tissue (44). Thus, antioxidant action of lycopene may prevent or alleviate LUTS related to oxidative damage or prostate inflammation (45). In addition, it is possible that lycopene affects LUTS by decreasing insulin-like growth factor-1 (IGF1) and the IGF1 ratio to its major binding protein (IGFBP3) (46,47). There is growing evidence that higher IGF1 and IGF1:IGFBP3 increase BPH risk (48,49). Other possible mechanisms for lycopene involve inhibition of cell cycle progression and altered androgen metabolism (50), although the role of sex steroids in LUTS remains controversial (51–53). β-Carotene closely follows behind lycopene in its ability to function as an antioxidant and its presence in prostate tissue (14,42,44). Unlike lycopene, β-carotene is a vitamin A precursor and a major source of vitamin A, which may explain our finding similar associations for β-carotene and vitamin A.

TABLE 3 Association of supplemental use of β-carotene or vitamin C and LUTS in 1466 men[1,2]

Nutrient	Dose category of intake				Continuous AUASI score
	Nonuser 1	Low-Medium 2	High 3	*P*-trend	*P*-trend
		OR (95% CI)			
β-Carotene[3]	Nonuser	<3000 μg	≥3000 μg		
n	914	439	113		
Median intake, *μg/d*	0	1200	7145		
Total LUTS	1.0	1.43 (1.04, 1.98)*	1.78 (1.04, 3.03)*	0.03	0.09
Voiding symptoms	1.0	1.54 (1.07, 2.23)*	1.29 (0.66, 2.53)	0.35	0.14
Storage symptoms	1.0	1.22 (0.92, 1.63)	1.39 (0.87, 2.21)	0.14	0.31
Vitamin C	Nonuser	<250 mg	≥250 mg		
n	835	412	219		
Median intake, *mg/d*	0	60	1060		
Total LUTS	1.0	1.29 (0.92, 1.82)	1.83 (1.21, 2.77)**	0.02	0.02
Voiding symptoms	1.0	1.37 (0.92, 2.04)	1.87 (1.17, 3.00)**	0.08	0.04
Storage symptoms	1.0	1.21 (0.90, 1.62)	1.54 (1.06, 2.23)*	0.04	0.04

[1] Values are OR (95% CI) for LUTS vs. no/low LUTS. Asterisks denote significant OR: *$P \leq 0.05$; ** $P \leq 0.01$.
[2] From multivariate models, adjusting for the factors listed in Table 2 footnotes. Trend tests were conducted using the median dose of each category of intake as a continuous variable and testing the significance of its coefficient by the Wald test. The overall mean ± SEM supplemental intake dose among users was 298 ± 17 mg/d for vitamin C and 3103 ± 258 μg/d for β-carotene.
[3] A significant interaction was observed between smoking status and β-carotene intake (*P*-interaction = 0.004): the positive associations for LUTS were stronger among current smokers, intermediate among past smokers, and null among nonsmokers.

Although other individual carotenoids and dietary vitamin C were not consistently associated with LUTS overall, among men with moderate-to-high dietary iron intake, strong inverse associations were observed, particularly with voiding symptoms. Prior studies noted an altered antioxidant capacity for vitamin C in the presence of transition metals such as iron. Excessive iron can increase oxidative stress by reactions with hydrogen peroxide catalyzing the generation of highly reactive hydroxyl radicals (54,55). Increased oxidative stress due to iron overload may generate a specific antioxidant role for vitamin C. Our results are consistent with a study of iron intake, oxidative stress-related genes, and prostate cancer risk, which found similar effect modification by vitamin C-rich fruits and vegetables for iron (54). Our finding that all carotenoids (except lycopene) also had interactions with iron suggests that they too may influence voiding symptoms via antioxidant pathways when oxidative stress is present. The unique lack of interaction between lycopene and iron is difficult to interpret. It may reflect emerging evidence that metabolic products of lycopene, the lycopenoids, are responsible for some of lycopene's reported bioactivity rather than antioxidant mechanisms (50). Also of note, we did not observe interactions for supplemental vitamin C. This may be due to saturation levels of vitamin C among men taking high-dose supplements or may indicate that other unmeasured components of vitamin C-rich foods accounted for the observed benefits of dietary vitamin C.

Our observed interaction between smoking and β-carotene is in accordance with prior studies' finding that high total β-carotene intake was associated with various adverse health outcomes in smokers (16,56,57). β-Carotene can act as a prooxidant at high oxygen pressures, a property that distinguishes β-carotene from other carotenoids (58). Another mechanism may involve diminished retinoid signaling; breakdown products of β-carotene destructed retinoic acid, diminished retinoid signaling, and enhanced cell proliferation in smoke-exposed animals (59).

Positive associations between supplemental vitamin C and LUTS could hypothetically be due to effects of high-dose vitamin C on acidity of urine composition. For the average adult, body stores of vitamin C are adequately maintained with 75 mg/d ascorbic acid, and doses above 200 mg are mostly excreted (15). In our analyses, men consuming vitamin C above this threshold for absorption were significantly more likely to report LUTS, and the odds continued to increase with increasing dose. The urothelium is an active tissue that responds to changes in its environment by releasing diffusible agents and modulating the

TABLE 4 Associations between dietary vitamin C (increase in 100 mg/d) and LUTS in 1466 men by dietary iron intake[1,2]

	Dietary iron intake			
	≤50th percentile (≤13.3 mg/d)	>50th percentile (>13.3 mg/d)	*P*-interaction	Continuous AUASI score *P*-interaction
Median iron intake, *mg/d*	12.0	16.5		
	OR (95% CI)			
Total LUTS	0.94 (0.72, 1.22)	0.62 (0.43, 0.89)**	0.01	<0.001
Voiding symptoms	1.10 (0.82, 1.47)	0.52 (0.33, 0.82)**	0.004	0.001
Storage symptoms	1.02 (0.80, 1.31)	0.74 (0.54, 1.00)*	0.02	0.01

[1] Values are OR (95% CI) for LUTS vs. no/low LUTS. Asterisks denote significant OR: *$P \leq 0.05$; **$P \leq 0.01$.
[2] From multivariate models, adjusting for the factors listed in Table 2 footnotes.

activity of afferent nerves and underlying smooth muscles (60). One study of the effects of urinary pH on bladder sensitivity in asymptomatic volunteers found that increased urine acidity led to increased micturition desire and urgency (20). Overall, our findings suggest that for some men, LUTS could be ameliorated by changing urine composition through modification of high-dose supplement use.

We found that black men consumed significantly more β-carotene and lutein; however, unlike Hispanics or whites, these nutrients were not associated with LUTS among blacks. Prior racial/ethnic diet studies in the US noted contributions of high consumption of leafy green vegetables and sweet potatoes among African Americans, resulting in higher carotenoid intake (61–63). One speculative explanation for our observed effect modification is that among black men, even men consuming relatively less β-carotene, had sufficient intakes, such that additional β-carotene procured no benefits for LUTS. Whether such a threshold of dietary β-carotene exists requires additional research.

Given that analyses were cross-sectional, whether our observed associations represent actual causal relationships between β-carotene or vitamins A or C and LUTS is uncertain. An advantage of the cross-sectional design here is that many of the hypothesized pathophysiological mechanisms are appropriately evaluated by proximate measurement of diet and LUTS (e.g. high-dose vitamin C affecting urine composition). Furthermore, given that carotenoids and vitamin C are not established mediators of LUTS, it is unlikely that men with LUTS changed their dietary intakes of these nutrients to help manage their symptoms. A limitation in our analysis of supplemental β-carotene is that doses were approximate, because the FFQ nutrient database assumed β-carotene dose based on whether it was taken as an individual supplement or part of a multivitamin. To minimize errors in β-carotene dose, we created categories to reflect these assumptions. Strengths of our study include its racial/ethnic diversity, inclusion of younger adults, and unique community-based recruitment, which allowed us to study LUTS below clinical thresholds and include men without access to health care.

In summary, we found that men consuming more β-carotene, lycopene, or vitamin A from their diets were less likely to report LUTS. Inverse associations for dietary vitamin C and most carotenoids were apparent among men who consumed moderate-to-high levels of iron, suggesting antioxidant mechanisms. Additional research is required to confirm whether high-dose vitamin C and urine acidity are contributors to LUTS. Clinically, our results provide support to recommendations for increased fruit and vegetable consumption, particularly those rich in carotenoids and vitamin C, as these may have benefits that extend to moderate-to-severe LUTS in men. If confirmed by other studies, the potential public health importance of dietary and supplement associations is underscored by the recognized need for noninvasive, modifiable lifestyle options for the prevention and treatment of LUTS (64,65).

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N.N.M. and J.B.M. designed and conducted the research; N.N. M. performed statistical analysis, wrote the paper, and had primary responsibility for the final content; E.L.G. provided critical scientific contributions for the analysis, interpretation, and presentation of data in the manuscript; and K.T.M. provided essential contributions to the clinical significance and interpretation of the data and revisions to the manuscript. All authors read and approved the final manuscript.

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