American Journal of Epidemiology

Vol. 189, No. 12
DOI: 10.1093/aje/kwaa097
Advance Access publication:
June 17, 2020

## Original Contribution

# Dietary Fat Intake and Risk of Uterine Leiomyomata: A Prospective Ultrasound Study

**Theodore M. Brasky*, Traci N. Bethea, Amelia K. Wesselink, Ganesa R. Wegienka, Donna D. Baird, and Lauren A. Wise**

* Correspondence to Dr. Theodore M. Brasky, The Ohio State University–James Comprehensive Cancer Center, 410 W. 12th Avenue, Suite 385N, Columbus, OH 43210 (e-mail: Theodore.Brasky@osumc.edu).

*Initially submitted January 2, 2020; accepted for publication June 4, 2020.*

Uterine leiomyomata (UL) are associated with severe reproductive morbidity and are the primary indication for hysterectomy in the United States. A recent prospective cohort study of Black women reported positive associations between intakes of marine-sourced ω-3 fatty acids and UL risk. We examined whether intakes of dietary fat were associated with UL incidence in a 5-year prospective study of premenopausal Black women living in Detroit who underwent serial ultrasound. At baseline (2010–2012) and 20, 40, and 60 months of follow-up, participants underwent transvaginal ultrasound. Among 1,171 UL-free women at baseline, incident UL were detected in 277 women. Cox regression was used to estimate hazard ratios and 95% confidence intervals for the association of dietary fat and UL incidence. Intakes of total fat and saturated, monounsaturated, polyunsaturated, and *trans*-fat were not appreciably associated with UL incidence. Intake of the marine ω-3 polyunsaturated fatty acid, docosahexaenoic acid, was associated with 49% higher UL incidence (quartile 4 vs. 1: hazard ratio = 1.49, 95% confidence interval: 1.04, 2.14; *P* for trend = 0.01). Intakes of total marine ω-3 polyunsaturated fatty acids were similarly associated with elevated UL incidence (hazard ratio = 1.35, 95% confidence interval: 0.94, 1.93; *P* for trend = 0.03). It remains unclear whether the fatty acids or persistent environmental pollutants drive the association.

cohort; diet; fat; uterine leiomyoma; ω-3 fatty acids

Abbreviations: BWHS, Black Women's Health Study; CI, confidence interval; HR, hazard ratio; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SELF, Study of the Environment, Lifestyle, and Fibroids; SFA, saturated fatty acid; UL, uterine leiomyoma.

Uterine leiomyomata (UL, or fibroids) are associated with severe reproductive morbidity and are the primary indication for hysterectomy in the United States (1–3). Among reproductive-aged women, the prevalence of clinical diagnosis is approximately 25%–30% (4). However, a large proportion of UL are undiagnosed (5), and data from standardized ultrasound screening of women 35–49 years of age indicated that the estimated cumulative incidence of ultrasound-detectable UL by age 50 years was >70% (4). Black women have a 2- to 3-fold higher incidence of clinically diagnosed UL compared with White women and experience greater symptom severity (3, 4, 6). UL are also responsible for significant medical expenditures (7), with pronounced racial disparities in health-care costs, that disproportionately affect Black women (8). Aside from racial and reproductive factors, few established risk factors for UL have been identified (1, 9), and these factors do not fully explain the racial disparity in incidence (3, 6).

The underlying sources of dietary fat intake differ between Black and White women in the United States, with Black women generally consuming more dietary fat (10), and a greater proportion of fat from meat and seafood but less fat from dairy, compared with White women (11, 12). To address whether dietary fat intake could explain part of the racial disparity in UL incidence, it is worthwhile to examine the relationship between dietary fat and UL. The Black Women's Health Study (BWHS), a cohort comprised exclusively of Black women, was the first prospective

study to examine associations of dietary fat with UL risk. Investigators reported positive associations of individual dietary monounsaturated fatty acids (MUFAs) and marine-sourced ω-3 polyunsaturated fatty acids (PUFAs) and inverse associations for individual saturated fatty acids (SFAs) with UL risk (13). No appreciable associations were observed for intakes of total fat or most fat groups, with the exception of total MUFA intake, for which a positive association was reported. The results from this study, however, were likely affected by outcome misclassification because identification of UL cases was based on self-report.

To expand on the existing literature, we examined the association between dietary fat intake and UL incidence in the Study of Environment, Lifestyle, and Fibroids (SELF), a prospective cohort study of Black women who underwent serial ultrasound screening for incident UL.

## METHODS

### The Study of Environment, Lifestyle and Fibroids

SELF is a prospective cohort of Black women living in the Detroit, Michigan, metropolitan area (14). Recruitment of SELF participants occurred from 2010 through 2012, with community outreach through radio, television, newspapers, event booths, and informational letters to women in the Henry Ford Health System, the clinical institution collaborating on SELF (14). Enrolled women ($n = 1{,}693$) were self-identified as Black/African-American, were 23–35 years of age without self-reported history of hysterectomy (partial or total, verified at baseline ultrasound), and reported no prior diagnoses of UL, cancer, or autoimmune diseases requiring regular medication. Women who were pregnant at the time of recruitment delayed their enrollment into the study until after delivery to assure optimum ultrasound imaging.

At baseline and every 20 months during a 5-year follow-up period, participants completed computer-assisted telephone and Web-based questionnaires, self-administered paper questionnaires, and attended in-person clinic visits. Participants were queried on their personal medical history, physical activity, lifestyle and behaviors (e.g., smoking, alcohol intake), reproductive history, and use of contraceptives. Transvaginal ultrasound was performed during in-person clinic visits at enrollment (baseline), and at 20, 40, and 60 months of follow-up. Pregnant women were asked to return to the clinic at 4 months postpartum. For women whose pregnancy was identified at follow-up ultrasound, data were recorded if the participant was ≤12 weeks pregnant based upon fetal measures, otherwise they were asked to return to the clinic at 4 months postpartum. Study sonographers were registered diagnostic medical sonographers with ≥3 years of experience in gynecological sonography (15). Sonographers received additional training for the study to assure consistency in completing research documentation about the ultrasound and received regular refresher trainings during the course of the study (14). At each clinic visit trained study staff measured height and weight, from which body mass index was calculated (as weight (kg)/height $(m)^2$). All participants gave written informed consent, and the study was approved by the institutional review boards of the Henry Ford Health System, the National Institute of Environmental Health Sciences, and Boston University Medical Campus.

### Dietary measurement

At baseline, women completed a validated Web-based semiquantitative Block food frequency questionnaire (16–18). Participants reported their usual frequencies and serving sizes (in cups: 0.25, 0.50, 1, or 2) of 110 foods and beverages in the past 12 months. Average daily intakes of dietary fat and individual fatty acids were calculated by multiplying the serving-size and season-adjusted frequency of each food item by its fat content as determined by the US Department of Agriculture Food and Nutrient Database for Dietary Studies (19). Data for total dietary fat and fat groups (SFA, MUFA, PUFA, and *trans*-fatty acids) are given in grams/day, whereas data for individual fatty acids were given in milligrams/day. Summary measures were calculated for total dietary marine ω-3 PUFA, as the sum of eicosapentaenoic (20:5n3), docosapentaenoic (22:5n3), and docosahexaenoic acids (22:6n3), and total ω-6 PUFA as the sum of linoleic (18:2n6) and arachidonic acids (20:4n6). Total fin-fish and shellfish intake was calculated as the sum of serving-size adjusted grams/day of tuna (including tuna salad and tuna casserole), fried fish or fish sandwich, other fish (not fried), shellfish (including shrimp, scallops, and crabs), and oysters.

For the present analysis, we excluded 384 women with prevalent UL identified by ultrasound at enrollment. We excluded an additional 78 women with total energy intakes of <400 or ≥5,000 kcal/day and 60 women who were missing follow-up data, leaving 1,171 women followed for a median of 5 years for incident UL. Among them, we identified 277 incident UL cases (primary outcome) first detected at their 20- ($n = 110$), 40- ($n = 88$), or 60-month follow-up visit ($n = 79$). The remaining women were right-censored at hysterectomy (n = 8), withdrawal from the study after completing at least 1 follow-up visit ($n = 66$), or their 60-month follow-up visit ($n = 820$), whichever came first. There were no apparent differences in baseline characteristics among women with no follow-up data ($n = 60$; excluded), women who withdrew from the study after completing at least 1 follow-up visit ($n = 66$; censored), and the remaining analytical cohort ($n = 1{,}105$) (Web Table 1, available at https://academic.oup.com/aje).

### Statistical analysis

Dietary fats were energy-adjusted using the nutrient residual method (20). We categorized dietary variables into quartiles to avoid the assumption of linearity between dietary fats and UL risk and to make our findings comparable with those of the BWHS (13). We used Cox proportional hazards models, with follow-up time as the time metric, to estimate hazard ratios and 95% confidence intervals for the association between dietary fat and UL incidence. In addition to accounting for follow-up time, all models adjusted for age (stratification variable) and total energy intake. A priori we determined additional baseline factors for inclusion in

multivariable models; they included education (up to high school, some college, college or advanced degree), body mass index (continuous), age at menarche (in years: <11, 11, 12, 13, ≥14), parity (nulliparous and tertiles of births: 1, 2, and ≥3 births), age at first birth (nulliparous and tertiles of age in years at first birth: <19, 19–22, ≥23), years since last birth (nulliparous and tertiles of years since last birth: 0–2.6, 2.7–5.7, ≥5.8), ever used oral contraceptives, ever used progestin-only injectable contraceptives, alcohol intake (quartiles of drinks/week: <0.33, 0.33–1.27, 1.28–3.98, ≥3.99), smoking status (none, former, current for <10 years, current for ≥10 years), and history of hypertension (yes/no). We calculated *P* values from tests for trend (*P* for trend) by assigning the median value to each category of ordinal dietary variables and including them as continuous variables in regression models.

Because progestin-only injectable contraceptives strongly suppress ovarian hormones (estradiol and progesterone), we performed a sensitivity analysis in which we additionally excluded 76 women (including 10 with incident UL cases) who were using these contraceptives at baseline. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All reported *P* values are 2-sided, and $P < 0.05$ was considered statistically significant.

## RESULTS

Baseline characteristics of SELF participants, stratified by total dietary fat intake, are shown in Table 1. With the exception of fish intake, participants' baseline characteristics were not appreciably associated with total dietary fat intake. Women who consumed more dietary fat were more likely to consume fish. Household income, body mass index, and reproductive factors including age at menarche, parity, age at first birth, years since last birth, and use of injectable progestin-only contraceptives were similar across categories of dietary fat intake.

Associations of energy-adjusted quartiles of total fat and individual fatty acid intakes with UL incidence are presented in Table 2 (reduced table) and Web Table 2 (full table). Hazard ratios comparing the highest versus lowest quartiles of fat consumption were: 1.08 (95% confidence interval (CI): 0.76, 1.52) for total dietary fat, 0.97 (95% CI: 0.67, 1.38) for SFA, 1.17 (95% CI: 0.83, 1.64) for MUFA, 0.91 (95% CI: 0.64, 1.31) for PUFA, and 0.83 (95% CI: 0.59, 1.18) for *trans*-fatty acids. Greater intake of each of the 3 marine ω-3 PUFAs was positively associated with UL incidence (quartiles 4 vs. 1: docosahexaenoic acid (PUFA 22:6) hazard ratio (HR) = 1.49, 95% CI: 1.04, 2.14 (*P* for trend = 0.01); eicosapentaenoic acid (PUFA 20:5) HR = 1.25, 95% CI: 0.87, 1.81 (*P* for trend = 0.06); docosapentaenoic acid (PUFA 22:5) HR = 1.22, 95% CI: 0.85, 1.75 (*P* for trend = 0.21)). The hazard ratios for quartiles 2, 3, and 4 versus 1 of total dietary marine ω-3 PUFA were 0.87 (95% CI: 0.59, 1.29), 1.14 (95% CI: 0.79, 1.66), and 1.35 (95% CI: 0.94, 1.93), respectively, and a linear trend was observed (*P* for trend = 0.03). Additionally, there was a suggestive association with intake of palmitoleic acid (MUFA 16:1) (HR = 1.42, 95% CI: 0.99, 2.04; *P* for trend = 0.10; Web Table 2). Hazard ratios for intakes of individual SFAs and *trans*-fatty acids, as well as the remaining MUFAs and PUFAs did not suggest appreciable associations.

Associations of fish intake and UL risk are given in Table 3. Similar to the marine ω-3 PUFAs, hazard ratios for total fish intake were also elevated: hazard ratio = 1.19 (95% CI: 0.93, 1.71), hazard ratio = 1.33 (95% CI: 0.93, 1.91), and hazard ratio = 1.37 (95% CI: 0.94, 2.00) for quartiles 2, 3, and 4 versus 1 (*P* for trend = 0.14), respectively. Associations were generally similar for fin fish and shellfish.

After excluding women who used progestin-only injectable contraceptives at baseline, findings for marine ω-3 PUFA were stronger (Table 4). For docosahexaenoic acid specifically, the hazard ratio comparing quartile 4 versus 1 was 1.59 (95% CI: 1.10, 2.30; *P* for trend < 0.01). Findings for palmitoleic acid were unchanged (data not shown).

## DISCUSSION

In this prospective cohort study of reproductive-aged Black women who underwent serial ultrasound during a 5-year period, dietary intakes of total fat and most individual fatty acids were not appreciably associated with UL incidence. However, higher dietary intakes of total marine ω-3 PUFAs, particularly docosahexaenoic acid, were associated with increases in UL incidence. To our knowledge, this study represents the first prospective ultrasound study of dietary fat and UL incidence.

In SELF, findings regarding intake of the marine ω-3 PUFA docosahexaenoic acid (quartile 4 vs. 1: HR = 1.49) were consistent with a prior report from the BWHS (2,695 cases), in which higher intakes of marine ω-3 PUFA (along with their fish sources) were associated with 13%–21% increased risks of UL (13). Although hazard ratios were imprecise, our findings for the marine ω-3 PUFAs eicosapentaenoic acid (HR = 1.25) and docosapentaenoic acid (HR = 1.22) are similar in magnitude to those of the BWHS. Two other studies have reported on fish intake and UL risk in White women (21, 22). Similar to our findings on fish intake, a cohort study examining Great Lakes sport-caught fish intake reported 20% increase in risk of self-reported UL associated with fish consumption (22). In contrast, an Italian clinic-based case-control study reported 30% reductions in the odds of UL among women in the second (odds ratio = 0.7, 95% CI: 0.5, 0.8) and third tertiles (odds ratio = 0.7, 95% CI: 0.6, 0.9) of fish consumption relative to the first (21); however, this study might have been prone to recall bias.

Our observation of 43% higher UL risk for greater intakes of palmitoleic acid (which derives from vegetable oils and animal fats) is not clearly supported by data from the BWHS (quintile 5 vs. 1: HR = 1.09, 95% CI: 0.97, 1.23) (13). Additionally, in the BWHS, total MUFA (HR = 1.15, 95% CI: 1.02, 1.30), as well as individual MUFAs oleic acid (HR = 1.13, 95% CI: 1.00, 1.27) and erucic acid (HR = 1.17, 95% CI: 1.04, 1.32), were positively associated with UL risk (13). Although imprecise, our results for intake of total MUFA (HR = 1.17) and oleic acid (HR = 1.23) were also similar in direction and magnitude to those found in the BWHS (Web Table 2).

**Table 1.** Characteristics of Participants According to Categories of Total Dietary Fat Intake ($n$ = 1,171), Study of Environment, Lifestyle and Fibroids, Michigan, 2010–2018

| Characteristic | Energy-Adjusted Quartiles of Total Fat, g/day | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <76.96 | | 76.96–84.07 | | 84.08–91.15 | | ≥91.16 | |
| | No. | % | No. | % | No. | % | No. | % |
| Age, years[a] | 28.10 (3.53) | | 28.63 (3.45) | | 28.62 (2.52) | | 28.36 (3.34) | |
| Education | | | | | | | | |
| Up to high school | 66 | 22.60 | 53 | 18.09 | 61 | 20.82 | 68 | 23.21 |
| Some college | 151 | 51.71 | 158 | 53.92 | 147 | 50.17 | 155 | 52.90 |
| College degree or beyond | 75 | 25.68 | 82 | 27.99 | 85 | 29.01 | 70 | 23.89 |
| Household income, $ | | | | | | | | |
| <20,000 | 133 | 46.34 | 116 | 39.86 | 123 | 42.12 | 146 | 50.17 |
| 20,001–50,000 | 110 | 38.33 | 124 | 42.61 | 121 | 41.44 | 101 | 34.71 |
| >50,000 | 44 | 15.33 | 51 | 17.53 | 48 | 16.44 | 44 | 15.12 |
| Body mass index[a,b] | 33.90 (9.68) | | 33.51 (9.49) | | 33.09 (9.89) | | 34.44 (10.10) | |
| Age at menarche, years | | | | | | | | |
| <11 | 59 | 20.21 | 46 | 15.70 | 48 | 16.38 | 47 | 16.04 |
| 11 | 56 | 19.18 | 59 | 20.14 | 62 | 21.16 | 65 | 22.18 |
| 12 | 82 | 28.08 | 88 | 30.03 | 79 | 26.96 | 79 | 26.96 |
| 13 | 44 | 15.07 | 50 | 17.06 | 55 | 18.77 | 44 | 15.02 |
| ≥14 | 51 | 17.47 | 50 | 17.06 | 49 | 16.72 | 58 | 19.80 |
| No. of live births[a] | 1.24 (1.37) | | 1.30 (1.32) | | 1.33 (1.44) | | 1.34 (1.55) | |
| Age at first birth, years[a,c] | 20.48 (3.74) | | 20.85 (4.08) | | 20.39 (3.32) | | 20.79 (3.84) | |
| Years since last birth[a,c] | 4.91 (3.67) | | 4.80 (3.65) | | 5.33 (4.08) | | 4.40 (3.32) | |
| Current hormonal contraceptive use | | | | | | | | |
| None | 194 | 66.44 | 191 | 65.19 | 202 | 68.94 | 204 | 69.62 |
| Oral contraceptive | 33 | 11.30 | 34 | 11.60 | 41 | 13.99 | 27 | 9.22 |
| Intrauterine device (hormonal) | 29 | 9.93 | 32 | 10.92 | 12 | 4.10 | 18 | 6.14 |
| Injectable progestin-only | 18 | 6.16 | 17 | 5.80 | 19 | 6.48 | 22 | 7.51 |
| Other | 18 | 6.16 | 19 | 6.48 | 19 | 6.48 | 22 | 7.51 |
| Oral contraceptive use | | | | | | | | |
| Never | 79 | 27.05 | 77 | 26.28 | 96 | 32.76 | 87 | 29.69 |
| Ever | 213 | 72.95 | 216 | 73.72 | 197 | 67.24 | 206 | 70.31 |
| Age at first oral contraceptive use, years | | | | | | | | |
| Never | 79 | 27.05 | 77 | 26.28 | 96 | 32.76 | 87 | 29.79 |
| 12–17 | 91 | 31.16 | 105 | 35.84 | 87 | 29.69 | 108 | 36.99 |
| 18–33 | 122 | 41.78 | 111 | 37.88 | 110 | 37.54 | 97 | 33.22 |
| Injectable progestin-only contraceptive use | | | | | | | | |
| Never | 170 | 58.22 | 164 | 55.97 | 168 | 57.34 | 148 | 50.51 |
| Ever | 122 | 41.78 | 129 | 44.03 | 125 | 42.66 | 145 | 49.49 |

**Table continues**

**Table 1.** Continued

| Characteristic | Energy-Adjusted Quartiles of Total Fat, g/day | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <76.96 | | 76.96–84.07 | | 84.08–91.15 | | ≥91.16 | |
| | No. | % | No. | % | No. | % | No. | % |
| Alcohol intake, drinks/week | | | | | | | | |
| <0.33 | 72 | 24.66 | 69 | 23.55 | 77 | 26.28 | 72 | 24.57 |
| 0.33–1.27 | 62 | 21.23 | 79 | 26.96 | 80 | 27.30 | 71 | 24.23 |
| 1.28–3.98 | 60 | 20.55 | 75 | 25.60 | 73 | 24.91 | 88 | 30.03 |
| ≥3.99 | 98 | 33.56 | 70 | 23.89 | 63 | 21.50 | 62 | 21.16 |
| Smoking status | | | | | | | | |
| Never smoker | 206 | 70.55 | 219 | 74.74 | 229 | 78.16 | 218 | 74.40 |
| Former smoker | 24 | 8.22 | 19 | 6.48 | 21 | 7.17 | 19 | 6.48 |
| Current, <10 years | 47 | 16.10 | 42 | 14.33 | 32 | 10.92 | 47 | 16.04 |
| Current, ≥10 years | 15 | 5.14 | 13 | 4.44 | 11 | 3.75 | 9 | 3.07 |
| History of hypertension | | | | | | | | |
| No | 256 | 87.97 | 264 | 91.35 | 267 | 91.75 | 256 | 88.58 |
| Yes | 35 | 12.03 | 25 | 8.65 | 24 | 8.25 | 33 | 11.42 |
| History of diabetes | | | | | | | | |
| No | 278 | 96.19 | 286 | 97.95 | 284 | 97.59 | 278 | 94.88 |
| Yes | 11 | 3.81 | 6 | 2.05 | 7 | 2.41 | 15 | 5.12 |
| Fish intake, g/day | | | | | | | | |
| <9.59 | 84 | 28.77 | 83 | 28.33 | 78 | 26.62 | 47 | 16.04 |
| 9.59–21.39 | 64 | 21.92 | 82 | 27.99 | 79 | 26.96 | 68 | 23.21 |
| 21.40–39.99 | 68 | 23.29 | 73 | 24.91 | 71 | 24.23 | 81 | 27.65 |
| ≥40.00 | 76 | 26.03 | 55 | 18.77 | 65 | 22.18 | 97 | 33.11 |
| Red meat intake, g/day | | | | | | | | |
| <16.53 | 68 | 23.29 | 92 | 31.40 | 83 | 28.33 | 49 | 16.72 |
| 16.53–28.35 | 75 | 25.68 | 87 | 29.69 | 69 | 23.55 | 61 | 20.82 |
| 28.36–48.48 | 71 | 24.32 | 66 | 22.53 | 80 | 27.30 | 74 | 25.26 |
| ≥48.49 | 78 | 26.71 | 48 | 16.38 | 61 | 20.82 | 109 | 37.20 |
| Poultry intake, g/day | | | | | | | | |
| <11.82 | 64 | 21.92 | 90 | 30.72 | 83 | 28.33 | 54 | 18.43 |
| 11.82–22.08 | 75 | 25.68 | 80 | 27.30 | 81 | 27.65 | 58 | 19.80 |
| 22.09–42.81 | 81 | 27.74 | 69 | 23.55 | 65 | 22.18 | 77 | 26.28 |
| ≥42.82 | 72 | 24.66 | 54 | 18.43 | 64 | 21.84 | 104 | 35.49 |

[a] Values are expressed as mean (standard deviation).
[b] Body mass index calculated as weight (kg)/height $(m)^2$.
[c] Among parous women.

We did not observe associations for the remaining fat groups or individual fatty acids. In the BWHS, there were relatively small inverse associations for intakes of SFAs caprylic acid (HR = 0.89, 95% CI: 0.78, 0.99) and caproic acid (HR = 0.86, 95% CI: 0.76, 0.97) (13). In the present study, hazard ratios for caprylic acid (HR = 0.92) were consistent, but those for caproic acid (HR = 1.04) were contrary to those reported previously (13) (Web Table 2).

The present study has several limitations. Foremost, with 1,171 women under study and 277 incident cases, the study had low power to identify small associations between dietary fats and UL risk. The use of dietary self-report is also subject to error (23). Given the study's prospective design, we expect this error to be nondifferential, but it could have attenuated our results. Further, the FFQ did not collect data on the specific types of fish consumed, which would be expected

**Table 2.** Associations of Dietary Fat Intake With Uterine Leiomyomata Risk ($n$ = 1,171), Study of Environment, Lifestyle and Fibroids, Michigan, 2010–2018

| Dietary Fat | Energy-Adjusted Quartiles of Fat Intake[a] | | | | | | | | | | | | *P* for Trend |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | |
| | No. of Cases | HR[b] | 95% CI | No. of Cases | HR[b] | 95% CI | No. of Cases | HR[b] | 95% CI | No. of Cases | HR[b] | 95% CI | |
| Total fat | 67 | 1.00 | Referent | 68 | 0.89 | 0.62, 1.27 | 67 | 0.80 | 0.56, 1.14 | 75 | 1.08 | 0.76, 1.52 | 0.78 |
| Total SFA | 66 | 1.00 | Referent | 71 | 0.92 | 0.65, 1.32 | 74 | 1.05 | 0.74, 1.48 | 66 | 0.97 | 0.67, 1.38 | 0.98 |
| Total MUFA | 67 | 1.00 | Referent | 70 | 0.90 | 0.63, 1.29 | 60 | 0.72 | 0.50, 1.04 | 80 | 1.17 | 0.83, 1.64 | 0.53 |
| Total PUFA | 61 | 1.00 | Referent | 71 | 1.10 | 0.76, 1.58 | 79 | 1.28 | 0.89, 1.83 | 66 | 0.91 | 0.64, 1.31 | 0.67 |
| ω-3 fatty acids | | | | | | | | | | | | | |
| α-linolenic acid | 66 | 1.00 | Referent | 81 | 1.10 | 0.78, 1.56 | 67 | 0.84 | 0.59, 1.21 | 63 | 0.82 | 0.58, 1.18 | 0.14 |
| Eicosapentaenoic acid | 61 | 1.00 | Referent | 59 | 0.83 | 0.56, 1.23 | 78 | 1.14 | 0.78, 1.66 | 79 | 1.25 | 0.87, 1.81 | 0.06 |
| Docosapentaenoic acid | 61 | 1.00 | Referent | 68 | 1.01 | 0.69, 1.47 | 70 | 1.00 | 0.68, 1.47 | 78 | 1.22 | 0.85, 1.75 | 0.21 |
| Docosahexaenoic acid | 56 | 1.00 | Referent | 67 | 1.04 | 0.71, 1.52 | 68 | 1.12 | 0.74, 1.59 | 86 | 1.49 | 1.04, 2.14 | 0.01 |
| Total marine ω-3 | 59 | 1.00 | Referent | 61 | 0.87 | 0.59, 1.29 | 76 | 1.14 | 0.79, 1.66 | 81 | 1.35 | 0.94, 1.93 | 0.03 |
| Total *trans*-fat | 73 | 1.00 | Referent | 64 | 0.75 | 0.52, 1.07 | 75 | 0.91 | 0.64, 1.30 | 65 | 0.83 | 0.59, 1.18 | 0.53 |

Abbreviations: CI, confidence interval; HR, hazard ratio; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

[a] Category cutpoints and minimally adjusting regression models are presented in Web Table 2.

[b] Adjusted for age, education, income, body mass index, age at menarche, parity, age at first birth, years since last birth, oral contraceptive use, progestin-only injectable contraceptive use, alcohol intake, smoking, history of hypertension, and total energy intake.

**Table 3.** Associations of Fish Intake With Uterine Leiomyomata Risk ($n$ = 1,171), Study of Environment, Lifestyle and Fibroids, Michigan, 2010–2018

| Fish | Quartiles of Fish Intake | | | | | | | | | | | | *P* for Trend |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | |
| | No. of Cases | HR[a] | CI | No. of Cases | HR[a] | CI | No. of Cases | HR[a] | CI | No. of Cases | HR[a] | CI | |
| Total fish[b] | 61 | 1.00 | Referent | 69 | 1.19 | 0.93, 1.71 | 76 | 1.33 | 0.93, 1.91 | 71 | 1.37 | 0.94, 2.00 | 0.14 |
| Fin fish[c] | 57 | 1.00 | Referent | 79 | 1.50 | 1.05, 2.14 | 73 | 1.41 | 0.98, 2.03 | 68 | 1.40 | 0.95, 2.06 | 0.27 |
| Shellfish[d] | 69 | 1.00 | Referent | 60 | 1.17 | 0.81, 1.67 | 68 | 1.38 | 0.97, 1.97 | 80 | 1.26 | 0.89, 1.79 | 0.31 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age, education, income, body mass index, age at menarche, parity, age at first birth, years since last birth, oral contraceptive use, progestin-only injectable contraceptive use, alcohol intake, smoking, history of hypertension, and total energy intake.

[b] The cutpoints are as follows, quartile 1, <9.59 g/day; quartile 2, 9.59–21.39 g/day; quartile 3, 21.40–39.99 g/day; and quartile 4, ≥40.00 g/day.

[c] The cutpoints are as follows, quartile 1, <7.27 g/day; quartile 2, 7.27–16.03 g/day; quartile 3, 16.04–29.77 g/day; and quartile 4, ≥29.78 g/day.

[d] The cutpoints are as follows, quartile 1, <1.00 g/day; quartile 2, 1.00–3.07 g/day; quartile 3, 3.08–9.10 g/day; and quartile 4, >9.10 g/day.

to add nondifferential error in the estimation of marine ω-3 PUFAs. Unfortunately, we did not measure fatty acids in circulation (e.g., plasma phospholipids), which could provide a more reliable estimate of association with UL risk. We additionally could not account for supplemental intakes of ω-3 PUFAs. As is the case with any observational study, residual confounding could have influenced our findings. For instance, participants were not queried at baseline on childhood abuse (24–26) or past uterine infections, which may confound the fat-UL association. In addition, analyses were not adjusted for prevalent diabetes due to small numbers, nor did they account for multiple comparisons. Finally, it is important to note that our results among a study population comprised exclusively of Black women cannot fully address whether dietary fats explain the racial disparity in UL incidence.

These limitations notwithstanding, the present study has several strengths. It focuses on a population of women at high risk of UL. To our knowledge, ours is only the second prospective study and the first ultrasound-based study to examine associations of dietary fat intake with UL risk. The utilization of serial ultrasound to classify UL and minimize detection bias is a major strength, given the high proportion of UL that are undiagnosed (4). We know of no prior study of diet and UL risk has been able to discern incident from prevalent disease using ultrasound, a detection method with high sensitivity and specificity relative to histologic evidence (27). Finally, we were able to adjust for a wide range of potential confounders, including known and suspected risk factors for UL.

There is no clear explanation for the increased UL risk observed among women with high intakes of marine ω-3 PUFA. Indeed, a wealth of evidence suggests that marine ω-3 PUFA would be expected to have an inhibitory effect on uterine neoplasms given that they are thought to reduce inflammation through the inhibition of nuclear factor κ-B (28, 29), which acts as a transcription factor for targets associated with inflammation, including interleukin-6 and cyclooxygenase-2. Because eicosapentaenoic acid and docosahexaenoic acid are incorporated into cell phospholipids partly at the expense of arachidonic acid (ω-6 PUFA), they attenuate the ability of cyclooxygenase enzymes to synthesize proinflammatory eicosanoids (29, 30). Among observational studies, marine ω-3 PUFAs have been associated with reductions in circulating C-reactive protein, interlukin-6, and tumor necrosis factor-α (31). In human trials, fish oil supplementation reduced several blood biomarkers of inflammation, including C-reactive protein (32, 33) and tumor necrosis factor-α (32, 34), when contrasted against a placebo.

An alternative hypothesis is that persistent pollutants such as polychlorinated biphenyls or mercury—both of which bioaccumulate in fish—might explain the positive associations that we observed; however, evidence remains limited. In a cross-sectional analysis of the National Health and Nutrition Examination Survey (35), unadjusted geometric mean levels of whole blood mercury were significantly higher in women with UL versus without UL, and positive associations were found with self-reported UL diagnosis. Data from a recent prospective analysis of blood and urinary

**Table 4.** Associations of Marine ω-3 Polyunsaturated Fatty Acid Intake With Uterine Leiomyomata Risk Among Women Not Using Injectable Progestin-Only Contraceptives at Baseline ($n$ = 1,095), Study of Environment, Lifestyle and Fibroids, Michigan, 2010–2018

| ω-3 Fatty Acids | Energy-Adjusted Quartiles of Fat Intake[a] | | | | | | | | | | | | *P* for Trend |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | |
| | No. of Cases | HR[b] | CI | No. of Cases | HR[b] | CI | No. of Cases | HR[b] | CI | No. of Cases | HR[b] | CI | |
| Eicosapentaenoic acid | 57 | 1.00 | Referent | 55 | 0.85 | 0.56, 1.28 | 77 | 1.18 | 0.80, 1.74 | 78 | 1.27 | 0.88, 1.85 | 0.06 |
| Docosapentaenoic acid | 57 | 1.00 | Referent | 65 | 1.11 | 0.74, 1.64 | 68 | 1.10 | 0.74, 1.64 | 77 | 1.28 | 0.89, 1.85 | 0.18 |
| Docosahexaenoic acid | 51 | 1.00 | Referent | 64 | 1.12 | 0.75, 1.66 | 67 | 1.26 | 0.85, 1.87 | 85 | 1.59 | 1.10, 2.30 | <0.01 |
| Total marine ω-3 | 55 | 1.00 | Referent | 57 | 0.92 | 0.62, 1.38 | 75 | 1.25 | 0.86, 1.84 | 80 | 1.41 | 0.97, 2.03 | 0.02 |

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Category cutpoints are given in Web Table 2.
[b] Adjusted for age, education, income, body mass index, age at menarche, parity, age at first birth, years since last birth, oral contraceptive use, progestin-only injectable contraceptive use, alcohol intake, smoking, history of hypertension, and total energy intake.

mercury concentrations and UL prevalence, as determined by laparoscopic surgery (likely missing intramural and submucosal UL, the most common types of UL), did not support these findings (36). In the same study, authors reported that high visceral fat concentrations of several polychlorinated biphenyls were associated with 52%–88% increased prevalence of UL (37).

The present prospective study of Black women who underwent serial ultrasound provides additional evidence that intakes of marine ω-3 PUFAs, particularly docosahexaenoic acid, are associated with increased UL risk. If the association is real, it remains unclear whether the fatty acids themselves or persistent environmental pollutants are an underlying causal agent. Additional prospective studies with careful measurement of dietary marine ω-3 fatty acids or biomarkers of their intake, as well as ultrasound-detected UL, are needed. Biomarker measurements of exposure to persistent organic and inorganic pollutants would further help clarify the extent to which the association is explained by environmental pollutants, the fatty acids themselves, or other factors.

## ACKNOWLEDGMENTS

Author affiliations: Division of Medical Oncology, College of Medicine, The Ohio State University, Columbus, Ohio (Theodore M. Brasky); Department of Medicine, School of Medicine, Boston University, Boston, Massachusetts (Traci N. Bethea); Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts (Amelia K. Wesselink, Lauren A. Wise); Department of Public Health Sciences, Henry Ford Health System, Detroit, Michigan (Ganesa R. Wegienka); and Epidemiology Branch, Women's Health Group, National Institute for Environmental Health Sciences, Research Triangle, North Carolina (Donna D. Baird).

This work was supported by the National Institute of Environmental Health Sciences (grant R01-ES024749). This research was also supported by the Intramural Research Program, National Institute of Environmental Health Sciences, National Institutes of Health, and in part by funds allocated for health research by the American Recovery and Reinvestment Act.

We thank Alison M. Newton for her contribution to this work.

Data described in the manuscript, code book, and analytical code will not be made available due to institutional review board restrictions.

Conflict of interest: none declared.

## REFERENCES

1. Wise LA, Laughlin-Tommaso SK. Epidemiology of uterine fibroids: from menarche to menopause. *Clin Obstet Gynecol*. 2016;59(1):2–24.

2. Coronado GD, Marshall LM, Schwartz SM. Complications in pregnancy, labor, and delivery with uterine leiomyomas: a population-based study. *Obstet Gynecol*. 2000;95(5):764–769.
3. Kjerulff KH, Langenberg P, Seidman JD, et al. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. *J Reprod Med*. 1996;41(7):483–490.
4. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in Black and White women: ultrasound evidence. *Am J Obstet Gynecol*. 2003;188(1):100–107.
5. Wegienka G, Baird DD, Hertz-Picciotto I, et al. Uterine leiomyomata (fibroids): are bleeding symptoms more likely to be reported after diagnosis? *J Clin Epidemiol*. 2004;57(3):318–320.
6. Marshall LM, Spiegelman D, Barbieri RL, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet Gynecol*. 1997;90(6):967–973.
7. Cardozo ER, Clark AD, Banks NK, et al. The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol*. 2012;206(3):211.e1–211.e9.
8. Flynn M, Jamison M, Datta S, et al. Health care resource use for uterine fibroid tumors in the United States. *Am J Obstet Gynecol*. 2006;195(4):955–964.
9. Bulun SE. Uterine fibroids. *N Engl J Med*. 2013;369(14):1344–1355.
10. Wright JD, Wang CY. Trends in intake of energy and macronutrients in adults from 1999-2000 through 2007-2008. *NCHS Data Brief*. 2010;(49):1–8.
11. Kristal AR, Shattuck AL, Patterson RE. Differences in fat-related dietary patterns between Black, Hispanic and White women: results from the Women's Health Trial Feasibility Study in Minority Populations. *Public Health Nutr*. 1999;2(3):253–262.
12. Razzaghi H, Tinker SC. Seafood consumption among pregnant and non-pregnant women of childbearing age in the United States, NHANES 1999–2006. *Food Nutr Res*. 2014;58:23287.
13. Wise LA, Radin RG, Kumanyika SK, et al. A prospective study of dietary fat and risk of uterine leiomyomata. *Am J Clin Nutr*. 2014;99(5):1105–1116.
14. Baird DD, Harmon QE, Upson K, et al. A prospective, ultrasound-based study to evaluate risk factors for uterine fibroid incidence and growth: Methods and results of recruitment. *J Womens Health (Larchmt)*. 2015;24(11):907–915.
15. Moshesh M, Peddada SD, Cooper T, et al. Intraobserver variability in fibroid size measurements: estimated effects on assessing fibroid growth. *J Ultrasound Med*. 2014;33(7):1217–1224.
16. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. *Epidemiology*. 1990;1(1):58–64.
17. Boucher B, Cotterchio M, Kreiger N, et al. Validity and reliability of the Block98 food-frequency questionnaire in a sample of Canadian women. *Public Health Nutr*. 2006;9(1):84–93.
18. Paul DR, Rhodes DG, Kramer M, et al. Validation of a food frequency questionnaire by direct measurement of habitual ad libitum food intake. *Am J Epidemiol*. 2005;162(8):806–814.
19. US Department of Agriculture. Food and nutrient database for dietary studies (FNDDS). Washington, DC: US Department of Agriculture; 2007. https://data.nal.usda.gov/dataset/food-and-nutrient-database-dietary-studies-fndds. Accessed December 2019.
20. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr*. 1997;65(4 suppl):1220S–1228S.
21. Chiaffarino F, Parazzini F, La Vecchia C, et al. Diet and uterine myomas. *Obstet Gynecol*. 1999;94(3):395–398.
22. Lambertino A, Turyk M, Anderson H, et al. Uterine leiomyomata in a cohort of Great Lakes sport fish consumers. *Environ Res*. 2011;111(4):565–572.
23. Kristal AR, Lampe JW. Prioritization of diet and cancer manuscripts: a brief primer. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):725–726.
24. Baird D, Wise LA. Childhood abuse and fibroids. *Epidemiology*. 2011;22(1):15–17.
25. Boynton-Jarrett R, Rich-Edwards JW, Jun HJ, et al. Abuse in childhood and risk of uterine leiomyoma: the role of emotional support in biologic resilience. *Epidemiology*. 2011;22(1):6–14.
26. Wise LA, Palmer JR, Rosenberg L. Lifetime abuse victimization and risk of uterine leiomyomata in Black women. *Am J Obstet Gynecol*. 2013;208(4):272.e1–272.e13.
27. Dueholm M, Lundorf E, Hansen ES, et al. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. *Am J Obstet Gynecol*. 2002;186(3):409–415.
28. Chapkin RS, Kim W, Lupton JR, et al. Dietary docosahexaenoic and eicosapentaenoic acid: emerging mediators of inflammation. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81(2–3):187–191.
29. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans*. 2017;45(5):1105–1115.
30. Pahl HL. Activators and target genes of Rel/NF-kappaB transcription factors. *Oncogene*. 1999;18(49):6853–6866.
31. Li K, Huang T, Zheng J, et al. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor alpha: a meta-analysis. *PloS One*. 2014;9(2):e88103.
32. Micallef MA, Garg ML. Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals. *Atherosclerosis*. 2009;204(2):476–482.
33. Ebrahimi M, Ghayour-Mobarhan M, Rezaiean S, et al. Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity. *Acta Cardiol*. 2009;64(3):321–327.
34. Malekshahi Moghadam A, Saedisomeolia A, Djalali M, et al. Efficacy of omega-3 fatty acid supplementation on serum levels of tumour necrosis factor-alpha, C-reactive protein and interleukin-2 in type 2 diabetes mellitus patients. *Singapore Med J*. 2012;53(9):615–619.
35. Jackson LW, Zullo MD, Goldberg JM. The association between heavy metals, endometriosis and uterine myomas among premenopausal women: National Health and Nutrition Examination Survey 1999–2002. *Hum Reprod*. 2008;23(3):679–687.
36. Johnstone EB, Louis GM, Parsons PJ, et al. Increased urinary cobalt and whole blood concentrations of cadmium and lead in women with uterine leiomyomata: findings from the ENDO Study. *Reprod Toxicol*. 2014;49:27–32.
37. Trabert B, Chen Z, Kannan K, et al. Persistent organic pollutants (POPs) and fibroids: results from the ENDO study. *J Expo Sci Environ Epidemiol*. 2015;25(3):278–285.