Prospective study of dietary fat and risk of uterine leiomyomata[1–4]

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ABSTRACT

Background: Uterine leiomyomata (UL) are the primary indication for hysterectomy and are 2–3 times more common in black than white women. High dietary fat intake has been associated with increased endogenous concentrations of estradiol, a sex steroid hormone that is known to influence UL risk.

Objective: We assessed the relation of dietary fat intake (total, subtypes, and selected food sources) with UL incidence.

Design: Data were from the Black Women's Health Study, a prospective cohort study. Over an 8-y period (2001–2009), 12,044 premenopausal women were followed for a first diagnosis of UL. Diet was assessed via a food-frequency questionnaire in 2001. Cox regression models were used to compute incidence rate ratios (IRRs) and 95% CIs with adjustment for potential confounders.

Results: During 75,687 person-years of follow-up, there were 2695 incident UL cases diagnosed by ultrasound (n = 2191) or surgery (n = 504). Intakes of total fat and fat subtypes were not appreciably associated with UL risk overall, although statistically significant associations were observed for specific saturated (inverse) and monounsaturated and polyunsaturated (positive) fatty acids. With respect to polyunsaturated fats, the IRR for the highest compared with lowest quintiles of marine fatty acid intake [the sum of omega-3 (n−3) polyunsaturated fatty acids eicosapentanoic acid, docosapentaenoic acid, and docosahexaenoic acid] was 1.18 (95% CI: 1.05, 1.34; P-trend = 0.005). The IRR for the highest compared with lowest categories of dark-meat fish consumption was 1.13 (95% CI: 1.00, 1.28).

Conclusions: In US black women, the most consistent associations of fat intake with UL were small increases in risk associated with intakes of long-chain omega-3 fatty acids. Future studies are warranted to confirm these findings and elucidate which components of fatty foods, if any, are related to UL risk. *Am J Clin Nutr* 2014;99:1105–16.

INTRODUCTION

Uterine leiomyomata (UL)[5], or fibroids, are benign neoplasms of the myometrium and are clinically recognized in 30% of reproductive-aged women (1). UL are the primary indication for hysterectomy in women of all ages in the United States (2–4) and account for up to $34 billion each year in medical expenses and lost productivity (5). UL incidence is 2–3 times higher in black than white women, but reasons for the health disparity are unclear (6–8).

Sources of dietary fat differ for black and white women. For example, compared with white women, black women consume relatively more fat from meat sources and less fat from dairy foods (9). Also, unlike trends in fat consumption for the US population as a whole, national survey data indicated a significant increase in total fat consumption in black adults during the past decade (from 32.1% of kilocalories in 1999–2000 to 34.4% of kilocalories in 2007–2008 in black women), and a similar upward trend was also observed for saturated fat intake (10).

In vitro and in vivo studies have suggested that UL are responsive to sex steroid hormones, including estradiol and progesterone (11, 12). The literature on the role of dietary fat intake and endogenous hormones in premenopausal women has been conflicting. Although most dietary fat intervention studies in premenopausal women have shown statistically significant reductions in serum estradiol concentrations with reduced dietary fat intake (13, 14), a recent cross-sectional observational study showed little evidence of any association between total fat intake (or a low-fat and high-fiber diet) and estradiol (15), and another cross-sectional study showed plasma estradiol concentrations were positively associated with saturated fat intake but not total fat intake (16). Studies of dietary fat and plasma estrone, which is a less potent form of estrogen, have shown positive correlations (14, 17).

In the current study, we prospectively evaluated the association of UL with dietary intakes of total fat, subgroups of fatty acids (saturated, monounsaturated, polyunsaturated, and *trans* unsaturated), and individual fatty acids in a large cohort of premenopausal African American women. Previous studies of the association between dietary fat and UL risk have been limited. A case-control study that investigated UL risk in relation to butter, margarine, and oil (among other foods) showed little evidence of an association (18), and a cross-sectional study showed no association between total fat intake and UL risk (19). We could not

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[5] Abbreviations used: AA, arachidonic acid; DPA, docosapentaenoic acid; FFQ, food-frequency questionnaire; IRR, incidence rate ratio; MFA, marine fatty acid; PCB, polychlorinated biphenyl; UL, uterine leiomyomata.

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identify any prospective studies of dietary fat and UL risk. Epidemiologic studies of other hormone-dependent conditions showed that dietary fat is associated with increased risk of endometriosis (*trans* fat only) (20) and cancers of the endometrium (21–27), prostate (28), and ovary (29). Thus, we hypothesized that higher intake of dietary fat would be associated with increased risk of UL after adjustment for energy, other dietary factors, and other potential confounders. We also explored the association of UL with intakes of dark-meat fish and other fish because the intake of long-chain omega-3 fatty acids from these sources had been of interest with respect to risk of hormone-dependent cancers (30, 31).

SUBJECTS AND METHODS

Study population

The Black Women's Health Study is an ongoing US prospective cohort study of 59,000 African American women aged 21–69 y who enrolled by completing health questionnaires in 1995 (32). Participants update their exposure data and medical histories every 2 y by using mailed questionnaires. Study participants reside in >17 states, with the majority of subjects reside 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 2001 follow-up questionnaire, women reported whether they had been diagnosed 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 with other surgeries (eg, myomectomy), and "ultrasound" and "surgery" were asked as 2 separate questions. Cases were classified as surgically confirmed if they reported a diagnosis by "ultrasound/hysterectomy" (questionnaires before 2003) or "surgery" (questionnaires in 2003 and after) and also reported "hysterectomy" under a separate question on that questionnaire.

Our outcome definition included cases diagnosed by surgery or ultrasound because surgically confirmed cases represent only 10–30% of cases for whom ultrasound is available and because studies of such cases may spuriously identify risk factors associated with disease severity or preference for treatment (33). Ultrasound has high sensitivity (99%) and specificity (91%) relative to histologic evidence (34, 35). To maximize the specificity of the UL classification, cases confirmed by pelvic examination only were treated as noncases because their diagnoses could have represented another gynecologic pathology (36).

Assessment of diet

The usual diet in the past year was estimated in 2001 with an 85-item modified version of the National Cancer Institute–Block food-frequency questionnaire (FFQ) (37, 38). The 2001 FFQ was an expanded version of the 1995 FFQ validated in our cohort (38) and included items that women had written in on the 1995 questionnaire. The 2001 FFQ contained a greater number of items about fatty foods, including dark-meat fish compared with other fish and seafood, which permitted a more valid assessment of fat intake. Frequency responses for food items ranged from never or <1 serving/mo to ≥2 servings/d. Participants were asked to specify a small, medium, large, or super-size portion size. A medium portion size was defined for each item [eg, one-half cup (102 g) of tuna fish], and small, large, and super-size servings were weighted as 0.5, 1.5, and 2 times a medium serving size, respectively. Nutrient intake was computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portion.

We used National Cancer Institute's Diet*Calc software (version 1.4.1) (39) to estimate the consumption (in g) for all types of fat, including *trans* unsaturated, monounsaturated, and polyunsaturated fats as well as individual types of fatty acids. Fish consumption was ascertained by using FFQ questions about the consumption of the following foods: dark-meat fish, including sardines, mackerel, salmon, and bluefish; fried fish or a fish sandwich; other fish (broiled or baked); shellfish (eg, shrimp, crab, and lobster); and tuna fish (in sandwiches, salad, or a casserole). We created a composite variable called marine fatty acids (MFAs) that summed up grams of fatty acid intake from EPA, docosapentaenoic acid (DPA), and DHA long-chain omega-3 fatty acids (40).

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, geographic region, and medical illnesses (eg, diabetes). We asked about household income in 2003 and the recency of a pelvic examination and ultrasound screening in 2007. Reproductive factors, weight, smoking, marital status, physical activity, and region were updated on follow-up questionnaires and modeled as time-varying covariates in analyses.

On the 2001 FFQ, we asked about the frequency of meals eaten at restaurants (eg, burgers and fried chicken), intake of dairy products [milk, regular ice cream, low-fat ice cream, frozen yogurt, yogurt, cheese, and cheese spreads (not cottage cheese)] (41), and intake of individual fruits and vegetables (42). Intakes of fruit and vegetables and dairy products were considered potential confounders on the basis of previously reported inverse associations with UL in this cohort (41, 42). At baseline and on all follow-up questionnaires, women reported whether they were taking supplements such as fish oil, cod liver oil, or flax seed oil ≥3 d/wk and the names of the supplements. Intakes of vitamins A, C, E, β carotene, folate, and multivitamin supplements were not included as covariates on the basis of previous findings of a lack of association with UL incidence in this cohort (42) and in preliminary analyses related to the fat-UL association.

Validation studies

UL

We assessed the accuracy of self-report in a random sample of 248 cases diagnosed by ultrasound or surgery. Cases were mailed supplemental questionnaires regarding their initial date of diagnosis, method or methods of confirmation, symptoms, and

treatment and were asked for permission to review their medical records. We obtained medical records from 127 of 128 women who gave us permission and confirmed the self-report in 122 women (96%). In 188 women (76%) who provided supplemental survey data, 71% of participants reported UL-related symptoms before diagnosis, and 87% of participants reported their condition came to clinical attention because they sought treatment of symptoms or a tumor was palpable during a routine pelvic examination. There were no appreciable differences between women who did and did not release medical records with respect to UL risk factors (43).

Diet

We conducted a validation study of the 1995 FFQ in 1996–1998 (38). Approximately 400 Black Women's Health Study 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's correlation coefficients for the FFQ compared with the mean of combined diet records and recalls for total fat and saturated fat were 0.45 and 0.53, respectively (38).

Restriction criteria

Of the 47,744 subjects who responded to the 2001 questionnaire, we excluded postmenopausal women (n = 17,659), in whom new diagnoses of UL are rare (44), women with a diagnosis of UL before 2001 (n = 13,108), cases without a year of diagnosis (n = 75), women lost to follow-up (n = 726), women with missing covariate data (n = 348), and women with implausible energy intake (<400 or ≥3800 kcal/d) or >10 missing items on the baseline FFQ (n = 3784), which left 12,044 women followed from 2001 through 2009. Those women excluded because of missing or incomplete data were less educated and more likely to smoke than women who were included but were similar with respect to parity, age at menarche, and other UL risk factors (data not shown).

Data analysis

We defined cases as women who reported a first diagnosis of UL confirmed by ultrasound or surgery. Person-years were calculated from March 2001 until UL diagnosis, menopause, death, loss to follow-up, or March 2009 (end of follow-up), whichever came first. Cox regression models, which were stratified by age and time period (ie, questionnaire cycle), were used to estimate incidence rate ratios (IRRs) and 95% CIs for associations of interest (model 1).

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 (45). We analyzed data on total dietary fat, subtypes of fat (saturated, polyunsaturated, monounsaturated, and *trans* unsaturated), and individual fatty acids. We also assessed the ratio of omega-6 to omega-3 fats in relation to UL risk. There has been evidence that concentrations of omega-6 fats have increased and omega-3 fats have decreased over time in Western diets (46); omega-3 fatty acids have been shown to have antiinflammatory effects, whereas omega-6 fatty acids [linoleic acid and arachidonic acid (AA)] tend to be proinflammatory (47). In addition, we assessed the ratio of MFAs with AA only because of lack of consensus that linoleic acid is proinflammatory and observations that MFAs (EPA and DHA) decrease the production of inflammatory eicosanoids from AA (48). We created time-varying indicator variables for any use of fish-oil supplements (including fish oil, omega-3 fatty acids, cod liver oil, and DHA) and any use of flaxseed oil. Fish-oil supplements are a major source of EPA and DHA omega-3 fatty acids. Flaxseed oil contains both omega-3 and omega-6 fatty acids but is a major source of α-linolenic acid (18:3 omega-3 fatty acid), which the body (inefficiently) converts into EPA and DHA.

A covariate was included in multivariable analyses if it was a known or suspected confounder of the association between dietary fat and UL. 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 ≥1 births), age at first birth (y), years since last birth (<5, 5–9, 10–14, or ≥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 ≥35), smoking (current, past, or never), current alcohol use (<1, 1–6, or ≥7 drinks/wk), education (≤12, 13–15, 16, or ≥17 y), marital status (married or partnered; divorced, separated, or widowed; or single), occupation (white collar, nonwhite collar, unemployed, or missing), household income (≤$25,000, $25,001–$50,000, $50,001–$100,000, >$100,000, or missing), and geographic region of residence (South, Northeast, Midwest, and West) (model 2). A second multivariable model (model 3) was run to further adjust for intakes of dairy (0, 1, 2, 3, or ≥4 servings/d), dark-meat fish (quintiles), other fish or seafood (quintiles), fruit and vegetables (0, 1, 2–3, or ≥4 servings/d), and fast food (<3, 2–5. 6–8, 9–17, or ≥18 visits/mo). Control for fish-oil or flax seed–oil supplement use made little difference in effect estimates of total and subtypes of fats examined. IRRs from model 3 generally attenuated model 2 IRRs by <5%. Out of concern that we might have been overcontrolling for foods that made major contributions to intakes of various fatty acids, we present estimates from models 1 and 2 only.

We also analyzed UL risk in relation to fish consumption by comparing dark-meat fish with all other fish items. Dark-meat fish is particularly rich in long-chain omega-3 fatty acids and also more likely to contain environmental toxicants (49), which have been associated with UL (50). We ran the same multivariable models described previously (models 2 and 3) except that covariates did not include the fish variable or variables of interest in model 3.

Tests for trend were conducted by modeling a continuous version of the exposure variable assigned the median value of each category (51). We assessed whether results were modified by education or pelvic examination frequency or differed across confirmation type. 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 each 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 ≥35 y) and time period (2001–2005 compared with 2005–2009). Analyses were performed with SAS statistical software (version 9.2) (52).

RESULTS

Total fat intake was positively associated with overweight, current smoking, alcohol consumption, saturated fat intake, and restaurant food intake and inversely associated with fruit and vegetable consumption and residence in the Northeast (**Table 1**). Intake of dark-meat fish was positively associated with fruit and vegetable intake and residence in the Northeast and inversely associated with BMI and fast-food consumption, whereas other fish and seafood consumption was positively associated with BMI, fast-food consumption, and current smoking (**Table 2**).

During 75,687 person-years of follow-up, 2695 incident UL cases diagnosed by ultrasound (n = 2191) or surgery (n = 504) were reported (**Table 3**). We observed no association between total fat intake and UL risk (IRR: 1.09; 95% CI: 0.97, 1.23). Likewise, there were no clear patterns for UL risk in relation to total intakes of saturated fat, polyunsaturated fat, total *trans* unsaturated fat, or the ratio of omega-6 to omega-3 fat and UL risk. A marginally significant positive association was shown for monounsaturated fat intake (highest compared with lowest quintiles: IRR, 1.15; 95% CI, 1.02, 1.30; P-trend = 0.07), but there was little evidence of a dose-response relation. In stratified analyses, IRRs did not vary appreciably by time period, pelvic examination frequency, education, method of UL confirmation, or age (<35 compared with ≥35 y) (data not shown).

When we examined individual fatty acids that comprised larger groupings of fat intake (**Table 4**), we found weak inverse associations for the saturated fats butyric acid (P-trend = 0.02), caproic acid (P-trend = 0.009), caprylic acid (P-trend = 0.02), and myristic acid (P-trend = 0.01), with IRRs for highest compared with lowest quintiles of intake of 0.89 (95% CI: 0.79, 1.00), 0.86 (95% CI: 0.76, 0.97), 0.88 (95% CI: 0.78, 0.99), and 0.86 (95% CI: 0.76, 0.97), respectively. Of the monounsaturated fats, only erucic acid was positively associated with UL risk (highest compared with lowest quintiles: IRR, 1.17; 95% CI, 1.04, 1.32; P-trend = 0.006).

Within the category of polyunsaturated fats, we showed significant positive trends for each of the MFAs and UL risk. Specifically, IRRs were 1.21 (95% CI: 1.07, 1.37), 1.19 (95% CI: 1.06, 1.35), and 1.15 (95% CI: 1.02, 1.30) for highest compared with lowest quintiles of EPA, DPA, and DHA intakes, respectively (P-trend ≤ 0.01 for all). Intake of all MFAs (ie, combined intakes of EPA, DPA, and DHA) was also positively associated with UL risk (highest compared with lowest quintiles: IRR, 1.18; 95% CI, 1.05, 1.34; P-trend = 0.005).

TABLE 1
Characteristics of 12,044 premenopausal women by categories of total fat intake in the Black Women's Health Study, 2001[1]

	Quintiles of total dietary fat (g/d)					
	<53	53–59	60–64	65–69	≥70	P-trend
Women (n)	2409	2406	2389	2382	2456	—
Age (y)	37.8 ± 0.6[2]	37.7 ± 0.6	37.5 ± 0.6	38.0 ± 0.6	38.5 ± 0.6	<0.001
BMI (kg/m^2)	28.2 ± 3.0	28.8 ± 3.1	29.2 ± 3.2	29.6 ± 3.5	30.0 ± 3.6	<0.000
Age at menarche (y)	12.3 ± 0.7	12.3 ± 0.7	12.4 ± 0.7	12.4 ± 0.7	12.3 ± 0.7	0.84
Ever parous (%)	59	60	64	63	60	0.33
Recent pelvic examination in 2007 (%)	90	91	90	89	89	0.04
Age at first OC[3] use (y)	19.4 ± 1.8	19.6 ± 1.8	19.2 ± 1.7	19.0 ± 1.6	19.0 ± 1.7	<0.001
Current smoker (%)	10	10	11	13	14	<0.001
Alcohol intake (drinks/wk)	1.1 ± 1.1	1.3 ± 1.2	1.3 ± 1.2	1.5 ± 1.3	1.9 ± 1.7	<0.001
Energy intake (kcal/d)	1454 ± 296	1537 ± 311	1558 ± 305	1540 ± 309	1474 ± 309	0.37
Total dietary fat (g/d)	44.2 ± 9.9	56.9 ± 12.1	63.7 ± 13.0	68.5 ± 14.4	74.8 ± 16.1	<0.001
Total dietary saturated fat (g/d)	13.7 ± 3.4	18.0 ± 4.1	20.2 ± 4.5	21.9 ± 5.0	23.6 ± 5.4	<0.001
Dairy intake (servings/d)	1.0 ± 0.6	1.0 ± 0.5	1.0 ± 0.5	0.9 ± 0.4	0.8 ± 0.4	<0.001
Fruit and vegetable intake (servings/d)	2.7 ± 0.9	2.2 ± 0.7	2.0 ± 0.6	1.8 ± 0.6	1.6 ± 0.6	<0.001
Fast-food restaurant meals (≥18/mo) (%)	10	15	18	19	22	<0.001
Marine fatty acids (g/d)	0.21 ± 0.08	0.23 ± 0.08	0.24 ± 0.08	0.24 ± 0.08	0.24 ± 0.08	<0.001
Current use of fish-oil supplements (%)	0.8	0.7	1.3	0.9	0.8	0.82
Current use of flaxseed-oil supplements (%)	0.5	0.3	0.5	0.3	0.5	0.85
Marital status: married (%)	41	43	44	44	41	0.70
Educational attainment (y)	15.1 ± 0.7	15.1 ± 0.7	15.0 ± 0.7	15.0 ± 0.8	15.0 ± 0.8	<0.001
Household income in 2003 (%)						
<$50,000	41	39	41	41	44	0.11
$50,001–$100,000	40	41	40	41	38	0.47
>$100,000	19	20	19	18	18	0.26
Region of residence in the United States (%)						
South	34	33	36	34	36	0.13
Northeast	30	27	26	24	21	<0.001
Midwest	20	22	22	22	23	0.07
West	16	18	16	20	20	<0.001

[1] Characteristics were ascertained in 2001 unless otherwise noted. Values were standardized to the age distribution of the cohort in 2001. P values were determined from the age-adjusted test for linear trend across all quintiles.

[2] Mean ± SD (all such values).

[3] OC, oral contraceptive.

TABLE 2
Characteristics of 12,044 premenopausal women by categories of dark-meat fish and other fish and seafood in the Black Women's Health Study, 2001[1]

	Dark-meat fish (servings/wk)						Other fish and seafood (servings/wk)					
	None	<0.3	0.3–0.6	0.7–0.9	≥1.0	*P*-trend	None	<0.9	0.9–1.6	1.7–2.5	≥2.6	*P*-trend
Women (*n*)	4643	753	2365	2139	2144	—	599	2865	2782	2872	2926	—
Age (y)	37.2 ± 0.6[2]	38.3 ± 0.6	38.0 ± 0.6	38.2 ± 0.6	38.8 ± 0.6	<0.001	36.6 ± 0.6	37.4 ± 0.6	38.2 ± 0.6	38.0 ± 0.6	38.2 ± 0.6	<0.001
BMI (kg/m^2)	29.6 ± 3.4	28.3 ± 3.1	29.2 ± 3.2	29.0 ± 3.2	28.6 ± 3.2	<0.001	28.3 ± 3.2	28.8 ± 3.2	29.2 ± 3.3	29.5 ± 3.4	29.4 ± 3.3	<0.001
Age at menarche (y)	12.3 ± 0.7	12.4 ± 0.7	12.3 ± 0.7	12.3 ± 0.7	12.4 ± 0.7	0.98	12.2 ± 0.7	12.3 ± 0.7	12.3 ± 0.7	12.3 ± 0.7	12.4 ± 0.7	0.04
Ever parous (%)	62	65	61	62	57	0.006	54	63	63	62	59	0.02
Recent pelvic examination in 2007 (%)	90	87	90	90	92	0.008	89	90	90	90	91	0.22
Age at first OC[3] use (y)	19.2 ± 1.7	19.2 ± 1.6	19.3 ± 1.7	19.1 ± 1.7	19.4 ± 1.8	0.26	19.7 ± 1.8	19.3 ± 1.8	19.3 ± 1.7	19.1 ± 1.7	19.2 ± 1.8	0.001
Current smoker (%)	11	13	12	13	11	0.48	8	11	12	11	13	<0.001
Alcohol intake (drinks/wk)	1.3 ± 1.3	1.6 ± 1.6	1.4 ± 1.3	1.5 ± 1.3	1.6 ± 1.4	<0.001	1.1 ± 1.2	1.2 ± 1.3	1.5 ± 1.4	1.5 ± 1.3	1.6 ± 1.4	<0.001
Energy intake (kcal/d)	1434 ± 305	1292 ± 273	1467 ± 298	1558 ± 291	1761 ± 316	<0.001	1306 ± 297	1254 ± 268	1392 ± 274	1553 ± 285	1884 ± 319	<0.001
Total dietary fat (g/d)	58.3 ± 14.0	52.4 ± 12.5	60.0 ± 13.7	63.5 ± 13.3	72.0 ± 14.7	<0.001	51.1 ± 13.0	50.1 ± 12.2	56.8 ± 12.6	63.7 ± 13.1	77.7 ± 15.0	<0.001
Total dietary saturated fat (g/d)	18.7 ± 4.8	16.8 ± 4.4	19.2 ± 4.7	20.1 ± 4.7	21.9 ± 4.9	<0.001	16.1 ± 4.4	16.1 ± 4.2	18.2 ± 4.4	20.3 ± 4.6	24.0 ± 5.1	<0.001
Dairy intake (servings/d)	0.9 ± 0.5	0.9 ± 0.6	1.0 ± 0.5	1.0 ± 0.5	1.1 ± 0.5	<0.001	0.8 ± 0.5	0.8 ± 0.4	0.9 ± 0.5	1.0 ± 0.5	1.1 ± 0.5	<0.001
Fruit and vegetable intake (servings/d)	1.8 ± 0.7	1.8 ± 0.7	2.0 ± 0.6	2.2 ± 0.6	2.8 ± 0.8	<0.001	2.1 ± 0.9	1.7 ± 0.7	1.8 ± 0.6	2.1 ± 0.6	2.7 ± 0.8	<0.001
Fast-food restaurant meals (≥18/mo) (%)	18	19	16	16	16	0.006	12	13	15	18	22	<0.001
Marine fatty acids (g/d)	0.13 ± 0.04	0.17 ± 0.04	0.20 ± 0.04	0.28 ± 0.04	0.48 ± 0.09	<0.001	0.06 ± 0.04	0.13 ± 0.04	0.19 ± 0.04	0.25 ± 0.05	0.39 ± 0.09	<0.001
Current use of fish-oil supplements (%)	0.6	0.6	0.9	1.1	1.2	0.008	0.2	0.5	1.0	1.1	1.0	0.009
Current use of flaxseed-oil supplements (%)	0.3	0.2	0.3	0.4	0.7	0.11	0.2	0.3	0.4	0.6	0.4	0.18
Marital status: married (%)	43	40	43	43	42	0.72	41	43	43	44	40	0.10
Educational attainment (y)	14.9 ± 0.8	14.7 ± 0.8	15.0 ± 0.8	15.1 ± 0.7	15.2 ± 0.7	<0.001	15.2 ± 0.7	15.0 ± 0.8	15.0 ± 0.8	15.0 ± 0.8	15.1 ± 0.7	0.25
Household income in 2003 (%)												
≤$50,000	42	48	40	30	38	<0.001	37	43	42	41	40	0.18
$50,001–$100,000	42	37	40	38	41	0.13	43	41	39	40	41	0.65
>$100,000	16	15	20	22	21	<0.001	19	17	19	20	20	0.04
Region of residence in the United States (%)												
South	35	38	35	33	34	0.19	30	33	35	36	36	0.003
Northeast	21	24	25	29	32	<0.001	23	24	25	24	29	<0.001
Midwest	25	20	22	21	17	<0.001	24	24	22	23	19	<0.001
West	19	18	18	17	17	0.001	23	19	18	17	16	<0.001

[1] Characteristics were ascertained in 2001 unless otherwise noted. Values were standardized to the age distribution of the cohort in 2001. *P* values were determined from the age-adjusted test for linear trend across all quintiles.

[2] Mean ± SD (all such values).

[3] OC, oral contraceptive.

TABLE 3
Risk of ultrasound- or surgery-confirmed uterine leiomyomata in relation to intake of total fat and fat subtypes in the Black Women's Health Study, 2001–2009[1]

	Quintile of intake					
Summary variables of fat intake by category	1	2	3	4	5	*P*-trend
Total fat						
Quintile median (g)	48	56	62	67	75	—
Cases (*n*)	522	529	554	530	560	—
Person-years	15,168	15,120	15,143	15,136	15,110	—
Age- and energy-adjusted IRR (95% CI)	1.00[2]	1.02 (0.90, 1.15)	1.07 (0.95, 1.21)	1.02 (0.90, 1.15)	1.08 (0.96, 1.21)	0.26
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.02 (0.91, 1.16)	1.08 (0.96, 1.22)	1.04 (0.92, 1.17)	1.09 (0.97, 1.23)	0.17
Total saturated fat						
Quintile median (g)	14	17	19	22	25	—
Cases (*n*)	543	534	561	535	515	—
Age- and energy-adjusted IRR (95% CI)	1.00[2]	0.98 (0.87, 1.10)	1.03 (0.91, 1.16)	0.98 (0.87, 1.10)	0.93 (0.82, 1.05)	0.25
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.00 (0.88, 1.12)	1.06 (0.94, 1.19)	1.02 (0.90, 1.15)	0.97 (0.85, 1.09)	0.61
Total monounsaturated fat						
Quintile median (g)	17	21	23	25	29	—
Cases (*n*)	510	555	529	527	573	—
Age- and energy-adjusted IRR (95% CI)	1.00[2]	1.09 (0.97, 1.23)	1.04 (0.92, 1.17)	1.04 (0.92, 1.17)	1.12 (1.00, 1.27)	0.15
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.12 (0.99, 1.26)	1.07 (0.95, 1.21)	1.07 (0.95, 1.21)	1.15 (1.02, 1.30)	0.07
Total polyunsaturated fat						
Quintile median (g)	9.8	12.0	13.6	15.4	18.7	—
Cases (*n*)	507	551	556	522	555	—
Age- and energy-adjusted IRR (95% CI)	1.00[2]	1.09 (0.97, 1.23)	1.11 (0.99, 1.26)	1.05 (0.93, 1.19)	1.12 (0.99, 1.26)	0.18
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.09 (0.97, 1.23)	1.12 (0.99, 1.26)	1.04 (0.92, 1.18)	1.10 (0.97, 1.24)	0.34
Total omega-6 fatty acid intake						
Quintile median (g)	8.6	10.5	12.0	13.6	16.6	—
Cases (*n*)	516	553	548	523	555	—
Age- and energy-adjusted IRR (95% CI)	1.00[2]	1.08 (0.96, 1.22)	1.08 (0.95, 1.21)	1.03 (0.91, 1.17)	1.10 (0.98, 1.24)	0.25
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.08 (0.96, 1.22)	1.08 (0.95, 1.21)	1.02 (0.91, 1.16)	1.08 (0.96, 1.22)	0.44
Total omega-3 fatty acid intake						
Quintile median (g)	0.96	1.2	1.4	1.6	2.0	—
Cases (*n*)	515	522	541	555	562	—
Age- and energy-adjusted IRR (95% CI)	1.00[2]	1.02 (0.90, 1.15)	1.06 (0.94, 1.19)	1.10 (0.97, 1.24)	1.12 (1.00, 1.27)	0.03
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.03 (0.91, 1.17)	1.07 (0.94, 1.20)	1.09 (0.97, 1.23)	1.11 (0.98, 1.25)	0.07
Ratio of omega-6 to omega-3 fatty acids						
Quintile median (g)	6.8	8.0	8.6	9.4	10.8	—
Cases (*n*)	557	559	507	548	524	—
Age- and energy-adjusted IRR (95% CI)	1.00[2]	1.00 (0.89, 1.13)	0.90 (0.80, 1.01)	0.96 (0.86, 1.09)	0.93 (0.83, 1.05)	0.20
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.04 (0.92, 1.17)	0.93 (0.82, 1.05)	0.99 (0.88, 1.12)	0.95 (0.84, 1.07)	0.33
Total *trans* fats						
Quintile median (g)	3.0	3.8	4.3	4.8	5.8	—
Cases (*n*)	527	527	531	544	560	—
Age- and energy-adjusted IRR (95% CI)	1.00[2]	1.00 (0.89, 1.13)	1.01 (0.90, 1.14)	1.03 (0.91, 1.16)	1.07 (0.95, 1.20)	0.24
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.02 (0.90, 1.15)	1.02 (0.91, 1.16)	1.04 (0.92, 1.17)	1.07 (0.95, 1.21)	0.22

[1] Fatty acid was classified according to the isomer that was most prevalent in the diet. Age- and energy-adjusted IRRs (95% CIs) were adjusted for age, questionnaire cycle (2-y period), and energy intake. Multivariable-adjusted IRRs (95% CIs) were adjusted for age, time period, energy intake, age at menarche, parity, age at first birth, years since last birth, ever use of oral contraceptives, age at first oral contraceptive use, alcohol, smoking, BMI, education, occupation, income, marital status, and US region of residence. *P*-test for trend values were derived from the test for linear trend by modeling the quintile median as a continuous variable. IRR, incidence rate ratio.

[2] Reference group.

The MFA-UL association was similar across strata of age (<35 compared with ≥35 y) and in women with a recent pelvic examination and did not vary materially by diagnostic method (ultrasound compared with surgery). IRRs for the highest compared with lowest quintiles of MFA intake were 1.39 (95% CI: 1.11, 1.75; *P*-trend = 0.01) in women with BMI <25 and 1.11 (95% CI: 0.96, 1.28; *P*-trend = 0.11) in women with BMI ≥25 (*P*-interaction by BMI = 0.23),and were 1.25 (95% CI: 1.05, 1.49; *P*-trend = 0.01) in college-educated women and 1.10 (95% CI: 0.91, 1.31; *P*-trend = 0.24) in women with less than a college education (*P*-interaction by education = 0.27). When we omitted DPA from the composite MFA variable out of concern that fish and shellfish are less-dominant sources of DPA, results were similar (highest compared with lowest quintiles of EPA and DHA combined: IRR, 1.17; 95% CI, 1.04, 1.32; *P*-trend = 0.012). The IRR for the comparison of highest compared with lowest quintiles of the MFA:AA ratio was 1.10 (95% CI: 0.97, 1.24; *P*-trend = 0.16).

TABLE 4
Risk of ultrasound- or surgery-confirmed uterine leiomyomata in relation to intake of individual fatty acids: the Black Women's Health Study, 2001–2009[1]

	Quintile of intake					
	1	2	3	4	5	*P*-trend
Saturated fats						
Fatty acid 4:0 (butyric acid)						
Quintile median (g)	0.14	0.23	0.31	0.41	0.59	—
Cases (*n*)	564	569	528	517	490	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.01 (0.90, 1.13)	0.95 (0.85, 1.08)	0.94 (0.83, 1.05)	0.89 (0.79, 1.00)	0.02
Fatty acid 6:0 (caproic acid)						
Quintile median (g)	0.07	0.12	0.16	0.22	0.32	—
Cases (*n*)	559	571	531	528	474	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.00 (0.89, 1.13)	0.97 (0.86, 1.09)	0.96 (0.85, 1.09)	0.86 (0.76, 0.97)	0.009
Fatty acid 8:0 (caprylic acid)						
Quintile median (g)	0.06	0.09	0.12	0.16	0.22	—
Cases (*n*)	578	563	534	505	498	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	0.96 (0.85, 1.08)	0.94 (0.83, 1.05)	0.88 (0.78, 0.99)	0.88 (0.78, 0.99)	0.02
Fatty acid 10:0 (capric acid)						
Quintile median (g)	0.12	0.19	0.26	0.33	0.46	—
Cases (*n*)	556	588	509	530	487	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.06 (0.94, 1.19)	0.93 (0.82, 1.05)	0.98 (0.87, 1.10)	0.89 (0.79, 1.01)	0.03
Fatty acid 12:0 (lauric acid)						
Quintile median (g)	0.24	0.34	0.43	0.54	0.74	—
Cases (*n*)	546	550	542	539	489	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	0.98 (0.87, 1.10)	1.00 (0.89, 1.13)	0.98 (0.86, 1.10)	0.89 (0.79, 1.01)	0.07
Fatty acid 14:0 (myristic acid)						
Quintile median (g)	0.81	1.1	1.4	1.7	2.3	—
Cases (*n*)	566	578	511	548	476	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.01 (0.90, 1.14)	0.91 (0.81, 1.03)	0.98 (0.88, 1.11)	0.86 (0.76, 0.97)	0.01
Fatty acid 16:0 (palmitic acid)						
Quintile median (g)	8.2	9.9	11	12	13	—
Cases (*n*)	550	522	538	539	542	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	0.96 (0.85, 1.08)	1.00 (0.89, 1.13)	1.02 (0.90, 1.15)	1.00 (0.88, 1.12)	0.78
Fatty acid 18:0 (stearic acid)						
Quintile median (g)	3.6	4.4	5.0	5.6	6.5	—
Cases (*n*)	541	516	538	565	527	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	0.96 (0.85, 1.09)	1.03 (0.91, 1.16)	1.08 (0.95, 1.21)	0.99 (0.87, 1.11)	0.64
Monounsaturated fats						
Fatty acid 16:1 (palmitoleic acid)						
Quintile median (g)	0.75	0.99	1.16	1.32	1.59	—
Cases (*n*)	539	521	536	521	575	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	0.99 (0.88, 1.12)	1.03 (0.92, 1.17)	0.98 (0.87, 1.11)	1.09 (0.97, 1.23)	0.19
Fatty acid 18:1 (oleic acid omega-9)						
Quintile median (g)	16.1	19.4	21.5	23.7	26.7	—
Cases (*n*)	515	539	542	532	565	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.07 (0.93, 1.19)	1.10 (0.97, 1.24)	1.06 (0.94, 1.20)	1.13 (1.00, 1.27)	0.09
Fatty acid 20:1 (gadoleic acid omega-9)						
Quintile median (g)	0.096	0.13	0.16	0.19	0.25	—
Cases (*n*)	498	523	540	581	542	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.07 (0.95, 1.22)	1.11 (0.98, 1.25)	1.20 (1.06, 1.35)	1.10 (0.97, 1.24)	0.09
Fatty acid 22:1 (erucic acid omega-9)						
Quintile median (g)	0.018	0.027	0.038	0.054	0.094	—
Cases (*n*)	491	498	556	539	579	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.00 (0.88, 1.13)	1.13 (1.00, 1.28)	1.10 (0.97, 1.24)	1.17 (1.04, 1.32)	0.006
Polyunsaturated fats						
Fatty acid 18:4 (parinaric acid omega-3)						
Quintile median (g)	0.0095	0.011	0.017	0.022	0.034	—
Cases (*n*)	515	523	543	533	581	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	0.98 (0.85, 1.12)	1.08 (0.95, 1.22)	1.00 (0.88, 1.14)	1.12 (0.99, 1.27)	0.03

(Continued)

TABLE 4 (*Continued*)

	Quintile of intake					
	1	2	3	4	5	*P*-trend
Omega-6 fatty acids						
Fatty acid 18:2 (linoleic acid omega-6)						
Quintile median (g)	8.5	10.4	11.9	13.5	16.5	—
Cases (*n*)	552	516	548	542	531	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.07 (0.95, 1.20)	1.06 (0.94, 1.20)	1.00 (0.89, 1.13)	1.08 (0.96, 1.22)	0.45
Fatty acid 20:4 (arachidonic acid omega-6)						
Quintile median (g)	0.078	0.11	0.14	0.17	0.22	—
Cases (*n*)	505	540	526	534	576	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.09 (0.96, 1.23)	1.06 (0.94, 1.20)	1.06 (0.94, 1.20)	1.14 (1.01, 1.29)	0.07
Omega-3 fatty acids						
Fatty acid 18:3 (α-linolenic acid omega-3)[3]						
Quintile median (g)	0.85	1.02	1.16	1.34	1.68	—
Cases (*n*)	515	551	541	511	572	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.10 (0.97, 1.24)	1.06 (0.94, 1.20)	1.02 (0.90, 1.15)	1.13 (1.01, 1.28)	0.15
Fatty acid 20:5 (EPA omega-3)						
Quintile median (g)	0.022	0.041	0.062	0.090	0.16	—
Cases (*n*)	475	525	541	535	576	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.11 (0.98, 1.26)	1.14 (1.01, 1.29)	1.13 (1.00, 1.28)	1.21 (1.07, 1.37)	0.01
Fatty acid 22:5 (DPA omega-3)[3]						
Quintile median (g)	0.018	0.025	0.031	0.039	0.056	—
Cases (*n*)	490	513	551	510	594	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.05 (0.92, 1.18)	1.10 (0.97, 1.24)	1.02 (0.90, 1.16)	1.19 (1.06, 1.35)	0.008
Fatty acid 22:6 (DHA omega-3)						
Quintile median (g)	0.046	0.080	0.11	0.15	0.26	—
Cases (*n*)	497	518	513	558	574	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.05 (0.93, 1.19)	1.03 (0.91, 1.16)	1.13 (1.00, 1.27)	1.15 (1.02, 1.30)	0.01
Marine fatty acids (sum of EPA, DPA, and DHA)						
Quintile median (g)	0.069	0.127	0.185	0.266	0.451	—
Cases (*n*)	490	523	515	556	583	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.07 (0.95, 1.22)	1.05 (0.92, 1.18)	1.13 (1.00, 1.28)	1.18 (1.05, 1.34)	0.005
trans Fatty acids						
trans Fat 16:1						
Quintile median (g)	0.026	0.039	0.050	0.063	0.087	—
Cases (*n*)	534	530	543	553	514	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.02 (0.90, 1.15)	1.04 (0.92, 1.17)	1.08 (0.95, 1.21)	1.00 (0.88, 1.13)	0.84
trans Fat 18:1						
Quintile median (g)	2.6	3.3	3.8	4.2	5.1	—
Cases (*n*)	521	525	531	543	569	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	1.03 (0.91, 1.16)	1.03 (0.92, 1.17)	1.05 (0.93, 1.18)	1.10 (0.97, 1.24)	0.12
trans Fat 18:2						
Quintile median (g)	0.33	0.41	0.47	0.53	0.62	—
Cases (*n*)	552	516	548	542	531	—
Multivariable-adjusted IRR (95% CI)	1.00[2]	0.96 (0.85, 1.08)	1.02 (0.91, 1.15)	1.01 (0.90, 1.14)	0.98 (0.86, 1.10)	0.93

[1] Multivariable-adjusted IRRs (95% CIs) were adjusted for age, questionnaire cycle, energy intake, age at menarche, parity, age at first birth, years since last birth, ever use of oral contraceptives, age at first oral contraceptive use, alcohol, smoking, BMI, education, occupation, income, marital status, and US region of residence. *P*-test for trend values were derived from the test for linear trend by modeling the quintile median as a continuous variable. DPA, docosapentaenoic acid; IRR, incidence rate ratio.

[2] Reference group.

[3] Isomer of fatty acid that was most prevalent in the diet.

We assessed associations of MFAs with fish consumption by examining the contribution of different types of fish to intakes of EPA, DPA, and EHA. The top 4 food sources that contributed to EPA in our cohort were dark-meat fish (45.4%), shellfish (22.8%), other fish (broiled or baked) (13.7%), and fried fish or fish sandwich (7.7%). The top 4 food sources that contributed to DPA were dark-meat fish (24.0%), other chicken or turkey with skin (19.5%), shellfish (13.5%), and other fish (broiled or baked) (11.1%). The top 4 food sources that contributed to DHA were dark-meat fish (35.3%), other fish (broiled or baked) (14.5%), shellfish (11.5%), and fried fish or fish sandwich (9.4%).

As shown in **Table 5**, the IRR for the highest category of dark-meat fish consumption compared with no consumption was 1.13 (95% CI: 1.00, 1.28; *P*-trend = 0.07). However, there was little evidence of a dose-response relation. The vast majority of women in our cohort were consumers of other fish and seafood

(ie, non–dark-meat fish), and rates of UL were very similar across all quartiles of consumption. When all types of fish and seafood were combined, there was no clear association with UL risk (highest category compared with no consumption: IRR, 0.94; 95% CI, 0.78, 1.15; *P*-trend = 0.68).

Although the prevalence of fish-oil and flax seed–oil supplementation in our cohort was low at the start of follow-up (0.8% and 0.4%, respectively), the use of these supplements increased to 3.8% and 1.6%, respectively, by the end of follow-up. The use of fish-oil supplements was not appreciably associated with UL risk (current use compared with nonuse on the basis of 71 exposed cases: IRR, 0.89; 95% CI, 0.70, 1.13), but the use of flax seed–oil supplements was positively associated with UL risk (current use compared with nonuse on the basis of 53 exposed cases: IRR, 1.42; 95% CI, 1.08, 1.88). Additional adjustment for fish-oil and flax seed–oil supplementation made little difference in the MFA-UL association (highest compared with lowest quintiles: IRR, 1.18; 95% CI, 1.05, 1.34; *P*-trend = 0.006). Likewise, the exclusion of fish-oil and flax seed oil–supplement users produced similar results for MFAs (highest compared with lowest quintiles: IRR, 1.17; 95% CI, 1.03, 1.33; *P*-trend = 0.012).

We investigated the role of other macronutrients, including protein and carbohydrate, and showed little association between these components of diet and UL risk (data not shown). Furthermore, isocaloric substitution models showed that the substitution of 5% *trans* unsaturated, polyunsaturated, or monounsaturated fat for saturated fat in the diet (with caloric intake kept constant) made little difference in UL risk, and substitutions of saturated fat with protein or carbohydrate did not appreciably alter UL risk (data not shown). When we repeated all analyses after including, as cases, the 205 women with incident UL diagnosed by pelvic examination only, results were similar (data not shown).

DISCUSSION

In the current study of US black women, there was little evidence of an overall association between UL and intakes of total fat or subgroups of saturated, monounsaturated, polyunsaturated, and *trans* unsaturated fat. Some inverse associations were observed between individual fatty acids and UL risk. The most consistent finding related to elevated UL risk in association with PUFAs. Higher intakes of long-chain omega-3 fatty acids, in particular MFAs (EPA, DPA, and DHA), were significantly and positively associated with UL risk. These associations, while relatively weak, were generally consistent across strata of age, educational attainment, and levels of gynecologic screening and did not vary materially by the diagnostic method for UL. The significant positive association of UL risk with the consumption of dark-meat fish, which was the main source of MFAs in this sample, was consistent with the finding for MFAs, although for dark-meat fish, there was no evidence of a dose-response relation. Moreover, the relative proportion of women who consumed dark-meat fish was small compared with that for the consumption of other fish and seafood. The finding for elevated risk in association with the use of flax seed–oil

TABLE 5
Risk of ultrasound- or surgery-confirmed uterine leiomyomata in relation to dietary intake of fish and seafood in the Black Women's Health Study, 2001–2009

	Category of intake					
	None	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-trend[1]
All fish and seafood						
Category median (servings/wk)	0	0.74	1.58	2.52	4.90	—
Cases (*n*)	124	638	629	656	648	—
Person-years	3253	18,430	17,880	17,922	18,202	—
Multivariable-adjusted IRR[2] (95% CI)[3]	1.00[4]	0.91 (0.75, 1.10)	0.93 (0.77, 1.13)	0.98 (0.80, 1.19)	0.95 (0.78, 1.15)	0.69
Multivariable-adjusted IRR (95% CI)[5]	1.00[4]	0.90 (0.74, 1.10)	0.93 (0.76, 1.13)	0.97 (0.80, 1.18)	0.94 (0.78, 1.15)	0.68
Dark-meat fish						
Category median (servings/wk)	0	0.14	0.28	0.63	1.47	—
Cases (*n*)	995	175	542	504	479	—
Person-years	29,491	4655	14,794	13,391	13,356	—
Multivariable-adjusted IRR (95% CI)[3]	1.00[4]	1.14 (0.97, 1.34)	1.10 (0.99, 1.22)	1.14 (1.03, 1.27)	1.10 (0.98, 1.23)	0.11
Multivariable-adjusted IRR (95% CI)[6]	1.00[4]	1.17 (0.99, 1.37)	1.12 (1.01, 1.25)	1.18 (1.05, 1.32)	1.13 (1.00, 1.28)	0.07
Other fish and seafood						
Category median (servings/wk)	0	0.60	1.26	2.03	3.85	—
Cases (*n*)	147	638	604	644	662	—
Person-years	3722	18,236	17,469	17,889	18,372	—
Multivariable-adjusted IRR (95% CI)[3]	1.00[4]	0.89 (0.74, 1.06)	0.89 (0.74, 1.07)	0.91 (0.76, 1.09)	0.92 (0.77, 1.11)	0.74
Multivariable-adjusted IRR (95% CI)[7]	1.00[4]	0.84 (0.70, 1.01)	0.83 (0.69, 1.00)	0.84 (0.69, 1.01)	0.84 (0.70, 1.02)	0.65

[1] Derived from the test for linear trend by modeling the quintile median as a continuous variable.
[2] IRR, incidence rate ratio.
[3] Adjusted for age, questionnaire cycle (2-y period), energy intake, age at menarche, parity, age at first birth, years since last birth, ever use of oral contraceptives, age at first use of oral contraceptives, alcohol, smoking, BMI, education, occupation, income, marital status, and US region of residence.
[4] Reference group.
[5] In addition, adjusted for dietary intake of dairy, fruit and vegetables, and fast food.
[6] In addition, adjusted for dietary intake of dairy, fruit and vegetables, fast food, and other fish.
[7] In addition, adjusted for dietary intake of dairy, fruit and vegetables, fast food, and dark-meat fish.

supplements was also consistent with the pattern of risk associated with long-chain omega-3 fatty acids overall, but this association was based on small numbers of exposed women.

Results indicated a slight reduction in UL risk in association with a higher consumption of certain SFAs is contrary to our hypothesis on the basis of data from studies of fat intake and hormone-dependent cancers (13, 14, 17, 21–29). Taken together with the consistent findings that UL incidence was higher in consumers of long-chain omega-3 PUFAs and fish that are key sources of these fatty acids, the grouping of fats with opposing effects may explain the mixed results of studies that have tried to link fat intake to UL directly or through the effects of estradiol. In support of our findings, a cross-sectional study of premenopausal Japanese women reported no significant association between total fat intake and UL risk but showed nonsignificant, positive associations between PUFAs and UL risk; ORs for middle and highest tertiles of consumption compared with the lowest tertile were 1.61 (95% CI: 0.71, 3.65) and 1.87 (95% CI: 0.80, 4.37), respectively (19). A hospital-based, case-control study reported an inverse association between total fish consumption and UL risk whereby the ORs for second and third tertiles of fish intake relative to the first tertile of intake were 0.7 (95% CI: 0.5, 0.8) and 0.7 (95% CI: 0.6, 0.9), respectively. However, the analysis was not specific to dark-meat fish. In addition, the case-control study did not adjust for other dietary factors or total calories, and participants were asked to recall their diets after diagnosis, which could have biased results if fish intake was perceived by participants to be part of a healthy diet (18). We showed no association between total fish and seafood consumption with UL risk.

Our results that showed a weak, positive association between dark-meat fish consumption and UL were also consistent with results of previous research that documented increased risk of UL in sport-fish consumers (50). In the Great Lakes Study (50), a prospective cohort study that included 541 premenopausal women, the duration of sport-fish consumption was positively associated with incident self-reported, physician-diagnosed UL [IRR: 1.20 (95% CI: 1.0, 1.3) per 10-y increment in the duration of consumption]. However, mechanisms involved in this association may not be related, or related solely, to MFAs. In a cross-sectional analysis of 177 participants with serum measurements of selected endocrine-disrupting chemicals from the Great Lakes Study cohort (50), UL risk was positively associated with higher concentrations of polychlorinated biphenyls (PCBs) (49), which are chemicals commonly present in fatty fish (50). Increases in UL risk were also associated with total PCBs, estrogenic PCBs, antiestrogenic PCBs, and dioxin-like PCBs, with ORs ranging from 1.6 to 1.9 (50).

Our findings of increased risk associated with omega-3 fatty acids are in disagreement with those from the Nurses' Health Study II on endometriosis (20), which is a hormone-dependent uterine condition. However, our results are generally in agreement with studies of fish intake in relation to hormone-dependent reproductive cancers. In a 2007 meta-analysis of studies on fish intake and endometrial cancer, the pooled OR on the basis of "high-quality" studies was 1.88 (95% CI: 1.20, 2.95) (53). The sole study that evaluated fish-subtype intake and adjusted for energy intake showed elevated risks for total fish, marine fish, fresh water fish, shrimp and crab, eel, and shellfish in relation to endometrial cancer, with ORs for the highest compared with lowest intakes of these fish subtypes that ranged from 1.3 to 2.4 (54). In a 2010 meta-analysis of studies on fish intake and ovarian cancer, high fish intake was inversely associated with risk (8 studies; pooled relative risk: 0.84; 95% CI: 0.68, 1.03) (55). In addition, our findings agree with those of studies of omega-3 fatty acids and prostate cancer (30, 31). Large prospective studies have shown increased risk of prostate cancer in men with high blood concentrations of long-chain omega-3 PUFAs (EPA, DPA, and DHA) (30, 31, 56). In a 2013 report from the Selenium and Vitamin E Cancer Prevention Trial, men in the highest quartile of plasma long-chain omega-3 PUFAs had increased risks for low-grade (RR: 1.44; 95% CI: 1.08, 1.93), high-grade (RR: 1.71; 95% CI: 1.00, 2.94), and total (RR: 1.43; 95% CI: 1.09, 1.88) prostate cancer relative to those for men in the lowest quartiles of these fatty acids (30). Associations were similar for individual omega-3 fatty acids. These results support earlier meta-analyses that showed a positive association between a high blood concentration of fish-oil contents EPA and DHA and a high-grade prostate tumor incidence (RR: 1.38; 95% CI: 1.05, 1.82; P-trend = 0.02) (57) and a positive association between dietary long-chain omega-3 PUFAs, which are composed of EPA and DHA, with prostate cancer risk (pooled RR: 1.13; 95% CI: 1.01, 1.28; P-trend = 0.04) (58).

The associations we observed between MFAs and UL may have some biologic plausibility. Although long-chain omega-3 PUFAs are considered antiinflammatory because of their ability to inhibit TNF-α and modulate eicosanoid activity (59), they also affect cell permeability, gene expression, and signal transduction (59), which could increase tumorigenesis. In addition, 5α-reductase interference and free radical formation from fatty acid oxidation have been suggested as possible pathways for increased risk (60–62).

Strengths of our study included the prospective design and quality of diet and UL measures. With respect to the findings for fish consumption, several items regarding fish and seafood intake were included in the FFQ, and fish was separated out according to whether it was dark-meat fish compared with not dark-meat fish. With prospective data collection, the error in the reporting of the diet was unlikely to depend on disease status. In addition, we adjusted for numerous variables associated with both diet and UL. High cohort retention minimized the potential for selection bias. In addition, few differences were shown between subjects who were and were not lost to follow-up by total fat intake or UL risk factors.

A validation study indicated that UL diagnoses were accurately reported in our study. However, not all participants were screened for UL. Therefore, misclassification of true cases as noncases, particularly subjects with asymptomatic tumors, was an important limitation. In addition, our inability to measure plasma concentrations of fatty acids or endocrine-disrupting chemicals found in fish and other fatty foods limited the extent to which we could make causal inferences about nutrients, foods, and other risk factors that we examined. Although numerous studies have shown moderate to good correlation between diet and plasma concentrations of fats (63, 64), there has been little information on how well fatty fish consumption correlates with PCB consumption (65). National data have shown that black women have significantly higher concentrations of PCBs in their bodies than do other populations (66), which supports the hypothesis that PCBs in fatty fish could play an etiologic role. If the association

between UL and MFAs is real, we can only speculate as to whether PCBs or the fatty acids themselves are implicated.

Although the Black Women's Health Study is a self-selected sample with higher levels of education than in the general black population, FFQ estimates for fat intake have been consistent with national data on black adults (10). Moreover, prevalence estimates of UL risk factors, such as age at menarche and parity, have been similar to those shown in national studies (67). These observations, coupled with the fact that our results did not vary materially by other covariates, suggest that our findings might be generalizable to other black women.

In conclusion, in a large cohort of US black women, we found little evidence that the consumption of total fat or fat subtypes overall were related to UL risk. However, we showed internally consistent evidence that long-chain omega-3 fatty acids, including MFAs (DHA, EPA, and DPA), were positively associated with UL risk after adjustment for a wide range of confounding factors. We also showed evidence that supplementation with flax seed oil (which is a major source of α-linolenic acid omega-3 fatty acids) was associated with increased risk, but this result was based on small numbers. It is unclear whether the observed associations might be explained by omega-3 fatty acids in general, the endocrine-disrupting chemicals commonly shown in fish (a major source of omega-3 fatty acids) (49), or effects of chance, bias, or residual confounding. Inverse associations of specific SFAs with UL risk also bear additional exploration. Future studies are warranted to confirm these findings and evaluate whether specific components of fatty foods are related to increased risk of UL, a common and debilitating gynecologic disorder in black women.

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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 on the basis of diet and UL, conducted the literature review, took the lead in drafting the manuscript for publication, and took primary responsibility for the final content of the manuscript; SKK: performed the validation study of diet in our cohort; RGR and LAW: managed and analyzed data; and all authors: made contributions to the interpretation of results, drafting of the manuscript, and critical revision of the manuscript for intellectual content. None of the authors had a conflict of interest.

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