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Intake of Lycopene and other Carotenoids and Incidence of Uterine Leiomyomata: A Prospective Ultrasound Study

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ABSTRACT

Background Uterine leiomyomata (UL) are the leading indication for hysterectomy in the United States. Dietary supplementation with lycopene was associated with reduced size and incidence of oviduct leiomyoma in the Japanese quail. Two US prospective cohort studies of women reported little association between intake of lycopene, or other carotenoids, and UL incidence. However, these studies relied on self-reported physician-diagnosed UL, which is prone to misclassification.

Objective This study examines the association between dietary intake of carotenoids and UL incidence.

Design Data were derived from the Study of the Environment, Lifestyle, and Fibroids, a prospective cohort study. Women completed self-administered baseline questionnaires on demographic characteristics, reproductive history, and lifestyle, including a 110-item validated food frequency questionnaire, from which dietary intakes of carotenoids—including alpha carotene, beta carotene, cryptoxanthin, lutein-zeaxanthin, and lycopene—and vitamin A were estimated.

Participants/setting One thousand two hundred thirty Black women aged 23 to 35 years who did not have a previous diagnosis of UL, cancer, or autoimmune disease were eligible for enrollment (2010-2012). Participants were residents of the Detroit, MI, metropolitan area.

Main outcome measures Transvaginal ultrasound was used to assess UL at baseline and 20, 40, and 60 months of follow-up.

Statistical analyses performed Cox regression was used to estimate hazard ratios and 95% CIs, adjusted for energy intake, age at menarche, education, body mass index, parity, age at first birth, years since last birth, current use of oral contraceptives or progestin-only injectables, alcohol intake, and cigarette smoking.

Results Among 1,230 women without prevalent UL at baseline, 301 incident UL cases during follow-up were identified. Intakes of lycopene, other carotenoids, and vitamin A were not appreciably associated with UL incidence. Hazard ratios comparing quartiles 2 (2,376 to 3,397 μg/day), 3 (3,398 to 4,817 μg/day), and 4 ($\geq$4,818 μg/day) with quartile 1 (<2,376 μg/day) of lycopene intake were 1.03 (95% CI 0.72 to 1.47), 1.22 (95% CI 0.86 to 1.72), and 0.95 (95% CI 0.67 to 1.36), respectively.

Conclusions Study findings do not support the hypothesis that greater carotenoid intake is associated with reduced UL incidence.
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UTERINE LEIOMYOMATA (UL) ARE THE LEADING indication for hysterectomy in the United States[1,2] and account for more than $2.2 billion annually in health care costs.[3] Compared with other racial/ethnic groups, non-Hispanic Black women have higher incidence rates of UL, earlier ages at diagnosis and surgery, and more severe symptoms at the time of initial diagnosis.[4-7] Risk factors identified in epidemiologic studies to date do not explain the racial disparity in UL.[7]

For reasons related to structural racism, food insecurity, and food deserts (eg, lack of access to supermarkets offering fresh fruits and vegetables at affordable prices) in predominantly Black neighborhoods,[8-11] US Black adults tend to have lower intakes of fruits, vegetables, and fiber than White adults,[12-14] and they are less likely to use vitamin supplements.[15,16] Black adults also tend to have lower dietary intakes of carotenoids.[13,14] Carotenoids belong to the tetraterpenes family (C40-based isoprenoids)[17] and are found in fruits, vegetables, and fish.[18,19] The most commonly consumed carotenoids include beta carotene, alpha carotene, lycopene, lutein, and cryptoxanthin.[20] Carotenoids can be divided into provitamin A compounds (eg, beta carotene, alpha carotene, and beta cryptoxanthin) found in plant-based foods and preformed vitamin A compounds (eg, retinol) in animal products.[21] Retinyl acetate or palmitate (provitamin A compounds) are often found in vitamin A supplements. Vitamin A is derived from carotenoids by oxidative cleavage.[22]

Like lipids, carotenoids are absorbed in the body and transported through the lymphatic system into the liver. Absorption depends on many factors. For instance, a high-cholesterol and/or high-fat diet increases the absorption of carotenoids, whereas a low-fat diet reduces their absorption.[23-25] Individuals with greater body fat have reduced capacity to convert beta carotene to vitamin A.[26] Some carotenoids, such as beta carotene[27] and lycopene,[17] can decrease reactive oxygen species generated by cigarette smoke and can modulate redox-sensitive cell targets.

Carotenoid intake has been associated with lower incidence of hormone-dependent reproductive cancers (eg, prostate), cardiovascular disease, and age-related macular degeneration.[20,22] Lycopene, which provides the red pigment in tomatoes, is considered a more potent antioxidant than other carotenoids.[28-32] Possible mechanisms involved in the inhibitory effects of lycopene on tumor growth include upregulation of detoxification systems, scavenging of reactive oxygen species,[20,28,33] interference with cell proliferation,[32,34,35] apoptosis,[34,35] and inhibition of cell cycle progression[35,36] and angiogenesis.[37-40]

The influence of carotenoid intake on UL risk in humans is unclear. In the Japanese quail, dietary supplementation with lycopene or tomato powder was associated with a reduction in the incidence and size of leiomyoma in the oviduct.[41,42] Two large US prospective cohort studies have examined the association between self-reported carotenoid intake via food frequency questionnaire (FFQ) and UL incidence: the Nurses' Health Study II[43] and Black Women's Health Study.[44] Neither study found an appreciable association between intake of carotenoids, including lycopene, and UL incidence. Both studies relied on self-reported physician-diagnosed UL, which is prone to misclassification because a large proportion of UL are asymptomatic.[5] Studies designed to reduce UL misclassification could clarify the extent to which carotenoid intake influences UL incidence.

This study assessed the association between carotenoid intake and UL incidence in a prospective cohort of Black

RESEARCH SNAPSHOT

Research Question: What is the association between carotenoid intake and incidence of uterine leiomyomata in a 5-year prospective cohort study of African American women who were screened every 20 months with transvaginal ultrasound?

Key Findings: Intake of carotenoids, including lycopene, was not appreciably associated with incidence of uterine leomyomata.

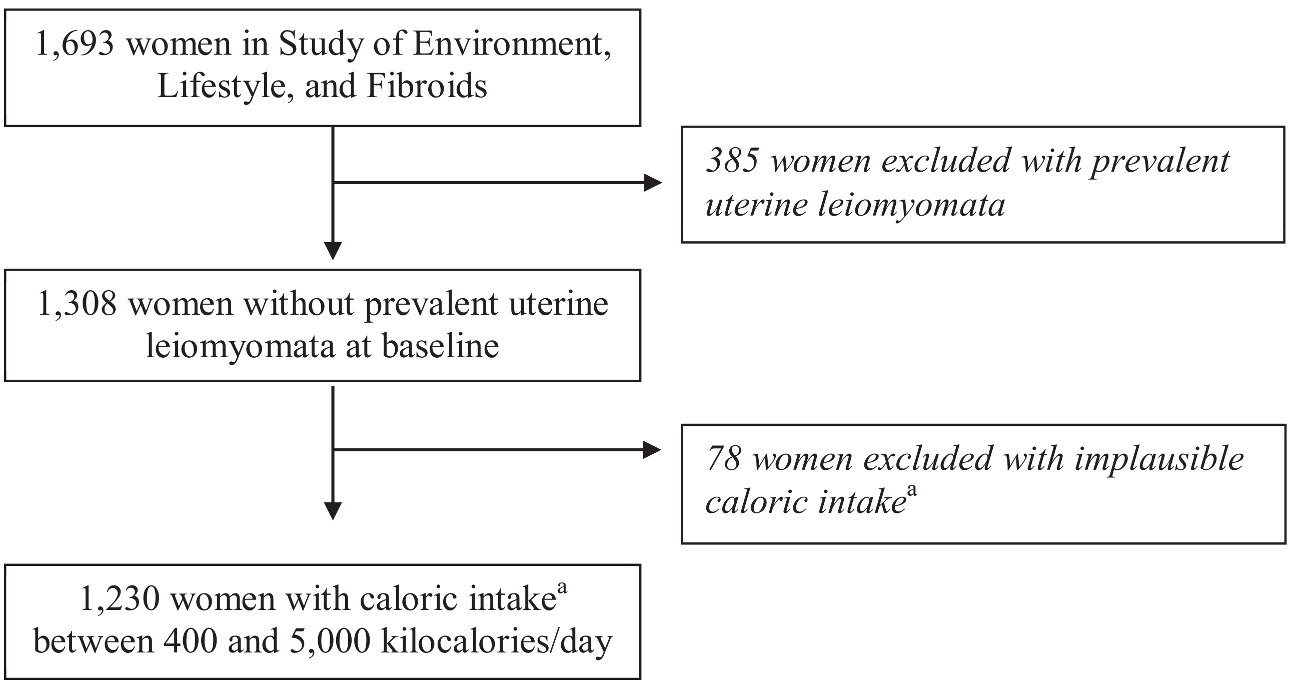

Figure 1. Flow chart of exclusions for analysis of carotenoid intake and uterine leiomyomata (UL) incidence in the Study of the Environment, Lifestyle, and Fibroids (SELF) cohort. [a]Caloric intake was estimated using the self-administered web-based semi-quantitative Block food frequency questionnaire.[48,49]

Table 1. Distribution of energy-adjusted reported carotenoid intake (μg/day)[a] among 1,230 SELF[b] participants at baseline (2010-2012)

Carotenoid	Distribution of variable			
	Mean (standard deviation)	Median (interquartile range)	Minimum	Maximum
Dietary lycopene	4,041.8 (3,172.7)	3,396.7 (2,375.5-4,817.5)	254.9	40,601.1
Dietary beta carotene	4,409.9 (3,259.3)	3,563.7 (2,276.3-5,525.4)	224.4	27,888.0
Total beta carotene (dietary + supplemental)	4,864.5 (4,406.8)	3,755.7 (2,366.5-5,713.7)	223.0	49,344.0
Dietary alpha carotene	441.6 (515.0)	289.5 (148.4-522.2)	25.1	4,660.7
Dietary cryptoxanthin	165.2 (114.4)	133.5 (85.0-212.0)	20.0	977.5
Dietary lutein-zeaxanthin	4,117.8 (3,397.5)	3,197.1 (1,909.3-5,128.8)	193.8	32,672.3
Dietary vitamin A (RAE[c])	823.6 (357.8)	759.3 (592.6-954.8)	137.9	2,896.3
Dietary vitamin A (retinol)	435.0 (185.5)	406.4 (315.1-511.0)	82.5	2,401.9
Total vitamin A (dietary + supplemental)	1,303.1 (1,230.8)	844.3 (627.0-1423.6)	128.5	11,552.2

[a]Estimated via the web-based semiquantitative Block food frequency questionnaire.[48,49]
[b]SELF = Study of Environment, Lifestyle and Fibroids.
[c]RAE = retinol activity equivalents from dietary sources only.

women. Serial transvaginal ultrasounds were used to screen participants at baseline and every 20 months during a 5-year period to identify UL. Results were stratified by factors that have been shown to influence carotenoid bioavailability, including dietary fat intake,[24,25] adiposity[26] as characterized by body mass index (BMI), and cigarette smoking.[27]

SUBJECTS AND METHODS

Study Population

The Study of the Environment, Lifestyle, and Fibroids (SELF) is a Detroit-based prospective cohort of 1,693 reproductive-aged Black women.[45] Recruitment of SELF participants occurred during 2010 through 2012 with community outreach through radio, television, newspapers, event booths, and informational letters to women who had received care for any reason at Henry Ford Health System, the clinical institution collaborating on SELF.[45] Enrolled women (n = 1,693) self-identified as Black or African-American, were 23 to 35 years of age at the first clinic visit, and reported no history of hysterectomy (partial or total) or diagnoses of UL, cancer, or autoimmune diseases requiring regular medication.

At baseline and every 20 months during a 5-year follow-up period, participants completed computer-assisted telephone questionnaires, web-based questionnaires and self-administered paper questionnaires, and attended in-person clinic visits. Participants were queried on their medical history, physical activity, lifestyle and behaviors (eg, alcohol and tobacco intake), reproductive history, and use of contraception. Transvaginal ultrasounds were performed during each in-person clinic visit. Ultrasound has high sensitivity and specificity to detect UL relative to histologic evidence.[46] Among pregnant women, data were recorded if the participant was ≤12 weeks pregnant based on fetal measures, otherwise pregnant women were asked to return to the clinic 4 months postpartum. Staff members who performed ultrasounds were registered diagnostic medical sonographers with ≥3 years of experience in gynecologic sonography.[47] Sonographers received additional training to ensure consistency in conducting examinations and completing research documentation about the ultrasound. Regular refresher trainings were also conducted during the study.[45] At each clinic visit, trained study staff measured height and weight, from which BMI was calculated. Specifically, staff recorded two measurements of standing height (in feet and inches) to the nearest one-quarter inch. If the two heights differed by >½ in, the measurement was repeated and recorded a third time. Weight (in pounds) was measured twice and recorded to the nearest 1/10 lb. If the two weights differed by > 1 lb, the measurement was repeated and recorded a third time. The average of all measurements for height and weight, respectively, was used in analysis. All participants gave written informed consent and the study was approved by the institutional review boards of Henry Ford Health System, the National Institute of Environmental Health Sciences, and Boston University Medical Campus.

Assessment of Dietary Intake

At baseline, women completed a validated web-based semi-quantitative Block FFQ.[48-50] Participants reported their average intake (ie, frequency and serving size) of 110 foods and beverages during the previous 12 months. The FFQ included 28 questions on fruit and vegetable consumption. Average daily intakes of dietary carotenoids were calculated by multiplying the season- and serving size-adjusted frequency of each food item by its carotenoid content as determined by the US Department of Agriculture Food and Nutrient Database for Dietary Studies.[51] Data for individual carotenoids are given in micrograms per day.

Dietary carotenoids of interest included alpha carotene, beta carotene, cryptoxanthin, lutein-zeaxanthin, and lycopene. Data were also analyzed on vitamin A (retinol) and a measure of retinol activity equivalents (RAE) because provitamin A carotenoids (alpha carotene, beta carotene, and beta

Table 2. Top-five food contributors to reported individual dietary carotenoid intake,[a] SELF [b] cohort

Carotenoid	Foods	Percent contributed
Lycopene	Spaghetti with meat sauce	23.8
	Pizza	18.7
	Tomato juice	13.3
	Catsup	11.5
	Watermelon	4.0
Beta carotene	Green salad	32.1
	Carrots	14.3
	Spinach	10.9
	Sweet potato	10.5
	Greens	5.3
Alpha carotene	Carrots	64.6
	Other vegetables	8.5
	Other chicken dishes	3.4
	Pumpkin pie	3.1
	Other beef dishes	2.9
Cryptoxanthin	Orange juice	19.8
	Calcium-fortified orange juice	17.5
	Oranges	12.0
	Pancakes	7.7
	Canned fruit	7.4
Lutein-zeaxanthin	Green salad	38.5
	Spinach	23.0
	Greens	9.3
	Broccoli	6.2
	Other vegetables	3.7
Vitamin A (RAE[c])	Green salad	13.9
	Carrots	7.8
	Liver	5.2
	Spinach	4.8
	Sweet potato	4.7
Vitamin A (retinol)	Liver	9.6
	Other eggs	6.5
	Reduced-fat milk	6.4
	Cheese	5.6
	Sweetened cereals	5.0

[a]Estimated via the web-based semiquantitative Block food frequency questionnaire.[48,49]
[b]SELF = Study of Environment, Lifestyle, and Fibroids.
[c]RAE = retinol activity equivalents from dietary sources only.

Table 3. Baseline characteristics of 1,231 women according to reported dietary lycopene intake, SELF[a], 2010-2012

	Dietary lycopene intake (μg/d)[c]			
Characteristic[b]	<2,375	2,375-3,392	3,393-4,814	≥4,815
No. of women	307	308	308	307
Age (y)	28.0	28.6	28.7	28.4
Body mass index	34.0	33.7	34.1	33.3
Age at menarche <12 y (%)	36.8	35.1	39.0	37.7
Parous (%)	66.6	66.1	62.6	56.6
Current use of progestin-only injectables (%)	7.2	5.9	2.3	8.5
Multivitamin supplement use, (%)	25.5	26.4	31.1	30.2
Vitamin A supplement use[d] (%)	19.9	26.8	29.4	31.5
Beta carotene supplement used[e] (%)	16.0	19.7	23.8	23.5
Current smoker (%)	26.5	20.3	14.3	12.4
Alcohol (drinks/wk)	4.5	3.1	3.2	3.1
Married or partnered (%)	23.2	30.5	32.1	29.2
Education, ≤12 y (%)	28.9	20.2	19.9	15.1
Household income <$20,000 (%)	57.1	46.0	40.3	37.2

[a]SELF = Study of Environment, Lifestyle, and Fibroids.
[b]Values are means or percentages standardized to the age distribution of the cohort population at baseline.
[c]Estimated via food frequency questionnaire[48,49] and categorized into quartiles that were energy-adjusted using the nutrient residual method.
[d]Includes supplemental vitamin A from multivitamins or prenatal vitamins.
[e]Includes supplemental beta carotene from multivitamins or prenatal vitamins.

cryptoxanthin) have less vitamin A activity than preformed vitamin A carotenoids. The predominant carotenoid in the human diet, beta carotene, is believed to have the greatest vitamin A activity, with 12 μg β-carotene from food being equivalent to 1 μg retinol, or 1 μg RAE.[52] For the other provitamin A carotenoids, 24 μg from food is equivalent to 1 μg RAE.[52] In foods of animal origin, except for some organ meats and dairy, all of the vitamin A activity is contributed by retinol.[52]

In a validation study of the Block FFQ[50] conducted in a multiethnic population (44% Black and 47% women), non-attenuated Pearson correlation coefficients (95% CI) between nutrients estimated by two FFQs (reliability) were 0.82 (95% CI 0.74 to 0.88) for vitamin A and 0.76 (95% CI 0.65 to 0.83) for beta carotene; de-attenuated Pearson correlation coefficients comparing the one FFQ with the average of two 24-hour recalls (validity) were 0.55 (95% CI 0.22 to 0.88) for vitamin A (international units per day) and 0.49 (95% CI 0.05 to 0.93) for beta carotene (milligrams per day).

Table 4. Reported carotenoid intake[a] and incidence of uterine leiomyomata, SELF[b], 2010-2017

				Among nonusers of supplements[d]
Exposure (μg/d)	Cases/ total	Unadjusted Hazard ratio (95% CI)	Adjusted[c] Hazard ratio (95% CI)	Adjusted[c] Hazard ratio (95% CI)
Dietary lycopene				
Q1: <2,376	71/307	Reference	Reference	Reference
Q2: 2,376-3,397	73/308	1.04 (0.73-1.47)	1.03 (0.72-1.47)	1.27 (0.82-1.99)
Q3: 3,398-4,817	88/308	1.30 (0.92-1.82)	1.22 (0.86-1.72)	1.45 (0.92-2.27)
Q4: ≥4,818	69/307	1.02 (0.72-1.44)	0.95 (0.67-1.36)	1.26 (0.80-1.99)
Dietary beta carotene				
Q1: <2,276	69/307	Reference	Reference	Reference
Q2: 2,276-3,564	77/308	1.09 (0.77-1.54)	1.04 (0.72-1.49)	0.96 (0.63-1.47)
Q3: 3,565-5,225	78/308	1.13 (0.80-1.60)	1.04 (0.72-1.51)	1.02 (0.68-1.55)
Q4: ≥5,226	77/307	1.14 (0.81-1.61)	1.02 (0.71-1.48)	1.09 (0.71-1.68)
Total beta carotene (dietary + supplemental)				
Q1: <2,366	67/307	Reference	Reference	—
Q2: 2,366-3,755	79/308	1.09 (0.77-1.54)	1.11 (0.78-1.58)	—
Q3: 3,756-5,713	71/308	1.00 (0.70-1.43)	0.91 (0.62-1.32)	—
Q4: ≥5,714	84/307	1.26 (0.90-1.76)	1.14 (0.80-1.64)	—
Dietary alpha carotene				
Q1: <148	71/307	Reference	Reference	Reference
Q2: 148-288	80/308	1.12 (0.80-1.58)	1.04 (0.73-1.48)	0.97 (0.64-1.46)
Q3: 289-521	75/308	1.01 (0.72-1.41)	0.98 (0.69-1.38)	0.88 (0.57-1.34)
Q4: ≥522	75/307	1.05 (0.74-1.49)	1.00 (0.69-1.44)	1.07 (0.69-1.65)
Dietary cryptoxanthin				
Q1: <85	82/307	Reference	Reference	Reference
Q2: 85-133	85/308	1.10 (0.80-1.51)	1.08 (0.78-1.50)	1.07 (0.72-1.59)
Q3: 134-211	59/308	0.73 (0.51-1.03)	0.76 (0.53-1.08)	0.62 (0.39-0.99)
Q4: ≥212	75/307	0.95 (0.68-1.31)	0.98 (0.70-1.37)	0.97 (0.63-1.48)
Dietary lutein-zeaxanthin				
Q1: <1,909	72/307	Reference	Reference	Reference
Q2: 1,909-3,197	78/308	1.13 (0.81-1.59)	1.11 (0.78-1.58)	1.14 (0.75-1.72)
Q3: 3,198-5,127	80/308	1.17 (0.83-1.64)	1.17 (0.81-1.68)	1.30 (0.85-1.98)
Q4: ≥5,128	71/307	0.98 (0.69-1.38)	0.87 (0.60-1.26)	0.95 (0.60-1.49)
Dietary vitamin A (RAE[e])				
Q1: <593	79/307	Reference	Reference	Reference
Q2: 593-759	63/308	0.73 (0.51-1.04)	0.75 (0.52-1.08)	0.70 (0.46-1.08)
Q3: 760-954	78/308	0.90 (0.65-1.25)	0.88 (0.62-1.24)	0.96 (0.64-1.44)
Q4: ≥955	81/307	1.05 (0.76-1.44)	0.99 (0.71-1.40)	1.11 (0.72-1.70)
Dietary vitamin A (retinol)				
Q1: <315	76/307	Reference	Reference	Reference
Q2: 315-406	71/308	0.81 (0.58-1.14)	0.84 (0.60-1.18)	0.81 (0.52-1.27)
Q3: 407-511	68/308	0.81 (0.57-1.14)	0.85 (0.60-1.20)	0.92 (0.60-1.43)
Q4: ≥512	86/307	1.11 (0.81-1.52)	1.13 (0.82-1.56)	1.37 (0.89-2.10)

(*continued on next page*)

Table 4. Reported carotenoid intake[a] and incidence of uterine leiomyomata, SELF[b], 2010-2017 (*continued*)

				Among nonusers of supplements[d]
Exposure (μg/d)	Cases/ total	Unadjusted Hazard ratio (95% CI)	Adjusted[c] Hazard ratio (95% CI)	Adjusted[c] Hazard ratio (95% CI)
Total vitamin A (dietary + supplemental)				
Q1: <627	69/307	Reference	Reference	—
Q2: 627-844	75/308	1.03 (0.74-1.45)	1.10 (0.78-1.55)	—
Q3: 845-1,423	82/308	1.21 (0.87-1.70)	1.25 (0.88-1.77)	—
Q4: ≥1,424	75/307	1.10 (0.78-1.56)	1.00 (0.65-1.55)	—

[a]Estimated via the web-based semiquantitative Block food frequency questionnaire.[48,49]
[b]SELF = Study of Environment, Lifestyle, and Fibroids.
[c]Adjusted for total energy intake, education, income, marital status, age at menarche, parity, years since last birth, current use of progestin-only injectable contraceptives, body mass index, smoking history, current alcohol use, and multivitamin use.
[d]Restricted to women not regularly taking multivitamins, supplemental vitamin A, or supplemental beta carotene at baseline.
[e]RAE = retinol activity equivalents from dietary sources only.

At baseline and on follow-up questionnaires, participants reported whether they took multivitamins, prenatal vitamins, vitamin A, or beta carotene supplements "fairly regularly," and the frequency of intake of each supplement. Average vitamin doses contained in multivitamins were imputed from data based on recommended nutrient values for women in standard US supplements.[53] Total daily intake of each vitamin was calculated by summing the average intakes from dietary sources, supplements of single vitamins, and multivitamins/prenatal vitamins.

The analysis excluded 385 women with prevalent UL identified by ultrasound at enrollment. It also excluded an additional 78 women with total energy intakes <400 or ≥5,000 kcal/day (trimmed at the <first and >95th percentiles of the distribution), leaving 1,230 women followed for incident UL for approximately 5 years (Figure 1). In this analytic population, 301 incident UL cases were detected at their 20- (n = 109), 40- (n = 88), or 60-month follow-up (n = 79) or imputed among women with no follow-up (see below). In addition, women were right-censored at hysterectomy for non-UL indications (n = 8), withdrawal from the study (n = 103), or their 60-month follow-up visit (n = 828).

Statistical Analysis

Carotenoid intakes were adjusted for total energy using the nutrient residual method[54] and categorized into quartiles to avoid the assumption of linearity between carotenoids and UL risk. In addition to categorical analyses, restricted cubic splines were used to model the association between carotenoid intake and UL incidence without imposing linearity on the association.[55] Person-time (in years) was calculated from baseline until the diagnosis of UL by ultrasound, hysterectomy, withdrawal, or the end of follow-up (5 years), whichever came first. Cases were assigned 0.5 years of follow-up time in the interval during which UL were detected. Cox proportional hazards models, with follow-up time in years, were used to estimate hazard ratios (HRs) and 95% CIs for the association between carotenoid intake and UL incidence. In addition to accounting for follow-up time, all multivariable models were adjusted for age in 1-year intervals (stratification variable) and total energy intake (continuous). Using causal diagrams guided by previous literature, multivariable models controlled for potential confounders at baseline, including education

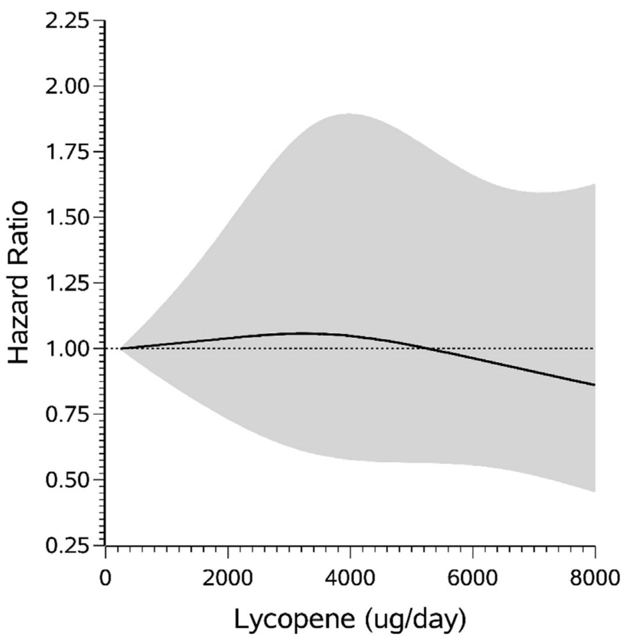

Figure 2. Association between reported dietary lycopene intake and incidence of uterine leiomyomata, fit using restricted cubic splines. The solid line represents the hazard ratio and the shaded band represents the 95% confidence band. Lycopene intake was estimated using the web-based semi-quantitative Block food frequency questionnaire.[48,49] The reference value is 255 μg/day, the lowest reported value in the data set. The curves are adjusted for total energy intake, education, income, marital status, age at menarche, parity, years since last birth, current use of progestin-only injectable contraceptives, body mass index, smoking history, current alcohol use, and multivitamin use. Three knots are located at the 10th, 50th, and 90th percentile and the splines are trimmed at the 95th percentile.

Table 5. Reported carotenoid intake[a] and incidence of uterine leiomyomata, stratified by body mass index and cigarette smoking, SELF[b], 2010-2017

	Body mass index				Current smoking			
	<30 (n = 504)		≥30 (n = 726)		Yes (n = 227)		No (n = 1,003)	
Exposure (μg/d)	Cases/ total	Adjusted[c] Hazard ratio (95% CI)	Cases/ total	Adjusted[c] Hazard ratio (95% CI)	Cases/ total	Adjusted[c] Hazard ratio (95% CI)	Cases/ Total	Adjusted[c] Hazard ratio (95% CI)
Dietary lycopene								
Q1: <2,376	25/130	Reference	46/177	Reference	16/82	Reference	55/225	Reference
Q2: 2,376-,3397	32/128	1.22 (0.69-2.16)	41/180	0.85 (0.54-1.33)	15/63	1.47 (0.63-3.44)	58/245	0.95 (0.65-1.40)
Q3: 3,398-4,817	33/114	1.52 (0.85-2.70)	55/194	1.14 (0.74-1.78)	8/44	1.26 (0.47-3.39)	80/264	1.21 (0.84-1.75)
Q4: ≥4,818	26/132	1.02 (0.56-1.87)	43/175	0.87 (0.55-1.38)	7/38	1.22 (0.41-3.65)	62/269	0.89 (0.61-1.30)
Dietary beta carotene								
Q1: <2,276	27/139	Reference	42/168	Reference	16/74	Reference	53/233	Reference
Q2: 2,276-3,564	30/124	1.54 (0.83-2.84)	47/184	0.92 (0.59-1.45)	10/64	0.60(0.21-1.73)	67/244	1.16 (0.78-1.71)
Q3: 3,565-5,225	36/124	1.84 (1.01-3.35)	42/184	0.81 (0.50-1.31)	13/53	1.40 (0.54-3.62)	65/255	1.04 (0.70-1.54)
Q4: ≥5,226	23/117	1.18 (0.61-2.27)	54/190	0.97 (0.62-1.52)	7/36	1.15 (0.36-3.66)	70/271	1.04 (0.70-1.54)
Total beta carotene (dietary + supplemental)								
Q1: <2,366	26/140	Reference	41/167	Reference	15/71	Reference	52/236	Reference
Q2: 2,366-3,755	29/119	1.49 (0.83-2.68)	50/189	1.01 (0.65-1.57)	10/66	0.49 (0.17-1.37)	69/242	1.25 (0.85-1.84)
Q3: 3,756-5,713	36/125	1.82 (1.03-3.22)	35/183	0.63 (0.38-1.05)	14/57	1.32 (0.51-3.43)	57/251	0.86 (0.57-1.30)
Q4: ≥5,714	25/120	1.29 (0.69-2.38)	59/187	1.08 (0.68-1.70)	7/33	1.11 (0.34-3.59)	77/274	1.16 (0.78-1.71)
Dietary alpha carotene								
Q1: <148	23/124	Reference	48/183	Reference	13/76	Reference	58/231	Reference
Q2: 148-288	38/133	1.77 (0.95-3.33)	42/175	0.81 (0.52-1.26)	14/54	1.81 (0.75-4.40)	66/254	0.97 (0.66-1.43)
Q3: 289-521	29/126	1.47 (0.78-2.75)	46/182	0.82 (0.53-1.26)	9/53	0.76 (0.26-2.18)	66/255	0.98 (0.67-1.43)
Q4: ≥522	26/121	1.65 (0.84-3.23)	49/186	0.88 (0.57-1.37)	10/44	1.19 (0.43-3.28)	65/263	0.94 (0.63-1.38)
Dietary cryptoxanthin								
Q1: <85	33/131	Reference	49/176	Reference	15/69	Reference	67/238	Reference
Q2: 85-133	32/123	1.06 (0.62-1.79)	53/185	1.13 (0.74-1.75)	14/60	1.33 (0.51-3.41)	71/248	1.05 (0.73-1.51)
Q3: 134-211	25/123	0.95 (0.54-1.68)	34/185	0.67 (0.42-1.07)	8/50	0.84 (0.29-2.41)	51/258	0.77 (0.52-1.13)
Q4: ≥212	26/127	0.96 (0.55-1.66)	49/180	0.99 (0.64-1.52)	9/48	0.76 (0.26-2.22)	66/259	1.00 (0.69-1.44)
Dietary lutein-zeaxanthin								
Q1: <1,909	28/144	Reference	44/163	Reference	14/80	Reference	58/227	Reference
Q2: 1,909-3,197	33/119	1.85 (1.01-3.39)	45/189	0.93 (0.60-1.44)	14/56	1.40 (0.52-3.81)	64/252	1.07 (0.72-1.58)
Q3: 3,198-5,127	33/129	1.96 (1.09-3.52)	47/179	0.94 (0.60-1.48)	12/55	1.55 (0.56-4.30)	68/253	1.13 (0.77-1.68)
Q4: ≥5,128	22/112	1.00 (0.52-1.93)	49/195	0.85 (0.54-1.34)	6/36	0.98 (0.32-3.04)	65/271	0.83 (0.56-1.23)
Dietary vitamin A (RAE[d])								
Q1: <593	29/126	Reference	50/181	Reference	17/78	Reference	62/229	Reference
Q2: 593-759	30/141	0.95 (0.53-1.71)	33/167	0.66 (0.40-1.09)	8/61	0.56 (0.19-1.60)	55/247	0.75 (0.50-1.11)

(*continued on next page*)

Table 5. Reported carotenoid intake[a] and incidence of uterine leiomyomata, stratified by body mass index and cigarette smoking, SELF[b], 2010-2017 (*continued*)

	Body mass index				Current smoking			
	<30 (n = 504)		≥30 (n = 726)		Yes (n = 227)		No (n = 1,003)	
Exposure (μg/d)	Cases/ total	Adjusted[c] Hazard ratio (95% CI)	Cases/ total	Adjusted[c] Hazard ratio (95% CI)	Cases/ total	Adjusted[c] Hazard ratio (95% CI)	Cases/ Total	Adjusted[c] Hazard ratio (95% CI)
Q3: 760-954	35/126	1.03 (0.59-1.80)	43/182	0.84 (0.54-1.31)	14/50	1.59 (0.66-3.86)	64/258	0.82 (0.56-1.19)
Q4: ≥955	22/111	0.89 (0.49-1.61)	59/196	1.06 (0.69-1.62)	7/38	1.23 (0.39-3.87)	74/269	0.95 (0.66-1.37)
Dietary vitamin A (retinol)								
Q1: <315	33/132	Reference	43/175	Reference	14/61	Reference	62/246	Reference
Q2: 315-406	25/132	0.77 (0.44-1.34)	46/176	0.90 (0.57-1.44)	13/57	0.63 (0.22-1.83)	58/251	0.83 (0.57-1.20)
Q3: 407-511	30/123	0.91 (0.52-1.61)	38/185	0.80 (0.51-1.27)	9/63	0.51 (0.19-1.39)	59/245	0.92 (0.63-1.34)
Q4: ≥512	28/117	0.83 (0.48-1.45)	58/190	1.32 (0.86-2.02)	10/46	1.13 (0.44-2.90)	76/261	1.14 (0.80-1.63)
Total vitamin A (dietary + supplemental)								
Q1: <627	24/124	Reference	45/183	Reference	16/78	Reference	53/229	Reference
Q2: 627-844	35/131	1.68 (0.94-2.98)	40/177	0.83 (0.52-1.35)	15/65	1.02 (0.43-2.42)	60/243	1.07 (0.73-1.59)
Q3: 845-1,423	26/121	1.28 (0.68-2.46)	56/187	1.25 (0.81-1.93)	11/61	1.13 (0.44-2.88)	71/247	1.29 (0.87-1.90)
Q4: ≥1,424	31/128	1.40 (0.64-3.06)	44/179	0.82 (0.49-1.38)	4/23	0.53 (0.10-2.70)	71/284	1.03 (0.64-1.64)

[a]Estimated via the web-based semiquantitative Block food frequency questionnaire.[48,49]
[b]SELF = Study of Environment, Lifestyle, and Fibroids.
[c]Adjusted for total energy intake, education, income, marital status, age at menarche, parity, years since last birth, current use of progestin-only injectable contraceptives, body mass index, smoking history (where appropriate), current alcohol use, and multivitamin use. Models stratified by body mass index further adjusted for body mass index as a continuous variable.
[d]RAE = retinol activity equivalents from dietary sources only.

(high school or less, some college, or college or advanced degree), BMI (<25, 25 to 29, 30 to 34, or ≥35 kg/m^2), age at menarche (<11, 11, 12, 13, or ≥14 years), parity (0, 1, 2, or ≥3 births), years since last birth (<2, 2 to 4, or ≥5 years), current use of progestin-only injectable contraceptives, alcohol intake (0, <7, or ≥7 drinks/week), and cigarette smoking (never, former, or current). Some nutrients were assessed based on food alone (eg, lycopene or alpha carotene) and some from foods and supplements (eg, beta carotene and vitamin A). Associations were also examined among nonusers of supplements. Data were further stratified by median dietary fat intake (<83.8 vs ≥83.8 g/day) and BMI (<30 vs ≥30) at baseline, as both dietary fat intake[24,25] and adiposity[26] have been shown to modify the bioavailability of carotenoids. For example, those with greater body fat have a lower capability of converting beta carotene to vitamin A.[26] Likewise, data were stratified by current cigarette smoking because smoking can directly degrade carotenoids[27] and some studies have shown an interaction between current smoking and beta carotene on disease.[56-58] Analyses were performed using SAS statistical software version 9.4.[59]

RESULTS

At baseline, the mean age of cohort participants was 28 years, 20% had ≤12 years of education, 45% had household incomes <$20,000, 63% were parous, and mean BMI was 33. Table 1 shows distributions of individual carotenoids in the cohort. The top-five dietary contributors to each carotenoid among SELF participants are presented in Table 2. The top-five dietary contributors to lycopene were spaghetti with meat sauce, pizza, tomato juice, catsup, and watermelon. Baseline characteristics of SELF participants, stratified by intake of dietary lycopene intake are shown in Table 3. Lycopene intake was positively associated with vitamin A supplement use, being married or partnered, education, and household income, and inversely associated with parity, cigarette smoking, and alcohol use during the past year. Dietary beta carotene intake showed similar patterns to lycopene for all characteristics (data not shown).

There were 301 incident cases of UL detected via ultrasound during 5,336 person-years of follow-up. Intakes of carotenoids, including lycopene, were not appreciably associated with UL incidence (Table 4). Adjusted HRs comparing quartiles 2 (2,376 to 3,397 μg/day), 3 (3,398 to 4,817 μg/day), and 4 (≥4,818 μg/day) with quartile 1 (<2,376 μg/day) of lycopene intake were 1.03 (95% CI 0.72 to 1.47), 1.22 (95% CI 0.86 to 1.72), and 0.95 (95% CI 0.67 to 1.36), respectively. Results based on restricted cubic splines were consistent with the categorical results, indicating no appreciable association between lycopene intake and UL incidence (Figure 2). There was little association between vitamin A intake, whether from food or supplements, or weighted according to retinol activity equivalents (Table 4). Supplemental intake of beta carotene

Table 6. Reported carotenoid intake[a] and incidence of uterine leiomyomata, stratified by median dietary fat intake, SELF[b], 2010-2017

	Total fat intake (g/d)			
	< 83.8 (n = 616)		≥ 83.8 (n = 614)	
Exposure (μg/d)	Cases/total	Adjusted[c] Hazard ratio (95% CI)	Cases/total	Adjusted[c] Hazard ratio (95% CI)
Dietary lycopene				
Q1: <2,376	34/155	Reference	37/152	Reference
Q2: 2,376-3,397	28/149	0.83 (0.49-1.39)	45/159	1.21 (0.74-1.99)
Q3: 3,398-4,817	40/140	1.38 (0.85-2.26)	48/168	1.15 (0.71-1.85)
Q4: ≥4,818	39/172	1.19 (0.72-1.97)	30/135	0.98 (0.56-1.70)
Dietary beta carotene				
Q1: <2,276	32/148	Reference	37/159	Reference
Q2: 2,276-3,564	27/141	0.88 (0.51-1.53)	50/167	1.21 (0.69-2.11)
Q3: 3,565-5,225	34/150	1.11 (0.66-1.89)	44/158	1.05 (0.61-1.81)
Q4: ≥5,226	48/177	0.42 (0.85-2.39)	29/130	0.84 (0.49-1.47)
Total beta carotene (dietary + supplemental)				
Q1: <2366	33/145	Reference	34/162	Reference
Q2: 2366-3755	27/143	0.89 (0.51-1.56)	52/165	1.30 (0.74-2.28)
Q3: 3756-5713	29/152	0.84 (0.48-1.45)	42/156	1.01 (0.56-1.81)
Q4: ≥5714	52/176	1.47 (0.88-2.47)	32/131	1.02 (0.58-1.78)
Dietary alpha carotene				
Q1: <148	36/157	Reference	35/150	Reference
Q2: 148-288	29/143	0.93 (0.55-1.58)	51/165	1.17 (0.70-1.96)
Q3: 289-521	35/145	1.09 (0.65-1.84)	40/163	0.86 (0.50-1.48)
Q4: ≥522	41/171	1.22 (0.75-1.98)	34/136	0.94 (0.54-1.65)
Dietary cryptoxanthin				
Q1: <85	32/115	Reference	50/192	Reference
Q2: 85-133	35/132	1.12 (0.65-1.91)	50/176	1.08 (0.71-1.65)
Q3: 134-211	25/155	0.74 (0.41-1.33)	34/153	0.84 (0.51-1.38)
Q4: ≥212	49/214	1.18 (0.70-1.99)	26/93	1.03 (0.61-1.75)
Dietary lutein-zeaxanthin				
Q1: <1,909	34/158	Reference	38/149	Reference
Q2: 1,909-3,197	29/136	1.18 (0.69-2.02)	49/172	1.13 (0.68, 1.87)
Q3: 3,198-5,127	36/153	1.39 (0.80-2.41)	44/155	1.09 (0.64-1.88)
Q4: ≥5,128	42/169	1.37 (0.83-2.28)	29/138	0.65 (0.36-1.16)
Dietary vitamin A (RAE[d])				
Q1: <593	42/162	Reference	37/145	Reference
Q2: 593-759	22/147	0.61 (0.34-1.08)	41/161	0.89 (0.51-1.54)
Q3: 760-954	36/145	0.83 (0.50-1.36)	42/163	0.89 (0.54-1.47)
Q4: ≥955	41/162	1.07 (0.66-1.74)	40/145	1.07 (0.65-1.74)
Dietary vitamin A (retinol)				
Q1: <315	52/195	Reference	24/112	Reference
Q2: 315-406	35/153	0.89 (0.57-1.41)	36/155	0.85 (0.48-1.52)

(*continued on next page*)

Table 6. Reported carotenoid intake[a] and incidence of uterine leiomyomata, stratified by median dietary fat intake, SELF[b], 2010-2017 (*continued*)

	Total fat intake (g/d)			
	< 83.8 (n = 616)		≥ 83.8 (n = 614)	
Exposure (μg/d)	Cases/total	Adjusted[c] Hazard ratio (95% CI)	Cases/total	Adjusted[c] Hazard ratio (95% CI)
Q3: 407-511	28/141	0.70 (0.43-1.14)	40/167	1.00 (0.57-1.75)
Q4: ≥512	26/127	0.69 (0.41-1.15)	60/180	1.53 (0.94-2.52)
Total vitamin A (dietary + supplemental)				
Q1: <627	33/162	Reference	36/145	Reference
Q2: 627-844	29/139	1.12 (0.64-1.95)	46/169	1.08 (0.67-1.74)
Q3: 845-1,423	46/163	1.53 (0.92-2.54)	36/145	1.06 (0.64-1.76)
Q4: ≥1,424	33/152	1.09 (0.58-2.06)	42/155	1.03 (0.57-1.87)

[a]Estimated via food frequency questionnaire.
[b]SELF = Study of Environment, Lifestyle, and Fibroids.
[c]Adjusted for total energy intake, education, income, marital status, age at menarche, parity, years since last birth, current use of progestin-only injectable contraceptives, body mass index, smoking history, current alcohol use, and multivitamin use.
[d]RAE = retinol activity equivalents from dietary sources only.

(HR 1.16, 95% CI 0.87 to 1.54) or vitamin A (HR 1.02, 95% CI 0.77 to 1.35) were not appreciably associated with UL risk.

Results for carotenoid intake were relatively uniform across strata of BMI, smoking status (Table 5), and dietary fat intake (Table 6). In general, HRs across quartiles of carotenoid intake were not monotonic and the effect estimates had broad CI.

DISCUSSION

In this prospective cohort study of reproductive-aged Black women who underwent serial ultrasound every 20 months during a 5-year period, dietary intakes of carotenoids were not appreciably associated with UL incidence. Although bioavailability of carotenoids has been shown to be modified by dietary fat intake, adiposity, and cigarette smoking,[27] there was no clear evidence of effect measure modification by these variables.

Findings from SELF are consistent with previous reports from two other prospective cohort studies, both of which relied on time to clinical diagnosis rather than systematic ultrasound. The Nurses' Health Study II (6,302 cases, >90% of whom were non-Hispanic White)[43] and the Black Women's Health Study (6,627 Black cases)[44] reported no material associations between lycopene, or any of the carotenoids examined, and UL incidence. These human data conflict with animal data indicating a protective effect of lycopene supplementation on leiomyoma of the oviduct in the Japanese quail.[41,42] Reasons for the inconsistent results across animal and human studies could relate to differences in dose, as the quail was exposed to 100 to 200 mg lycopene per kilogram of diet, which is likely much higher than what most humans ingest via diet. In addition, the Japanese quail is limited as an animal model for human uterine leiomyomata. Although the oviduct has an inner mucosal lining, an outer layer of loose supporting tissue (serosa), and a wall of smooth muscle, similar to human myometrium, the quail oviduct is not equivalent to the human uterus.

SELF findings on vitamin A intake were not consistent with findings from a nationally representative cross-sectional study, in which greater serum concentrations of vitamin A were associated with a higher prevalence of self-reported UL in a dose-response fashion (odds ratios comparing middle and high tertiles vs low tertile: 2.43 [95% CI 1.35 to 4.37] and 2.66 [95% CI 1.16 to 6.10], respectively). The latter study included only 68 UL cases (37%, 43%, and 16% identified as non-Hispanic Black, non-Hispanic White, and Hispanic, respectively)[60] and the cross-sectional design could not elucidate temporality.

Limitations of the present study include the relatively small numbers of incident UL cases (N = 301) and limited precision of effect estimates. The use of dietary self-report via FFQ is also subject to appreciable measurement error.[50] Without data on plasma carotenoid concentrations, which have half-lives between 26 and 76 days[61,62] and can provide more valid measurements of internal exposure to carotenoids,[63] it is challenging to make causal inferences about specific micronutrients. Although some studies have shown moderate to high correlations between diet and plasma levels of vitamins and carotenoids,[63-69] the correlation between dietary intake of vitamin A and blood retinol levels tends to be weak in American populations, with the exception of some subpopulations (eg, obese individuals).[70] In addition, the present analyses modeled dietary exposures and covariates at baseline, which may not capture the etiologically relevant time window of exposure. Given the study's prospective design, error from inaccurately reported dietary data is expected to be nondifferential, which could have attenuated the results. As is the case with any observational study, residual or unmeasured confounding also could have influenced the findings. Finally, other UL characteristics, such as size, location, and growth were not assessed.

Strengths of the present study include its focus on a population at high risk of UL. It is the first ultrasound-based study to examine prospectively the association of carotenoid intake with UL risk. The utilization of serial ultrasound to accurately classify UL is a major strength given the high proportion of asymptomatic UL in the general population.[5] Ultrasound is a detection method with high sensitivity and specificity to detect UL relative to histologic evidence,[46] minimizing detection bias and losses in precision.[71] Analyses controlled for energy intake, which may reduce measurement error in dietary intake,[72] as well as a wide range of potential confounders, including variables like socioeconomic status that are typically associated with diet. High cohort retention, which minimizes potential for selection bias, is an additional strength. Few differences were found between those who were and were not lost to follow-up by carotenoid intake (data not shown). Finally, the distributions of carotenoid intake in SELF were consistent with distributions among premenopausal participants in the Black Women's Health Study.[44] Direct comparisons of dietary carotenoid distributions with nationally representative data from the National Health and Nutrition Examination Survey were not possible given the use of two different instruments to assess carotenoid intake (FFQ in SELF vs 24-hour recalls in the National Health and Nutrition Examination Survey).

CONCLUSIONS

This prospective ultrasound study of Black women does not support the hypothesis that greater intake of lycopene, or any other carotenoids, reduces the incidence of UL. Despite earlier reports of potential benefits conferred by lycopene supplementation in animals, null results from the present study and two earlier US prospective cohort studies[43,44] suggest that it is unlikely that carotenoid intake prevents UL incidence in humans.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

L. Wise serves as a fibroid consultant for AbbVie, Inc, on work that is unrelated to this article. No other potential conflict of interest was reported by the authors.

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AUTHOR CONTRIBUTIONS

D. D. Baird designed the parent study and D. D. Baird and G. Wegienka directed its overall implementation, including quality assurance and control. Dr. Wise directed the research project based on carotenoid intake and uterine leiomyomata. Q. Harmon and T. Block managed the datasets and A. K. Wesselink performed the statistical analyses. L. Wise conducted the literature review and took the lead in drafting the manuscript for final publication. All authors made contributions to interpretation of the results, drafting the manuscript, and revising the manuscript critically for intellectual content. L. Wise takes primary responsibility for the final content of the manuscript