Intake of fruit, vegetables, and carotenoids in relation to risk of uterine leiomyomata[1–4]

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ABSTRACT

Background: US black women have higher rates of uterine leiomyomata (UL) and lower intakes of fruit and vegetables than do white women. Whether fruit and vegetable intake is associated with UL in black women has not been studied.

Objective: We assessed the association of dietary intake of fruit, vegetables, carotenoids, folate, fiber, and vitamins A, C, and E with UL in the Black Women's Health Study.

Design: In this prospective cohort study, we followed 22,583 premenopausal women for incident UL (1997–2009). Diet was estimated by using food-frequency questionnaires in 1995 and 2001. Cox regression was used to derive incidence rate ratios (IRRs) and 95% CIs for the association between each dietary variable (in quintiles) and UL.

Results: There were 6627 incident cases of UL diagnosed by ultrasonography (n = 4346) or surgery (n = 2281). Fruit and vegetable intake was inversely associated with UL ($\geq$4 compared with $<$1 serving/d; IRR: 0.90; 95% CI: 0.82, 0.98; P-trend = 0.03). The association was stronger for fruit ($\geq$2 servings/d compared with $<$2 servings/wk; IRR: 0.89; 95% CI: 0.81, 0.98; P-trend = 0.07) than for vegetables ($\geq$2 servings/d compared with $<$4 servings/wk: IRR: 0.97; 95% CI: 0.89, 1.05; P-trend = 0.51). Citrus fruit intake was inversely associated with UL ($\geq$3 servings/wk compared with $<$1 serving/mo: IRR: 0.92; 95% CI: 0.86, 1.00; P-trend = 0.01). The inverse association for dietary vitamin A (upper compared with lower quintiles: IRR: 0.89; 95% CI: 0.83, 0.97; P-trend = 0.01) appeared to be driven by preformed vitamin A (animal sources), not provitamin A (fruit and vegetable sources). UL was not materially associated with dietary intake of vitamins C and E, folate, fiber, or any of the carotenoids, including lycopene.

Conclusion: These data suggest a reduced risk of UL among women with a greater dietary intake of fruit and preformed vitamin A. *Am J Clin Nutr* 2011;94:1620–31.

INTRODUCTION

UL[5] are the leading indication for hysterectomy in the United States (1, 2) and account for >$2.2 billion annually in health care costs (3). The incidence of UL in black women is 2–3 times that in white women (4, 5), and the identified risk factors do not explain the racial disparity (4, 6). Endogenous sex steroid hormones (ie, estrogens and progesterone) and locally derived growth factors have been implicated in UL etiology (7).

National surveys show that black adults have lower intakes of fruit, vegetables, fiber, carotenoids, and vitamins A and C than do white adults and are less likely to take vitamin and mineral supplements (8–12). Fruit and vegetables contain various antioxidants and phytochemicals that may decrease UL risk via apoptosis or hormone-dependent pathways (13–18). For example, phytoestrogens can compete with estradiol for estrogen receptors in a manner that might reduce risk (14, 15, 19–23). Also, human studies have shown that indole-3-carbinol, found in cruciferous vegetables, has antiestrogenic activity via induction of 2-carbon but not 16α-hydroxylation (24–28).

Lycopene, a 40-carbon open-chain hydrocarbon carotenoid, provides the red pigment in tomatoes and is a potent antioxidant in vitro (29–31). In Japanese quail, dietary supplementation with lycopene or tomato powder reduced the incidence and size of leiomyoma (32, 33). Only a handful of human studies have investigated the association of fruit and vegetable intake with UL risk. In a case-control study of Italian women (34), the risk of surgically confirmed UL was inversely associated with intake of green vegetables and fruit. The OR for a comparison of the upper compared with the lower tertiles was 0.5 (95% CI: 0.4, 0.6) for green vegetables and 0.8 (95% CI: 0.6, 1.0) for fruit. In a subsequent case-control study of US women (35), urinary excretion of lignans (phytoestrogens found in fruit and vegetables) was inversely associated with risk of UL confirmed by ultrasonography or surgery (highest compared with lowest quartiles: OR: 0.47; 95% CI: 0.23, 0.98). The only human study to examine the association between carotenoid intake and UL risk, a large US prospective study of white nurses (36), found no association with intake of lycopene or any other carotenoids.

To advance this area of research, we prospectively evaluated the relation of dietary intake of fruit and vegetables and some of

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[5] Abbreviations used: BWHS, Black Women's Health Study; FFQ, food-frequency questionnaire; IRR, incident rate ratio; RAE, retinol activity equivalents; UL, uterine leiomyomata.

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their components—including carotenoids, folate, fiber, and vitamins A, C, and E—to the risk of UL in a large prospective cohort study of African American women. Intakes of vitamin supplements, including multivitamins, were also evaluated.

SUBJECTS AND METHODS

Study population

The BWHS is an ongoing US prospective cohort study of 59,000 African American women aged 21–69 y (37). In 1995, *Essence* magazine subscribers, black members of 2 professional societies, and friends and relatives of early respondents were mailed an invitation to enroll in a long-term health study by completing a comprehensive self-administered baseline questionnaire. Participants update exposure and medical histories every 2 years by mailed questionnaire. Study participants reside in more than 17 states, with the majority residing in New York, California, Illinois, Michigan, Georgia, and New Jersey. The institutional review board of Boston University Medical Center approved the study protocol.

Assessment of outcome

On the 1999 and 2001 follow-up questionnaires, women reported whether they had received a diagnosis with "uterine fibroids" in the previous 2-y interval, the calendar year in which they were first diagnosed, and whether their diagnosis was confirmed by "pelvic exam" and/or by "ultrasound/hysterectomy." On the 2003, 2005, 2007, and 2009 follow-up questionnaires, "hysterectomy" was replaced by "surgery (eg, hysterectomy)" to capture women who had other surgeries (eg, myomectomy), and "ultrasound" and "surgery" were divided into separate subquestions. Cases were classified as "surgically confirmed" if the participants reported diagnosis by "surgery" on the 2003 or later questionnaires or if they reported a diagnosis by "ultrasound/hysterectomy" and also reported "hysterectomy" under a separate question in 1999 or 2001.

We used an expanded outcome definition that includes cases diagnosed by surgery and ultrasonography because surgically confirmed cases represent only 10–30% of cases for whom ultrasonography is available and because studies of such cases may spuriously identify risk factors associated with severity or treatment preference (38). Ultrasonography has high sensitivity (99%) and specificity (91%) relative to histologic evidence (39, 40). To maximize the specificity of UL classification, pelvic exam cases ($n = 502$) were treated as noncases because these diagnoses could have represented other gynecologic pathology (41).

Assessment of diet

Usual diet in the past year was estimated in 1995 with a 68-item modified version of the National Cancer Institute–Block FFQ and in 2001 with an 85-item version (42, 43). The frequency responses for food items ranged from "never or <1 serving/month" to "≥ 2 servings/day." In 1995, we asked participants to specify a "small," "medium," or "large" portion size. A medium portion size was defined for each item (eg, 100 g of sweet potatoes or yams), and small and large servings were weighted as 0.5 and 1.5 times a medium serving size, respectively. In 2001, the FFQ included a super-size portion, equivalent to ≥ 2 times the size of medium. Nutrients were estimated by using National Cancer Institute's DietCalc software (44).

The 1995 FFQ included 5 questions on fruit consumption and 8 questions on vegetable consumption. We summed daily intakes of fruit and vegetables to calculate total intake. We also evaluated specific groups of fruit and vegetables classified according to botanical taxonomy (45). Yellow-orange vegetables included carrots, tomatoes or tomato juice, and sweet potatoes or yams; cruciferous vegetables included broccoli, collard or mustard greens, and cabbage or coleslaw; and green leafy vegetables included spinach and green salad. The 1995 and 2001 questions differed in that grapefruit and oranges were asked about separately in 1995, but were listed together with tangerines in 2001. We considered citrus fruit to be the sum of grapefruit and oranges in 1995, and to be the sum of grapefruit, oranges, and tangerines in 2001. Other fruit comprised apples or pears, bananas, and cantaloupe. "Orange or grapefruit juice" consumption was reported on both the 1995 and 2001 questionnaires, but was analyzed separately from fruit intake.

In 1995 and on follow-up questionnaires, participants reported whether they took multivitamins, vitamin A, vitamin C, vitamin E, β-carotene, or folate supplements ≥ 3 d/wk; additional data on frequency, number, and dose of each supplement were ascertained in 1995. Information on average vitamin doses contained in multivitamins was imputed from data based on recommended nutrient values for women in standard US supplements (46). Total daily intake of each vitamin was calculated by summing the intakes from dietary sources, supplements of that vitamin, and multivitamins.

Vitamin A refers to several fat-soluble molecules (ie, retinol, retinal, retinoic acid, and retinyl ester) and provitamin A carotenoids that can be converted into retinol: β-carotene, α-carotene, and β-cryptoxanthin. Preformed vitamin A is derived from animal products (eg, liver, milk, cheese, and eggs), whereas provitamin A carotenoids are derived from colored fruit and vegetables (eg, yellow tubers and green leafy vegetables). DietCalc calculated total vitamin A intake in micrograms of RAEs, β-carotene (μg), α-carotene (μg), and β-cryptoxanthin (μg). One RAE is equivalent to 1 μg preformed vitamin A, 12 μg β-carotene, 24 μg α-carotene, and 24 μg β-cryptoxanthin (47). Total provitamin A carotenoid intake was calculated by summing the intake of each provitamin A carotenoid in RAE units. Preformed vitamin A intake was calculated as the difference in total vitamin A intake and total provitamin A carotenoid intake. In the BWHS, the top contributors to mean provitamin A intake were carrots (31%), sweet potatoes/yams (13%), and collard greens (12%). The top contributors to mean preformed vitamin A intake were liver (27%), breakfast cereals (16%), and milk (15%). The average proportion of dietary vitamin A derived from provitamin A carotenoids was $\sim$39% for BWHS participants, consistent with national data (47).

Assessment of covariates

In 1995, we collected data on age at menarche, oral contraceptive use, parity, age at each birth, height, weight, alcohol intake, physical activity, smoking, education, marital status, occupation, and geographic region. We asked about household income in 2003 and about the recency of pelvic exam and ultrasonography screening in 2007. Reproductive factors, weight,

smoking, marital status, physical activity, and geographic region were updated on follow-up questionnaires and were modeled as time-varying covariates in the analyses.

Validation studies

UL

We assessed the accuracy of self-report in a random sample of 248 cases diagnosed by ultrasonography or surgery. Cases were mailed supplemental questionnaires regarding their initial date of diagnosis, method(s) of confirmation, symptoms, and treatment and were asked for permission to review their medical records. We obtained medical records from 127 of the 128 women who gave us permission and confirmed the self-report in 122 (96%). Of the 188 (76%) women who provided supplemental survey data, 71% reported UL-related symptoms before diagnosis and 87% reported their condition came to clinical attention because they sought treatment of symptoms or a tumor was palpable during a routine pelvic exam. There were no appreciable differences between women who did and did not release medical records with respect to UL risk factors (48).

Diet

A validation study of the 1995 FFQ was conducted in 1996–1998 (43). Approximately 400 BWHS participants provided 3 nonconsecutive 24-h telephone recall interviews and one 3-d food record over a 1-y period. Energy-adjusted and deattenuated Pearson correlation coefficients for the FFQ compared with diet records and recalls for β-carotene, vitamin C, folate, and fiber ranged from 0.60 to 0.67, with the exception of vitamin E (r = 0.26) (43).

Restriction criteria

Follow-up began in 1997 because the method of UL diagnosis was first included on the 1999 questionnaire. Of the 53,152 respondents to the 1997 questionnaire, we excluded postmenopausal women (n = 16,520), in whom UL are rare (49); women with a history of UL (n = 10,653); women lost to follow-up after 1997 (n = 925); cases without data on diagnosis year (n = 117) or method (n = 115); and women with missing covariate data (n = 587), implausible energy intake ($<$400 or $\geq$3800 kcal/d), or $>$10 missing items on the baseline FFQ (n = 1652), which left 22,583 women followed from 1997 through 2009. Those excluded because of missing or incomplete data (n = 3406) were less educated than were those who were included, but were similar with respect to parity, age at menarche, and other UL risk factors.

Data analysis

We defined cases as women who reported a first diagnosis of UL confirmed by ultrasonography or surgery. Person-years were calculated from March 1997 until UL diagnosis, menopause, death, loss to follow-up, or March 2009 (end of follow-up), whichever came first. Age- and period-stratified Cox regression was used to estimate IRRs and 95% CIs for the associations of interest.

Foods were categorized on the basis of their frequency distributions within the analytic sample. Nutrients were categorized into quintiles after adjustment for total energy intake by using the nutrient residual method (50). Because the average of $\geq$2 FFQs may provide a more valid assessment of long-term dietary intake (51), we assessed 1995 diet in relation to UL diagnosed through 2001 (1997–2001) and the average of 1995 and 2001 FFQs in relation to UL diagnosed from 2001 through 2009. Participants with missing or implausible data for the 2001 FFQ (n = 7116) were assigned their 1995 FFQ values for 1997–2009.

A covariate was included in multivariable analyses if it was either an established risk factor for UL identified from the literature or a potential risk factor for UL associated with exposure at baseline (**Table 1**). On the basis of these criteria, we constructed a multivariable model that controlled for age (1-y intervals), time period (2-y intervals), energy intake (quintiles), age at menarche (y), parity (0 or $\geq$1 births), age at first birth (y), years since last birth ($<$5, 5–9, 10–14, or $\geq$15 y), oral contraceptive use (ever or never), age at first oral contraceptive use (y), BMI (in kg/m^2; $<$20, 20–24, 25–29, 30–34, or $\geq$35), smoking (current, past, or never), current alcohol use ($<$1, 1–6, or $\geq$7 drinks/wk), multivitamin use (yes or no), education ($\leq$12, 13–15, 16, or $\geq$17 y), marital status (married/partnered, divorced/separated/widowed, or single), occupation (white collar, nonwhite collar, unemployed, or missing), household income ($\leq$\$25,000, \$25,001–50,000, \$50,001–100,000, or $>$\$100,000, missing), and geographic region of residence (South, Northeast, Midwest, or West).

Tests for trend were conducted by modeling a continuous version of the exposure variable assigned the median value of each category (52). We assessed whether alcohol, BMI, oral contraceptive use, and cigarette smoking modified the association between carotenoids and UL risk. Metabolic studies indicate that alcohol may interfere with the conversion of β-carotene to vitamin A (53, 54), higher plasma carotenoid concentrations have been found in lean women and in women using hormone contraception (55, 56), and Terry et al (36) found a positive association between β-carotene and UL among current smokers. We used stratification to examine whether the diet-UL associations were modified by the above factors and by the use of multivitamins or supplements. P values from interaction tests were obtained by using the likelihood ratio test comparing models with and without cross-product terms between the covariate and dietary factor. Departures from proportional hazards were evaluated in the same manner by using cross-product terms between each dietary factor and age ($<$35 compared with $\geq$35 y) and time period (1997–2001 compared with 2001–2009). The analyses were performed by using SAS statistical software version 9.1 (57).

RESULTS

Fruit and vegetable intake was positively associated with age, vigorous exercise, multivitamin use, education, white-collar occupation, and living in the West or Northeast and was inversely associated with current smoking and living in the South and Midwest (Table 1). During 185,013 person-years of observation, 6627 incident cases of UL diagnosed by ultrasonography (n = 4346) or surgery (n = 2281) were reported (**Table 2**). Overall, fruit and vegetable intake was inversely associated with UL risk (Table 2). Multivariable IRRs comparing 1, 2–3, and $\geq$4 servings/d with $<$1 serving/d of total fruit and vegetables were 0.95 (95% CI: 0.89, 1.01), 0.95 (95% CI: 0.89, 1.02), and 0.90 (95%

TABLE 1
Characteristics of 22,583 women according to intake of fruit and vegetables: the Black Women's Health Study (United States, 1997)[1]

	Fruit and vegetables (servings/d)				
	<1 (n = 6324)	1 (n = 6808)	2–3 (n = 6610)	≥4 (n = 2841)	P value[2]
Age (y)	33.1 ± 0.09	34.6 ± 0.09	35.6 ± 0.09	36.6 ± 0.14	<0.001
BMI (kg/m^2)	27.8 ± 0.09	27.8 ± 0.08	28.1 ± 0.09	27.8 ± 0.13	0.67
Age at menarche (y)	12.4 ± 0.02	12.3 ± 0.02	12.3 ± 0.02	12.3 ± 0.03	0.007
Recent pelvic exam (%)[3]	88 ± 0.4	90 ± 0.4	90 ± 0.4	89 ± 0.7	0.25
Parous (%)	56 ± 0.6	57 ± 0.6	58 ± 0.6	57 ± 0.9	0.27
Age at first birth, parous women (y)	22.8 ± 0.09	23.2 ± 0.08	23.4 ± 0.08	23.1 ± 0.13	0.001
Age at first oral contraceptive use, ever users (y)	19.0 ± 0.04	19.0 ± 0.04	19.0 ± 0.04	19.2 ± 0.07	0.03
Multivitamin supplement use (%)	37 ± 0.6	42 ± 0.6	49 ± 0.6	54 ± 0.9	<0.001
Vitamin A supplement use (%)	2 ± 0.2	2 ± 0.2	3 ± 0.2	6 ± 0.4	<0.001
Vitamin C supplement use (%)	13 ± 0.4	17 ± 0.5	21 ± 0.5	29 ± 0.9	<0.001
Vitamin E supplement use (%)	8 ± 0.3	11 ± 0.4	14 ± 0.4	20 ± 0.8	<0.001
β-Carotene supplement use (%)	1 ± 0.1	1 ± 0.1	2 ± 0.2	4 ± 0.4	<0.001
Folic acid supplement use (%)	2 ± 0.2	3 ± 0.2	4 ± 0.2	5 ± 0.4	<0.001
Current smoker (%)	16 ± 0.4	15 ± 0.4	13 ± 0.4	13 ± 0.6	<0.001
Alcohol intake (drinks/wk)	1.4 ± 0.04	1.3 ± 0.04	1.3 ± 0.03	1.3 ± 0.06	0.03
Vigorous exercise, ≥5 h/wk (%)	10 ± 0.4	13 ± 0.4	19 ± 0.4	27 ± 0.4	<0.001
Married (%)	38 ± 0.6	40 ± 0.6	42 ± 0.6	39 ± 0.9	0.02
Education in 1995 (y)	14.7 ± 0.02	14.9 ± 0.02	15.0 ± 0.02	15.0 ± 0.03	<0.001
White-collar occupation in 1995 (%)	55 ± 0.6	60 ± 0.6	61 ± 0.6	61 ± 0.9	<0.001
Household income in 2003 (%)					
≤$25,000	13 ± 0.4	10 ± 0.3	9 ± 0.3	13 ± 0.5	0.05
$25,001–$50,000	34 ± 0.6	30 ± 0.5	30 ± 0.5	32 ± 0.8	0.008
$50,001–$100,000	39 ± 0.6	41 ± 0.6	41 ± 0.6	38 ± 0.9	0.59
>$100,000	15 ± 0.4	19 ± 0.4	21 ± 0.4	18 ± 0.6	<0.001
Region of residence in the United States (%)					
West	17 ± 0.4	17 ± 0.4	19 ± 0.4	20 ± 0.6	<0.001
South	35 ± 0.6	33 ± 0.6	31 ± 0.6	28 ± 0.8	<0.001
Northeast	24 ± 0.5	27 ± 0.6	29 ± 0.6	32 ± 0.9	<0.001
Midwest	24 ± 0.5	23 ± 0.5	21 ± 0.5	20 ± 0.8	<0.001

[1] All values are means or percentages ± SE standardized to the age distribution of the study population at the start of follow-up.
[2] Derived from test for linear trend.
[3] Restricted to 18,670 participants who responded to 2007 questionnaire on which this question was asked.

CI: 0.82, 0.98), respectively (P-trend = 0.03). Inverse associations for fruit and vegetable intake were observed among both case groups (ultrasonography and surgery), but the trends were not statistically significant. Multivariable IRRs from a comparison of the highest with the lowest intake categories of fruit intake were stronger than those for vegetable intake. The multivariable IRR for the comparison of ≥2 servings/d with <2 servings/wk of fruit was 0.89 (95% CI: 0.81, 0.98; P-trend = 0.07), and this association was evident for ultrasonographic (IRR: 0.83; 95% CI: 0.74, 0.94; P-trend = 0.02) but not for surgical (IRR: 1.02; 95% CI: 0.87, 1.19; P-trend = 0.85) diagnoses. An inverse association was found among those consuming ≥3 servings/wk of citrus fruit relative to <1 serving/mo (IRR: 0.92; 95% CI: 0.86, 1.00; P-trend: 0.01) and was apparent for both ultrasonographic (IRR: 0.93; 95% CI: 0.85, 1.03; P-trend: 0.06) and surgical (IRR: 0.91; 95% CI: 0.80, 1.03; P-trend: 0.07) diagnoses. On the basis of the 1995 FFQ data, we estimated that ~73% of the mean intake of citrus fruit was from oranges. No associations were observed for intakes of orange and grapefruit juice (Table 2), tomatoes or tomato juice, or carrots with UL risk (data not shown).

Citrus fruit intake was only moderately correlated with citrus juice intake [Spearman correlation (r) = 0.26, ($P < 0.001$) in 1995 and r = 0.30 ($P < 0.001$) in 2001]. The association for citrus fruit and UL risk, with further adjustment for citrus juice, was essentially unchanged from the main association (≥3 servings/wk relative to <1 serving/mo; IRR: 0.92; 95% CI: 0.85, 1.00). The results did not change appreciably when we examined citrus fruit intake among nondrinkers of citrus fruit juice and when we examined citrus juice intake among nonconsumers of citrus fruit (data not shown). When we examined results stratified by time period (1997–2001 compared with 2001–2009), citrus fruit juice intake based on the 1995 FFQ (1997–2001) was not associated with UL risk, whereas an inverse association with citrus fruit juice intake and UL was found based on the 2001 FFQ (2001–2009). In this latter time period, multivariable IRRs for the comparison of citrus fruit juice intake of ≥3 servings/wk, 1–2 servings/wk, and 1–3 servings/mo with <1 serving/mo were 0.88 (95% CI: 0.77, 0.99), 0.89 (95% CI: 0.79, 1.02), and 0.87 (95% CI: 0.78, 0.97), respectively (P-trend = 0.12). In analyses based on 1995 FFQ data only (1997–2001 incident period: cases = 3135, person-years = 83,072), we modeled oranges separately from grapefruits. Multivariable IRRs for the comparison of whole orange intake of ≥3 servings/wk, 1–2 servings/wk, and 1–3 servings/mo with <1 serving/mo were 0.96 (95% CI: 0.86, 1.07), 0.98 (95% CI: 0.88, 1.09), and 1.04 (95% CI: 0.95, 1.14), respectively (P-trend: 0.25). IRRs for the comparison of whole grapefruit intake of ≥3 servings/wk,

TABLE 2
Intake of fruit and vegetables in relation to risk of uterine leiomyoma by method of diagnosis: the Black Women's Health Study (United States, 1997–2009)[1]

		Method of diagnosis						
		Ultrasonography or surgery			Ultrasonography		Surgery	
	Person-years	Cases	IRR[2]	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]
Total fruit and vegetables								
<1/d	48,335	1748	1.00	1.00	1150	1.00	598	1.00
1/d	59,203	2112	0.96	0.95 (0.89, 1.01)	1387	0.95 (0.88, 1.03)	725	0.96 (0.86, 1.07)
2–3/d	56,285	2039	0.98	0.95 (0.89, 1.02)	1334	0.95 (0.87, 1.03)	705	0.97 (0.86, 1.09)
≥4/d	21,191	728	0.93	0.90 (0.82, 0.98)	475	0.89 (0.80, 1.00)	253	0.91 (0.78, 1.06)
P-trend[4]			0.16	0.03		0.06		0.30
Total vegetables								
<4/wk	52,718	1848	1.00	1.00	1208	1.00	640	1.00
4–6/wk	45,044	1602	0.99	0.98 (0.92, 1.05)	1025	0.96 (0.88, 1.04)	577	1.04 (0.92, 1.16)
1/d	55,627	2058	1.03	1.01 (0.94, 1.07)	1372	1.02 (0.94, 1.10)	686	0.98 (0.88, 1.10)
≥2/d	31,624	1119	1.00	0.97 (0.89, 1.05)	741	0.96 (0.87, 1.06)	378	0.97 (0.85, 1.11)
P-trend[4]			0.85	0.51		0.74		0.48
Cruciferous								
<1/wk	43,772	1519	1.00	1.00	1012	1.00	507	1.00
1–2/wk	78,965	2867	1.03	1.02 (0.96, 1.09)	1850	1.00 (0.93, 1.08)	1017	1.06 (0.95, 1.18)
3–5/wk	39,833	1451	1.04	1.01 (0.94, 1.09)	954	1.01 (0.92, 1.10)	497	1.03 (0.90, 1.17)
≥6/wk	22,444	790	1.00	0.97 (0.89, 1.06)	530	0.99 (0.89, 1.11)	260	0.93 (0.79, 1.08)
P-trend[4]			0.98	0.41		0.93		0.19
Green leafy								
<1/wk	51,894	1814	1.00	1.00	1193	1.00	621	1.00
1–2/wk	62,406	2191	0.98	0.96 (0.91, 1.03)	1417	0.94 (0.87, 1.01)	774	1.02 (0.92, 1.14)
3–5/wk	46,253	1779	1.08	1.04 (0.97, 1.11)	1180	1.03 (0.95, 1.12)	599	1.05 (0.94, 1.18)
≥6/wk	24,460	843	0.97	0.93 (0.85, 1.01)	556	0.91 (0.82, 1.01)	287	0.97 (0.84, 1.12)
P-trend[4]			0.86	0.37		0.37		0.75
Yellow-orange								
<1/wk	61,773	2172	1.00	1.00	1411	1.00	761	1.00
1–2/wk	65,597	2408	1.03	1.02 (0.97, 1.09)	1581	1.03 (0.96, 1.11)	827	1.02 (0.92, 1.12)
3–5/wk	36,564	1286	1.00	0.99 (0.92, 1.06)	846	0.98 (0.90, 1.07)	440	1.00 (0.88, 1.13)
≥6/wk	21,079	761	1.02	1.00 (0.92, 1.09)	508	1.01 (0.91, 1.13)	253	0.98 (0.85, 1.14)
P-trend[4]			0.99	0.74		0.84		0.74
Total fruit								
<2/wk	49,461	1770	1.00	1.00	1197	1.00	573	1.00
2–6/wk	74,560	2663	0.99	0.97 (0.91, 1.03)	1734	0.93 (0.86, 1.00)	929	1.06 (0.95, 1.18)
1/d	42,114	1564	1.02	1.00 (0.93, 1.07)	1024	0.97 (0.89, 1.06)	540	1.06 (0.94, 1.20)
≥2/d	18,879	630	0.91	0.89 (0.81, 0.98)	391	0.83 (0.74, 0.94)	239	1.02 (0.87, 1.19)
P-trend[4]			0.17	0.07		0.02		0.85
Citrus								
<1/mo	36,596	1346	1.00	1.00	883	1.00	463	1.00
1–3/mo	58,997	2163	0.99	1.00 (0.94, 1.08)	1417	1.01 (0.93, 1.10)	746	1.00 (0.89, 1.13)
1–2/wk	47,363	1709	0.98	0.99 (0.93, 1.07)	1122	0.99 (0.90, 1.08)	587	1.01 (0.89, 1.14)
≥3/wk	41,738	1405	0.91	0.92 (0.86, 1.00)	921	0.93 (0.85, 1.03)	484	0.91 (0.80, 1.03)
P-trend[4]			<0.01	0.01		0.06		0.07
Cantaloupe								
<1/mo	85,223	3009	1.00	1.00	2020	1.00	989	1.00
1–3/mo	56,496	2038	1.00	0.99 (0.94, 1.05)	1307	0.96 (0.89, 1.03)	731	1.07 (0.97, 1.18)
1–2/wk	27,377	1022	1.03	1.02 (0.95, 1.09)	671	1.01 (0.93, 1.11)	351	1.03 (0.91, 1.16)
≥3/wk	13,981	494	0.96	0.95 (0.86, 1.04)	300	0.89 (0.79, 1.01)	194	1.05 (0.90, 1.23)
P-trend[4]			0.64	0.42		0.17		0.61
Apples, pears, and bananas								
<1/mo	14,152	498	1.00	1.00	317	1.00	181	1.00
1–3/mo	39,769	1418	1.01	1.01 (0.91, 1.12)	931	1.04 (0.92, 1.19)	487	0.94 (0.80, 1.12)
1–2/wk	53,140	1911	1.01	0.99 (0.89, 1.09)	1259	1.02 (0.90, 1.15)	652	0.94 (0.79, 1.11)
≥3/wk	77,801	2798	1.00	0.98 (0.89, 1.08)	1838	1.02 (0.90, 1.15)	960	0.92 (0.78, 1.08)
P-trend[4]			0.82	0.49		0.85		0.37

(Continued)

TABLE 2 (*Continued*)

		Method of diagnosis						
		Ultrasonography or surgery			Ultrasonography		Surgery	
	Person-years	Cases	IRR[2]	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]
Orange and grapefruit juice								
<1/mo	20,164	746	1.00	1.00	491	1.00	255	1.00
1–3/mo	33,777	1220	0.99	1.01 (0.92, 1.10)	801	0.99 (0.89, 1.11)	419	1.03 (0.88, 1.21)
1–2/wk	40,508	1444	0.98	0.98 (0.90, 1.07)	945	0.95 (0.85, 1.06)	499	1.05 (0.90, 1.22)
3–6/wk	52,538	1840	0.97	0.98 (0.90, 1.07)	1210	0.94 (0.84, 1.04)	630	1.07 (0.92, 1.24)
≥1/d	36,541	1323	1.02	1.02 (0.93, 1.12)	864	0.97 (0.86, 1.08)	459	1.13 (0.97, 1.33)
P-trend[4]			0.52	0.60		0.58		0.08

[1] IRR, incidence rate ratio.
[2] Adjusted for age and energy intake.
[3] Adjusted for age, time period, energy intake, parity, age at first birth, years since last birth, ever use of oral contraceptive and age at first use, BMI, smoking, current alcohol intake, multivitamin use, education, income, marital status, and region of residence in the United States.
[4] Derived from test for linear trend, modeling the quintile median as a continuous variable.

1–2 servings/wk, and 1–3 servings/mo with <1 serving/mo were 0.92 (95% CI: 0.79, 1.06), 0.99 (95% CI: 0.86, 1.13), and 1.02 (95% CI: 0.94, 1.11), respectively (*P*-trend = 0.24).

We examined total intake (from diet, supplements, and multivitamins) and dietary intake alone for vitamins and other micronutrients commonly found in fruit and vegetables, including folate, carotenoids, and vitamins A, C, and E (**Table 3**). Dietary vitamin A (μg/d RAE) was inversely associated with UL risk. The multivariable IRR for the comparison of the highest with the lowest quintiles of intake was 0.89 (95% CI: 0.83, 0.97; *P*-trend = 0.01), and this association appeared to be stronger among ultrasonography cases (IRR: 0.87; 95% CI: 0.79, 0.96; *P*-trend = 0.007) than among surgical cases (IRR: 0.94; 95% CI: 0.82, 1.07; *P*-trend = 0.52). The association for dietary vitamin A appeared to be driven primarily by preformed vitamin A, not by provitamin A carotenoids. Although associations for provitamin A carotenoids were consistent with the null hypothesis, inverse associations were found for preformed vitamin A in comparisons of the highest with the lowest quintiles of intake: all cases (IRR: 0.93; 95% CI: 0.86, 1.01; *P*-trend = 0.07) and ultrasonography-diagnosed cases (IRR: 0.88; 95% CI: 0.79, 0.96; *P*-trend = 0.007). Additional control for dairy products, one of the main contributors to preformed vitamin A intake, attenuated the association toward the null (data not shown). There were no clear patterns for UL risk in relation to total intakes of each vitamin or dietary intake of vitamins C or E, folate, or any of the individual carotenoids, including lycopene (Table 3). Dietary fiber showed no association with UL risk (**Table 4**). The age- and energy-adjusted IRR for the comparison of vegetarians (n = 45 cases) with omnivores was 0.82 (95% CI: 0.62, 1.10).

IRRs for current use (yes or no) of supplements of vitamin A, vitamin C, folate, or multivitamins in regression models without dietary factors were all close to 1.0 in the overall sample (data not shown), but the incidence of UL was somewhat lower among those who at baseline had taken vitamin A supplements for ≥5 y than among nonusers (IRR: 0.86; 95% CI: 0.67, 1.10; *P*-trend = 0.53), particularly among nonusers of multivitamins (IRR: 0.55; 95% CI: 0.29, 1.02; *P*-trend = 0.29). However, no dose-response relation was observed in either model, and the numbers were small. The overall findings were similar when we restricted our sample to the 6877 women (30%) who were not using any supplements and when we controlled for relevant supplements in addition to multivitamins when assessing the effects of fruit, vegetables, and individual micronutrients (data not shown). Among women in the 2 lowest quintiles of dietary vitamin A intake, UL risk was not appreciably associated with multivitamin use (IRR: 1.04; 95% CI: 0.96, 1.13) or vitamin A supplementation (IRR: 0.89; 95% CI: 0.63, 1.26), although there were few users of vitamin A supplements in this subgroup (33 cases).

IRRs did not vary appreciably by time period (except for citrus juice intake), smoking status, oral contraceptive use, BMI, alcohol consumption, parity, or education (data not shown). The results were also similar among women reporting a pelvic exam <5 y ago: IRRs for total fruit (≥2 servings/d compared with <2 servings/wk), citrus fruit (≥3 servings/d compared with <1 serving/mo), and dietary vitamin A (highest compared with lowest quintiles) were 0.92 (95% CI: 0.83, 1.02; *P*-trend = 0.28), 0.92 (95% CI: 0.85, 1.00; *P*-trend = 0.02), and 0.89 (95% CI: 0.81, 0.97; *P*-trend = 0.01), respectively. Associations for total fruit (≥2 servings/d compared with <2 servings/wk) were stronger among women aged ≥35 y (IRR: 0.84; 95% CI: 0.75, 0.94; *P*-trend = 0.005) than among those aged <35 y (IRR: 1.04; 95% CI: 0.88, 1.23; *P*-trend = 0.27, *P*-interaction = 0.01). Likewise, associations for citrus fruit (≥3 servings/d compared with <1 serving/mo) were stronger among women aged ≥35 y (IRR: 0.87; 95% CI: 0.79, 0.95; *P*-trend = 0.004) than among those aged <35 y (IRR: 1.07; 95% CI: 0.93, 1.22; *P*-trend = 0.41, *P*-interaction = 0.02). IRRs for dietary vitamin A (highest compared with lowest quintiles) were 0.93 (95% CI: 0.80, 1.07; *P*-trend = 0.27) and 0.88 (95% CI: 0.80, 0.96; *P*-trend = 0.01) for women aged <35 y compared with women aged ≥35 y, respectively (*P*-interaction = 0.55). Of the 15,446 women who provided complete FFQ data in both 1995 and 2001, results for dietary vitamin A (highest compared with lowest quintiles) and UL risk were similar overall (IRR: 0.88; 95% CI: 0.81, 0.97; *P*-trend = 0.01) and among ultrasonography-diagnosed cases (IRR: 0.85; 95% CI: 0.76, 0.95; *P*-trend = 0.004), whereas the lycopene results remained null. Finally, use of a simple update method (ie, 2001 FFQ for 2001–2009 instead of the average of

TABLE 3
Intake of folate, carotenoids, and vitamins A, C, and E in relation to risk of uterine leiomyoma by method of diagnosis: the Black Women's Health Study (United States, 1997–2009)[1]

		Method of diagnosis						
		Ultrasonography or surgery			Ultrasonography		Surgery	
	Person-years	Cases	IRR[2]	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]
Total vitamin A (μg/d)								
Q1 (<561)	37,109	1294	1.00	1.00	866	1.00	428	1.00
Q2 (561–889)	35,280	1318	1.05	1.07 (0.99, 1.15)	875	1.06 (0.97, 1.17)	443	1.09 (0.95, 1.24)
Q3 (890–1268)	37,611	1308	0.98	1.00 (0.93, 1.08)	845	0.96 (0.87, 1.06)	463	1.08 (0.95, 1.24)
Q4 (1269–1600)	36,439	1352	1.04	1.06 (0.98, 1.14)	882	1.02 (0.93, 1.13)	470	1.13 (0.99, 1.29)
Q5 (≥1601)	36,512	1283	0.97	0.99 (0.92, 1.07)	837	0.98 (0.89, 1.07)	446	1.03 (0.90, 1.18)
P-trend[4]			0.28	0.65		0.36		0.64
Dietary vitamin A (μg/d)								
Q1 (<456)	33,950	1243	1.00	1.00	828	1.00	415	1.00
Q2 (456–609)	36,973	1288	0.93	0.93 (0.86, 1.01)	869	0.94 (0.85, 1.03)	419	0.91 (0.80, 1.05)
Q3 (610–784)	37,723	1445	1.03	1.03 (0.95, 1.11)	944	1.00 (0.91, 1.10)	501	1.08 (0.95, 1.23)
Q4 (785–1050)	37,643	1347	0.95	0.95 (0.88, 1.03)	880	0.93 (0.84, 1.02)	467	0.99 (0.86, 1.13)
Q5 (≥1051)	36,664	1232	0.88	0.89 (0.83, 0.97)	784	0.87 (0.79, 0.96)	448	0.94 (0.82, 1.07)
P-trend[4]			0.002	0.01		0.007		0.52
Provitamin A (μg/d)								
Q1 (<129)	33,380	1133	1.00	1.00	756	1.00	377	1.00
Q2 (129–202)	35,589	1284	1.03	1.03 (0.95, 1.11)	860	1.04 (0.94, 1.15)	424	1.01 (0.88, 1.16)
Q3 (203–292)	36,991	1320	1.01	1.00 (0.93, 1.09)	835	0.96 (0.87, 1.06)	485	1.09 (0.95, 1.25)
Q4 (293–443)	37,006	1380	1.04	1.03 (0.95, 1.12)	901	1.03 (0.94, 1.14)	479	1.04 (0.91, 1.20)
Q5 (≥444)	35,951	1290	1.00	0.98 (0.91, 1.07)	849	0.98 (0.89, 1.08)	441	1.00 (0.86, 1.14)
P-trend[4]			0.97	0.56		0.60		0.82
Preformed retinol (μg/d)								
Q1 (<250)	33,259	1253	1.00	1.00	847	1.00	406	1.00
Q2 (250–334)	35,613	1308	0.98	0.99 (0.91, 1.07)	867	0.96 (0.87, 1.05)	441	1.05 (0.92, 1.20)
Q3 (335–434)	36,352	1276	0/94	0.96 (0.88, 1.03)	853	0.93 (0.84, 1.02)	423	1.02 (0.89, 1.17)
Q4 (435–614)	36,875	1311	0.95	0.98 (0.90, 1.06)	846	0.92 (0.83, 1.01)	465	1.11 (0.97, 1.27)
Q5 (≥615)	35,708	1219	0.90	0.93 (0.86, 1.01)	766	0.88 (0.79, 0.96)	453	1.04 (0.91, 1.19)
P-trend[4]			0.004	0.07		0.007		0.55
Total vitamin C (μg/d)								
Q1 (<99)	35,431	1292	1.00	1.00	827	1.00	465	1.00
Q2 (99–146)	38,385	1364	0.98	0.99 (0.91, 1.06)	889	0.98 (0.89, 1.08)	475	0.99 (0.87, 1.13)
Q3 (147–199)	36,789	1241	0.93	0.95 (0.88, 1.03)	819	0.96 (0.87, 1.06)	422	0.94 (0.83, 1.08)
Q4 (200–318)	36,710	1333	1.01	1.02 (0.94, 1.10)	884	1.02 (0.93, 1.13)	449	1.01 (0.88, 1.15)
Q5 (≥319)	36,694	1366	1.02	1.00 (0.92, 1.08)	906	1.00 (0.91, 1.11)	460	0.99 (0.87, 1.13)
P-trend[4]			0.20	0.67		0.65		0.93
Dietary vitamin C (μg/d)								
Q1 (<79)	35,919	1326	1.00	1.00	851	1.00	475	1.00
Q2 (79–114)	37,545	1349	0.98	0.98 (0.90, 1.05)	879	0.97 (0.88, 1.06)	470	0.99 (0.87, 1.13)
Q3 (115–150)	37,583	1294	0.95	0.95 (0.88, 1.03)	847	0.94 (0.85, 1.03)	447	0.97 (0.86, 1.11)
Q4 (151–202)	37,229	1332	0.99	0.98 (0.91, 1.06)	917	1.01 (0.92, 1.11)	415	0.92 (0.81, 1.05)
Q5 (≥203)	35,732	1295	0.99	0.97 (0.90, 1.05)	831	0.94 (0.85, 1.04)	464	1.04 (0.92, 1.19)
P-trend[4]			0.96	0.69		0.45		0.69
Total vitamin E (μg/d)								
Q1 (<6.4)	37,043	1284	1.00	1.00	801	1.00	483	1.00
Q2 (6.4–8.4)	35,927	1266	1.00	1.00 (0.92, 1.08)	835	1.04 (0.95, 1.15)	431	0.92 (0.81, 1.05)
Q3 (8.5–28.3)	35,927	1278	1.02	1.02 (0.94, 1.10)	862	1.08 (0.98, 1.19)	416	0.92 (0.80, 1.04)
Q4 (28.4–31.5)	35,913	1279	1.01	1.02 (0.94, 1.10)	829	1.04 (0.94, 1.14)	450	0.99 (0.87, 1.12)
Q5 (≥31.6)	35,878	1348	1.07	1.06 (0.98, 1.14)	907	1.11 (1.01, 1.23)	441	0.96 (0.84, 1.09)
P-trend[4]			0.05	0.13		0.08		0.90
Dietary vitamin E (μg/d)								
Q1 (<5.4)	32,450	1150	1.00	1.00	717	1.00	433	1.00
Q2 (5.4–6.3)	35,425	1212	0.95	0.94 (0.87, 1.02)	804	0.99 (0.90, 1.10)	408	0.84 (0.73, 0.96)
Q3 (6.4–7.2)	36,921	1323	0.99	0.98 (0.90, 1.06)	878	1.03 (0.94, 1.14)	445	0.88 (0.77, 1.00)
Q4 (7.3–8.7)	38,064	1378	1.00	0.98 (0.90, 1.06)	900	1.02 (0.92, 1.12)	478	0.91 (0.79, 1.03)
Q5 (≥8.8)	37,831	1392	1.01	1.00 (0.92, 1.08)	935	1.06 (0.96, 1.17)	457	0.89 (0.78, 1.02)
P-trend[4]			0.29	0.53		0.19		0.43

(Continued)

TABLE 3 (*Continued*)

		Method of diagnosis						
		Ultrasonography or surgery			Ultrasonography		Surgery	
	Person-years	Cases	IRR[2]	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]
Total folate (μg/d)[5]								
Q1 (<190)	25,832	1007	1.00	1.00	668	1.00	339	1.00
Q2 (190–279)	25,857	976	0.97	0.97 (0.89, 1.06)	626	0.92 (0.82, 1.02)	350	1.07 (0.92, 1.25)
Q3 (280–827)	25,821	964	0.96	0.95 (0.87, 1.04)	638	0.91 (0.81, 1.01)	326	1.03 (0.88, 1.20)
Q4 (828–943)	25,844	1010	1.00	1.02 (0.93, 1.11)	636	0.95 (0.85, 1.06)	374	1.16 (0.99, 1.34)
Q5 (≥944)	25,840	1004	1.00	1.00 (0.91, 1.09)	689	0.98 (0.88, 1.10)	315	1.02 (0.88, 1.19)
P-trend[4]			0.83	0.64		0.98		0.44
Dietary folate (μg/d)[5]								
Q1 (<162)	25,043	938	1.00	1.00	609	1.00	329	1.00
Q2 (162–207)	25,871	1019	1.05	1.05 (0.97, 1.15)	672	1.06 (0.95, 1.18)	347	1.04 (0.90, 1.21)
Q3 (208–254)	26,234	1018	1.04	1.04 (0.95, 1.14)	645	1.00 (0.90, 1.12)	373	1.12 (0.96, 1.30)
Q4 (255–325)	26,260	1009	1.03	1.01 (0.93, 1.11)	660	0.98 (0.88, 1.10)	349	1.08 (0.92, 1.26)
Q5 (≥326)	25,787	977	1.01	0.99 (0.90, 1.08)	671	1.00 (0.89, 1.11)	306	0.97 (0.83, 1.14)
P-trend[4]			0.95	0.46		0.53		0.66
Carotenoids								
Lycopene (μg/d)								
Q1 (<1972)	34,127	1230	1.00	1.00	787	1.00	443	1.00
Q2 (1972–2859)	36,976	1322	0.99	0.99 (0.92, 1.07)	891	1.03 (0.94, 1.14)	431	0.92 (0.81, 1.05)
Q3 (2860–3914)	38,319	1358	0.98	0.98 (0.91, 1.06)	870	0.97 (0.88, 1.07)	488	1.00 (0.88, 1.14)
Q4 (3915–5574)	37,749	1321	0.96	0.97 (0.90, 1.05)	867	0.97 (0.88, 1.07)	454	0.97 (0.85, 1.11)
Q5 (≥5575)	35,217	1299	1.02	0.99 (0.91, 1.07)	864	0.98 (0.89, 1.08)	435	1.01 (0.88, 1.16)
P-trend[4]			0.49	0.87		0.53		0.54
α-Carotene (μg/d)								
Q1 (<161)	33,882	1173	1.00	1.00	761	1.00	412	1.00
Q2 (161–319)	36,532	1278	0.99	0.98 (0.91, 1.06)	858	1.02 (0.92, 1.12)	420	0.92 (0.80, 1.05)
Q3 (320–534)	37,006	1366	1.04	1.03 (0.95, 1.11)	890	1.04 (0.94, 1.14)	476	1.01 (0.88, 1.15)
Q4 (535–987)	38,015	1361	1.00	0.99 (0.92, 1.07)	879	1.00 (0.90, 1.10)	482	0.99 (0.86, 1.13)
Q5 (≥988)	35,687	1305	1.01	1.00 (0.92, 1.08)	865	1.02 (0.92, 1.13)	440	0.96 (0.83, 1.10)
P-trend[4]			0.80	0.96		0.91		0.80
β-Carotene (μg/d)								
Q1 (<1405)	34,081	1154	1.00	1.00	786	1.00	368	1.00
Q2 (1405–2214)	36,392	1312	1.03	1.03 (0.95, 1.12)	865	1.01 (0.92, 1.11)	447	1.08 (0.94, 1.24)
Q3 (2215–3231)	37,876	1356	1.01	1.00 (0.93, 1.09)	849	0.94 (0.85, 1.03)	507	1.16 (1.01, 1.33)
Q4 (3232–4904)	38,576	1407	1.05	1.04 (0.96, 1.12)	923	1.02 (0.93, 1.12)	484	1.08 (0.94, 1.24)
Q5 (≥4905)	36,852	1315	1.00	0.98 (0.91, 1.06)	870	0.97 (0.87, 1.07)	445	1.02 (0.89, 1.18)
P-trend[4]			0.91	0.51		0.61		0.69
Carotene (μg/d)								
Q1 (<278)	34,546	1187	1.00	1.00	789	1.00	398	1.00
Q2 (278–437)	36,399	1299	1.01	1.01 (0.93, 1.09)	873	1.02 (0.93, 1.13)	426	0.98 (0.86, 1.13)
Q3 (438–643)	37,731	1371	1.02	1.01 (0.93, 1.09)	868	0.97 (0.88, 1.07)	503	1.09 (0.96, 1.25)
Q4 (643–1011)	37,797	1369	1.01	1.00 (0.92, 1.08)	891	0.99 (0.90, 1.09)	478	1.02 (0.89, 1.16)
Q5 (≥1012)	36,329	1323	1.01	0.99 (0.92, 1.08)	879	1.00 (0.91, 1.10)	444	0.99 (0.86, 1.14)
P-trend[4]			0.87	0.74		0.85		0.78
β-Cryptoxanthin (μg/d)								
Q1 (<54)	33,526	1265	1.00	1.00	839	1.00	426	1.00
Q2 (54–94)	36,929	1339	0.97	0.97 (0.90, 1.05)	853	0.91 (0.82, 1.00)	486	1.09 (0.96, 1.25)
Q3 (94–141)	38,129	1300	0.92	0.93 (0.86, 1.00)	854	0.89 (0.81, 0.98)	446	1.00 (0.87, 1.14)
Q4 (142–213)	37,681	1285	0.93	0.92 (0.85, 1.00)	853	0.88 (0.80, 0.97)	432	1.00 (0.87, 1.15)
Q5 (≥214)	37,005	1383	1.01	0.99 (0.92, 1.07)	911	0.95 (0.86, 1.04)	472	1.08 (0.95, 1.24)
P-trend[4]			0.76	0.97		0.63		0.52
Lutein/zeaxanthin (μg/d)								
Q1 (<1029)	31,846	1072	1.00	1.00	722	1.00	350	1.00
Q2 (1029–1519)	35,947	1262	1.02	1.02 (0.94, 1.10)	828	1.00 (0.91, 1.11)	434	1.06 (0.92, 1.22)
Q3 (1520–2080)	36,683	1375	1.08	1.07 (0.99, 1.16)	869	1.02 (0.92, 1.13)	506	1.18 (1.03, 1.36)
Q4 (2081–3085)	37,855	1370	1.03	1.02 (0.94, 1.10)	899	1.00 (0.91, 1.11)	471	1.05 (0.91, 1.20)
Q5 (≥3086)	37,923	1374	1.04	1.01 (0.94, 1.10)	912	1.01 (0.92, 1.12)	462	1.03 (0.89, 1.18)
P-trend[4]			0.60	0.91		0.86		0.69

[1] FFQ, food-frequency questionnaire; IRR, incidence rate ratio; Q, quintile.

[2] Adjusted for age and energy intake.

[3] Adjusted for age, time period, energy intake, parity, age at first birth, years since last birth, ever use of oral contraceptive and age at first use, BMI, smoking, current alcohol intake, multivitamin use, education, income, marital status, and region of residence in the United States.

[4] Derived from test for linear trend, modeling the quintile median as a continuous variable.

[5] Based on 15,320 women who completed FFQs in both 1995 and 2001. Because widespread folate fortification of US foods began in 1998, folate values from 1995 were not carried forward for those with missing 2001 FFQ data.

TABLE 4
Dietary fiber in relation to risk of uterine leiomyoma by method of diagnosis: the Black Women's Health Study (United States, 1997–2009)[1]

		Method of diagnosis						
		Ultrasonography or surgery			Ultrasonography		Surgery	
	Person-years	Cases	IRR[2]	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]	Cases	IRR (95% CI)[3]
Total fiber (g/d)								
Q1 (<9.1)	34,518	1226	1.00	1.00	799	1.00	427	1.00
Q2 (9.1–11.3)	36,851	1280	0.96	0.94 (0.87, 1.02)	835	0.95 (0.86, 1.04)	445	0.94 (0.82, 1.07)
Q3 (11.4–13.8)	37,928	1317	0.96	0.94 (0.87, 1.01)	860	0.93 (0.85, 1.03)	457	0.95 (0.83, 1.08)
Q4 (13.9–17.2)	37,904	1389	1.01	0.98 (0.91, 1.06)	908	0.98 (0.89, 1.08)	481	0.98 (0.86, 1.12)
Q5 (≥17.3)	37,110	1389	1.02	0.97 (0.89, 1.05)	931	0.98 (0.89, 1.08)	458	0.94 (0.82, 1.07)
P-trend[4]			0.23	0.84		0.91		0.58
Insoluble fiber (g/d)								
Q1 (<5.7)	34,201	1206	1.00	1.00	785	1.00	421	1.00
Q2 (5.7–7.1)	37,003	1274	0.95	0.95 (0.88, 1.02)	836	0.96 (0.87, 1.05)	438	0.93 (0.81, 1.06)
Q3 (7.2–8.8)	37,835	1328	0.97	0.95 (0.88, 1.02)	872	0.95 (0.86, 1.05)	456	0.94 (0.82, 1.07)
Q4 (8.9–11.2)	38,034	1411	1.02	1.00 (0.93, 1.08)	910	0.99 (0.90, 1.09)	501	1.02 (0.89, 1.16)
Q5 (≥11.3)	37,238	1379	1.02	0.96 (0.89, 1.04)	928	0.98 (0.89, 1.08)	451	0.92 (0.80, 1.06)
P-trend[4]			0.20	0.87		0.95		0.69
Soluble fiber (g/d)								
Q1 (<3.3)	34,595	1228	1.00	1.00	802	1.00	426	1.00
Q2 (3.3–4.0)	36,836	1299	0.98	0.97 (0.90, 1.05)	842	0.96 (0.87, 1.06)	457	0.98 (0.86, 1.12)
Q3 (4.1–4.8)	37,631	1318	0.97	0.96 (0.88, 1.03)	849	0.93 (0.85, 1.03)	469	1.00 (0.87, 1.14)
Q4 (4.9–5.9)	38,020	1383	1.01	0.98 (0.91, 1.06)	920	0.99 (0.90, 1.09)	463	0.96 (0.84, 1.10)
Q5 (≥6.0)	37,077	1377	1.02	0.98 (0.90, 1.06)	920	0.99 (0.90, 1.09)	457	0.95 (0.83, 1.08)
P-trend[4]			0.39	0.71		0.87		0.38

[1] IRR, incidence rate ratio; Q, quintile.
[2] Adjusted for age and energy intake.
[3] Adjusted for age, time period, energy intake, parity, age at first birth, years since last birth, ever use of oral contraceptive and age at first use, BMI, smoking, current alcohol intake, multivitamin use, education, income, marital status, and region of residence in the United States.
[4] Derived from test for linear trend, modeling the quintile median as a continuous variable.

1995 and 2001 FFQs) produced IRRs similar to those of the cumulative-average method (data not shown).

DISCUSSION

In the current study, fruit intake was inversely associated with UL risk, with the strongest reduction in risk observed for a high intake of citrus fruit. Dietary vitamin A was also inversely associated with UL risk, but only intake derived from animal products (eg, liver and dairy products) appeared to be related to the reduction in risk. Furthermore, total vitamin A intake derived from both diet and supplements was not associated appreciably with UL, and dietary vitamin A was not more strongly associated with UL among the nonsupplement users. These findings suggest that other components of the foods from which vitamin A is derived (eg, dairy products), rather than vitamin A itself, explain the reduction in risk. A previous publication from our cohort, in which we found an inverse association between dairy intake and UL risk (58), supports this explanation. Another explanation for this finding is that the absorption and bioavailability of vitamin A from animal sources is greater than that from vegetable or synthetic sources (59–61). Our null associations for UL risk in relation to carotenoids, including lycopene, agree with previous epidemiologic data on this association (36), but conflict with animal data indicating a protective effect of lycopene supplementation on leiomyoma in the Japanese quail (32, 33). However, serum concentrations of vitamin A in the quail increased in response to lycopene supplementation (32, 33), which suggests that the protective agent in both animal and human studies might be high serum concentrations of vitamin A as opposed to lycopene itself. It is unclear whether these animal data are relevant to well-nourished human populations in whom dietary vitamin A intake is not as strongly correlated with serum vitamin A concentrations (62–64), but this hypothesis could be tested directly in future studies.

Vitamin A intake might play an etiologic role via the retinoic acid pathway (65), which has been shown in several in vitro cell culture studies to have altered expression in UL compared with normal myometrium (66–68). Diet and supplements are the only sources of retinoids, because these compounds cannot be synthesized de novo (65). Once ingested, vitamin A is converted to more active compounds, such as retinoic acid (through which it exerts its multiple effects on tissue homeostasis), cell proliferation, differentiation, and apoptosis (65). Retinoic acid is a signaling molecule that can specify cell identities and control gene expression through the activation of specific nuclear receptors. Specifically, variation in the expression levels and function of retinoic acid nuclear receptors—retinoid acid receptor-α and retinoid X receptor-α—have been implicated in leiomyoma development and growth (69). Moreover, retinoids have shown efficacy in inhibiting the growth of leiomyoma in vitro (68, 70, 71) and in animal models (72).

To our knowledge, an inverse association between intake of citrus fruit and UL has not been reported previously. This finding, however, is consistent with that of a case-control study of surgical cases that reported an inverse association between greater fruit intake and UL risk (34). The amount of vitamin A in citrus fruit ranges from trace amounts in oranges, clementines, and tangerines to moderate concentrations in grapefruit and kumquats; thus, it is unlikely that the association between citrus fruit and UL is explained by vitamin A. A more likely explanation is that citrus fruit may reduce UL risk through pathways mediated by sex steroid hormones, antioxidants, or both. For example, grapefruit juice has been shown to affect the bioavailability of estradiol in vivo (73–75). In addition, citrus flavonoids are effective inhibitors of both estrogen receptor–negative MDA-MB-435 and estrogen receptor-positive MCF-7 human breast cancer cells in vitro (17, 76, 77), which indicates the possibility that nonhormonal mechanisms are at play. Further support for a nonhormonal mechanism of citrus flavonoids comes from data on MCF-7 human breast cancer cell lines in which only the inhibition of cell proliferation by genistein was reversed with the addition of estrogen. Other flavonoids (baicalein, galangin, hesperetin, naringenin, and quercetin) also appeared to exert their antiproliferative activity via some other mechanism (77). Epidemiologic studies investigating the relation of grapefruit or grapefruit juice intake to risk of other neoplasms, such as breast cancer, have been mixed, with some showing positive associations (78) and others finding inverse (79) or null (80, 81) associations.

Whereas citrus fruit intake was inversely associated with UL risk in both time periods assessed, citrus fruit juice was inversely associated with UL risk only during 2001–2009. We were unable to explain why overall intake of citrus fruit, but not citrus juice, would exhibit a more consistent inverse association with UL. Although some nutrients get lost in the process of converting citrus fruit to juice, the flavonoid constituents remain and the main difference is lack of dietary fiber. Our null results for dietary fiber suggest that this is an unlikely explanation for the differences in association. In addition, we were limited in our ability to explore whether the inverse association for citrus fruit was driven primarily by grapefruit or orange consumption. FFQ data on oranges were collected separately from grapefruit in 1995 but were then grouped together with tangerines in 2001, and neither the 1995 nor the 2001 FFQ collected data separately for orange and grapefruit juice. However, based solely on the 1997–2001 incident period, the magnitude of association comparing extreme intake categories was slightly stronger for grapefruits (IRR: 0.92) than for oranges (IRR: 0.96). National dietary data from black females (8, 82) indicate that 94% of citrus juice intake represents orange juice intake, which suggests that the association between citrus juice intake and UL likely reflects the effect of orange juice. Whether the inconsistent results for citrus juice and UL in our cohort are explained by a true null association between oranges and UL remains unclear.

The strengths of our study included the prospective design and the validation of diet and UL. With prospective data collection, error in the reporting of diet is not likely to depend on UL status. We averaged diet over 2 time periods and controlled for energy intake, both of which can reduce measurement error (51). We adjusted for several determinants of UL and socioeconomic status variables associated with diet. High cohort retention, which minimizes the potential for selection bias, was an additional strength. Few differences were found between those who were and were not lost to follow-up by fruit and vegetable intake or UL risk factors.

Although self-reported UL was confirmed in almost all participants from whom we obtained medical records, not all participants were screened for UL. Therefore, misclassification of true cases as noncases, particularly those with asymptomatic disease, was an important limitation. The inability to measure plasma concentrations of vitamins and carotenoids limited the extent to which we could make causal inferences about specific micronutrients. In addition, whereas numerous studies have shown moderate to good correlation between diet and plasma concentrations of vitamins and carotenoids (83–88), the correlation between dietary intake of vitamin A and blood retinol concentrations has been shown to be weak in well-nourished populations (62–64). National data show that black women have significantly lower serum retinol concentrations than do white women (89, 90) and are 3 times as likely as white women to have inadequate ($<$1.05 μmol/L) retinol concentrations (90), which indicates that correlations between dietary vitamin A and serum retinol concentrations in our cohort may be stronger than those in the general US population.

Although the BWHS included a self-selected sample with higher levels of education than the general black population, FFQ estimates for fruit and vegetable intake were consistent with national data on black adults (8, 9), and prevalence estimates of UL risk factors (eg, age at menarche and parity) were similar to those found in national studies (91). These observations—coupled with the fact that the associations did not vary appreciably by other covariates—suggest that our findings should apply to a larger group of black women.

In summary, we found that a high intake of fruit, particularly citrus fruit, was inversely associated with UL risk among black women. An inverse association was also found for dietary intake of vitamin A derived from animal but not vegetable sources. Additional studies are needed to confirm our results.

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The authors' responsibilities were as follows—LR and JRP: designed the parent study and directed its overall implementation, including quality assurance and control; LAW: designed and directed the research project based on diet and UL; SKK: performed the validation study of diet in our cohort; RGR and DAB: managed and analyzed the data; RGR: performed the statistical analyses; and LAW: conducted the literature review, took the lead in drafting the manuscript for publication, and had primary responsibility for the final content of the manuscript. All authors contributed to interpreting the results, drafting the article, and revising it critically for intellectual content. None of the authors declared a conflict of interest.

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