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Original Contribution

A Prospective Study of Dairy Intake and Risk of Uterine Leiomyomata

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Rates of uterine leiomyomata are 2–3 times higher among black women than white women. Dietary factors that differ in prevalence between these populations that could contribute to the disparity include dairy intake. During 1997–2007, the authors followed 22,120 premenopausal US Black Women's Health Study participants to assess dairy intake in relation to uterine leiomyomata risk. Because soy may be substituted for dairy, the effect of soy intake was also evaluated. Diet was estimated by using food frequency questionnaires in 1995 and 2001. Incidence rate ratios and 95% confidence intervals were estimated with Cox regression. There were 5,871 incident cases of uterine leiomyomata diagnosed by ultrasound ($n = 3,964$) or surgery ($n = 1,907$). Multivariable incidence rate ratios comparing 1, 2, 3, and ≥4 servings/day with <1 serving/day of total dairy were 0.94 (95% confidence interval (CI): 0.88, 1.00), 0.87 (95% CI: 0.78, 0.98), 0.84 (95% CI: 0.70, 1.01), and 0.70 (95% CI: 0.58, 0.86), respectively (*P*-trend <0.001). Incidence rate ratios comparing the highest (≥2 servings/day) with the lowest (<1 serving/week) intake categories were 0.81 (95% CI: 0.66, 0.99) for high-fat dairy, 0.80 (95% CI: 0.70, 0.91) for low-fat dairy, and 0.78 (95% CI: 0.68, 0.89) for milk. Soy intake was unrelated to uterine leiomyomata risk. This large prospective study of black women provides the first epidemiologic evidence of reduced uterine leiomyomata risk associated with dairy consumption.

African Americans; dairy products; leiomyoma; prospective studies; soy foods

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; IRR, incidence rate ratio.

Uterine leiomyomata, benign neoplasms of the myometrium (1–3), are the primary indication for hysterectomy (4, 5) in the United States and account for $2.2 billion annually in health care costs (6). Although the pathogenesis of uterine leiomyomata is poorly understood, steroid hormones (7, 8) and growth factors (9) are thought to play a role. The incidence of uterine leiomyomata is 2–3 times higher in black women than white women (4, 10–12), but risk factors such as reproductive history and obesity do not explain the racial disparity (10, 13–15). Dietary factors are of interest because of their antioxidant effects and their ability to modify endogenous hormones. However, there has been little study of dietary factors that differ in prevalence between black women and white women that could contribute to the uterine leiomyomata disparity, such as dairy intake (16–19).

National surveys show that black Americans consume fewer mean daily servings of dairy foods than white Americans do, and they have lower mean intakes of calcium, magnesium, and phosphorus (20). Specifically, mean daily dairy intake for black Americans is approximately 60% that for white Americans, and most of this difference is attributable to lower intake of reduced-fat or skim milk, with whole-milk intake being higher for black Americans (21). Black Americans are also less likely to take vitamin and mineral supplements (22, 23). Dairy foods have antitumorigenic components, including calcium, vitamin D (24), butyric acid (25), branched-chain fatty acids (25), and milk proteins (25). Conversely, milk contains estrogens and progesterone (26, 27), and high-fat dairy products in the United States contain fat-soluble hormones and growth factors (28) that may increase risk of hormone-dependent neoplasms.

To our knowledge, the only study that has examined dairy intake and uterine leiomyomata risk, a case-control study of Italian women (17, 18), found no association with milk or cheese consumption. Studies of other hormone-responsive conditions, such as breast and endometrial cancers, have

Table 1. Characteristics of 22,120 Participants According to Dairy and Soy Intake, Black Women's Health Study, United States, 1997–2007[a]

	High-fat Dairy, Servings/Week			Low-fat Dairy, Servings/Week			Soy, Servings/Week[b]		
	<1	4–6	≥14	<1	4–6	≥14	<1	4–6	≥7
No. of women	7,388	2,917	606	9,051	2,716	1,319	9,290	266	361
Age, years (mean)	35.5	33.9	32.0	34.8	34.5	34.6	34.0	33.2	34.7
Body mass index, kg/m^2 (mean)	27.5	28.1	28.1	27.2	28.5	28.9	27.9	26.0	25.5
Age at menarche, years (mean)	12.3	12.3	12.5	12.4	12.2	12.3	12.3	12.2	12.3
Parous (%)	53.6	58.8	71.4	58.9	54.1	58.0	56.2	40.3	42.9
Age at first birth for parous women, years (mean)	23.2	23.2	22.4	22.8	23.4	23.8	23.6	23.6	24.9
Time since last birth for parous women, years (mean)	10.3	9.7	9.0	10.4	9.8	9.6	9.2	9.5	8.5
Vigorous exercise, hours/week (mean)	1.9	1.5	1.3	1.4	1.8	2.2	1.6	2.5	2.5
Age at first oral contraceptives use for ever users, years (mean)	19.4	19.2	19.1	19.3	19.2	19.2	19.2	18.9	18.9
Alcohol intake, drinks/week (mean)	1.2	1.4	1.4	1.5	1.2	1.2	1.2	0.9	1.1
Current smoker (%)	10.8	16.5	20.0	17.0	11.0	11.1	12.8	5.3	6.1
Dairy foods intake, servings/week	4.2	9.2	27.3	3.5	8.2	27.9	7.1	7.9	9.2
Soy foods intake, servings/week	0.8	0.6	0.4	0.5	0.8	1.2	0.1	5.2	15.1
Energy intake, kcal/day (mean)	1,294	1,943	2,554	1,506	1,671	2,223	1,624	1,572	1,724
Multivitamin supplements use (%)	71.8	71.8	71.3	66.0	74.0	80.0	68.9	81.0	84.6
Calcium supplement use (%)	15.9	15.1	15.9	13.0	13.7	15.8	12.0	23.2	29.3
Calcium with vitamin D use (%)	9.8	7.3	7.9	6.7	9.4	11.5	6.8	9.3	12.2
Diabetes (%)	3.0	2.9	1.8	2.7	3.2	4.3	2.8	2.3	1.5
Education in 1995, years (mean)	15.0	14.8	14.1	14.7	15.1	15.1	15.0	15.6	15.6
Married (%)	39.9	39.4	38.6	38.7	40.7	41.9	40.6	32.4	37.2
Household income in 2003 (%)									
≤$25,000	9.4	9.8	21.4	12.4	7.8	10.6	9.9	7.4	8.5
$25,001–$50,000	29.8	34.5	35.3	32.3	29.7	29.4	31.2	28.5	29.7
$50,001–$100,000	41.1	37.8	33.0	39.7	41.8	38.8	39.9	44.2	40.3
>$100,000	19.8	17.9	10.3	15.6	20.8	21.3	19.0	19.9	21.5
Occupation in 1995 (%)									
White collar	60.6	58.8	43.4	54.6	65.3	61.6	60.3	74.5	68.0
Non-white-collar	37.7	38.9	51.4	42.9	33.3	36.0	37.6	25.0	31.0
Not employed and other	1.8	2.3	5.2	2.6	1.4	2.5	2.1	0.5	1.0
Region of residence in the United States (%)									
Northeast	24.5	29.8	34.3	28.3	26.4	25.8	26.2	32.0	33.0
Midwest	22.1	21.3	19.3	20.1	22.8	27.0	23.8	15.7	15.6
South	34.3	30.2	30.8	34.0	32.0	29.3	32.9	29.4	27.6
West	19.1	18.7	15.6	17.6	18.7	16.9	17.1	22.9	23.9

[a] Means and percentages were standardized to the age distribution of the cohort in 1997. Variables reported at the start of follow-up unless otherwise noted.

[b] Restricted to 10,786 participants who completed a 2001 food frequency questionnaire (on which they were asked about soy products) and who were still at risk of uterine leiomyomata in 2001.

produced mixed results. While earlier case-control and cohort studies of dairy intake and breast cancer have yielded conflicting findings (29), some (30–33) but not all (34–36) prospective studies have reported inverse associations between dairy intake and breast cancer, particularly among premenopausal women (31–33). In a meta-analysis, the pooled odds ratio for a one-serving increase in dairy intake associated with endometrial cancer was 0.97 (95% confidence interval (CI): 0.93, 1.01), but results varied across studies (37).

We prospectively evaluated the relation of dairy intake and some of its components—calcium, phosphorus, vitamin D, and butyric acid—to risk of uterine leiomyomata in the Black Women's Health Study, a large US prospective cohort study. Because black women experience a higher prevalence of lactose maldigestion than white women do (38, 39) and may substitute soy products for dairy, we also assessed the association of soy foods with uterine leiomyomata risk.

MATERIALS AND METHODS

Study population

The Black Women's Health Study is a national prospective cohort study of 59,000 African-American women aged 21–69 years (40). In 1995, participants enrolled by completing self-administered questionnaires mailed primarily to subscribers of *Essence* magazine. Questionnaires are mailed biennially to update exposures and identify new illnesses. Cohort retention exceeded 80% through 2007. The institutional review board of Boston University Medical Center approved the study protocol.

Assessment of outcome

On the 1999 and 2001 follow-up questionnaires, women were asked whether they had been diagnosed with "uterine fibroids" in the previous 2-year interval, the calendar year in which they were first diagnosed, and whether their diagnosis was confirmed by "pelvic examination" and/or by "ultrasound/hysterectomy." On the 2003, 2005, and 2007 follow-up questionnaires, we changed "hysterectomy" to "surgery (e.g., hysterectomy)" to capture data on women who had other surgeries, and we divided "ultrasound" and "surgery" into separate questions. Cases were classified as "surgically confirmed" if they reported diagnosis by "surgery" on the 2003 or later questionnaires or if they reported diagnosis by "ultrasound/hysterectomy" and "hysterectomy" under a separate question in 1999 or 2001.

Ultrasound, the standard procedure used to confirm diagnoses in clinical practice (3), has high sensitivity (99%) and specificity (91%) relative to histologic evidence (41, 42). We used an expanded outcome definition that includes cases diagnosed by surgery *and 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 severity or treatment preference (43). To maximize the specificity of uterine leiomyomata classification, pelvic examination cases ($n = 505$) were treated as noncases because these diagnoses could have represented other gynecologic pathology (44).

Assessment of diet

Diet was assessed in 2 questionnaire cycles (1995 and 2001) by using a modified version of the National Cancer Institute–Block short-form food frequency questionnaire (FFQ) (45, 46). In 1995, a 68-item FFQ was used to collect data on the consumption of specified foods during the previous year, with frequencies ranging from "never or <1 per month" to "≥ 2 per day" and portion sizes of "small," "medium," or "large" (46). Beverage frequencies ranged from "never or <1 per month" to "≥ 6 per day." The 2001 FFQ added several items and an extra portion size ("super size").

The FFQ provided data on specific foods, fat, protein, carbohydrate, vitamins, minerals, fiber, and total energy intake. For the 1995 FFQ, values for calcium, phosphorus, and other nutrients were calculated by using DIETSYS software (version 4.01) (45). Software for the 2001 FFQ (DIETCALC version 1.4.1; National Cancer Institute, Rockville, Maryland) provided estimates for calcium, phosphorus, vitamin D, and individual fatty acids. In 1995, participants reported their use of multivitamins, calcium supplements, and calcium with vitamin D supplements in the past year. Multivitamin use was updated on all follow-up questionnaires, whereas use of calcium and calcium with vitamin D supplements was updated in 1997 only.

The dairy group included skim milk/1% milk/buttermilk, 2% milk, whole milk, milk/cream in coffee or tea, ice cream (1995), regular ice cream (2001), low-fat ice cream (2001), frozen yogurt, yogurt, cheese and cheese spreads (not cottage cheese), and butter. Total dairy intake was calculated by summing servings of all dairy foods except butter because it is composed almost entirely of fat. Low-fat dairy intake was calculated by summing servings of skim/low-fat milk, yogurt, and low-fat ice cream (2001). High-fat dairy intake was calculated by summing servings of whole milk, milk/cream in coffee or tea, regular ice cream (2001), and cheese and cheese spreads (not cottage cheese). The 1995 FFQ included "ice cream" as a single line item. Therefore, we classified women into "regular" and "low-fat" categories based on their response to the question, When you eat the following foods, how often do you eat a low-fat or nonfat version of that food? (always = 100% regular, sometimes = 50% each type, rarely = 100% low fat). Total soy intake, assessed on the 2001 FFQ only, was estimated by summing the servings of soy milk, tofu, and soy and soy/veggie burgers.

Assessment of covariates

On the baseline survey, we collected data on age at menarche, oral contraceptive use, parity, age at each birth, height, weight, alcohol intake, smoking, education, marital status, occupation, and geographic region. We asked about household income in 2003 and about recency of pelvic examination and ultrasound screening in 2007. Reproductive factors, weight, smoking, marital status, and region were updated on follow-up questionnaires and were modeled as time-varying covariates in analysis.

Validation studies

Uterine leiomyomata. We assessed the accuracy of self-report in a random sample of 248 cases diagnosed by ultrasound or surgery. Cases were mailed supplemental surveys regarding their initial date of diagnosis, method(s) of confirmation, symptoms, and treatment and were asked for permission to review their medical records. We obtained medical records from 127 of the 128 women who gave us permission and confirmed the self-report for 122 (96%). Among the 188 (76%) who provided supplemental survey data, 71% reported uterine leiomyomata–related symptoms

Table 2. Risk of Uterine Leiomyomata in Relation to Dairy Food Intake, Black Women's Health Study, United States, 1997–2007

	Category of Intake, No. of Servings					*P*-Trend
	<1/Day	1/Day	2/Day	3/Day	≥4/Day	
Total dairy foods						
No. of cases	3,834	1,436	367	131	103	
No. of person-years	103,138	41,042	11,619	4,420	4,138	
IRR (95% CI)[a]	1.00 (ref)	0.94 (0.88, 1.00)	0.85 (0.76, 0.95)	0.80 (0.67, 0.96)	0.67 (0.55, 0.81)	<0.0001
IRR (95% CI)[b]	1.00 (ref)	0.94 (0.88, 1.00)	0.87 (0.78, 0.98)	0.84 (0.70, 1.01)	0.70 (0.58, 0.86)	<0.0001
	<1/Week	1–3/Week	4–6/Week	7–13/Week	≥14/Week	
Total dairy foods						
No. of cases	537	1,977	1,320	1,436	601	
No. of person-years	14,897	50,932	37,310	41,042	20,177	
IRR (95% CI)[a]	1.00 (ref)	1.08 (0.98, 1.19)	1.00 (0.90, 1.10)	0.98 (0.88, 1.08)	0.83 (0.73, 0.94)	<0.0001
IRR (95% CI)[b]	1.00 (ref)	1.08 (0.98, 1.19)	1.00 (0.90, 1.11)	0.97 (0.88, 1.08)	0.86 (0.76, 0.98)	<0.0001
High-fat dairy foods						
No. of cases	1,802	2,708	809	445	107	
No. of person-years	48,297	73,519	24,164	14,179	4,198	
IRR (95% CI)[a]	1.00 (ref)	0.99 (0.93, 1.06)	0.91 (0.83, 1.00)	0.85 (0.76, 0.95)	0.70 (0.57, 0.85)	<0.0001
IRR (95% CI)[b]	1.00 (ref)	1.01 (0.95, 1.08)	0.95 (0.87, 1.04)	0.91 (0.82, 1.02)	0.81 (0.66, 0.99)	0.007
Low-fat dairy foods						
No. of cases	2,179	1,882	845	701	264	
No. of person-years	61,440	50,999	22,713	19,808	9,399	
IRR (95% CI)[a]	1.00 (ref)	1.05 (0.98, 1.11)	1.06 (0.98, 1.15)	1.00 (0.92, 1.10)	0.81 (0.71, 0.92)	0.007
IRR (95% CI)[b]	1.00 (ref)	1.02 (0.96, 1.09)	1.02 (0.94, 1.11)	0.97 (0.89, 1.06)	0.80 (0.70, 0.91)	0.002
Milk						
No. of cases	2,701	1,802	637	473	258	
No. of person-years	71,457	50,324	17,384	15,646	9,546	
IRR (95% CI)[a]	1.00 (ref)	0.95 (0.89, 1.01)	1.00 (0.92, 1.09)	0.81 (0.73, 0.89)	0.72 (0.63, 0.82)	<0.0001
IRR (95% CI)[b]	1.00 (ref)	0.98 (0.92, 1.04)	1.00 (0.92, 1.09)	0.84 (0.76, 0.93)	0.78 (0.68, 0.89)	<0.0001
High-fat milk						
No. of cases	4,910	659	145	104	53	
No. of person-years	132,772	20,528	4,251	4,486	2,321	
IRR (95% CI)[a]	1.00 (ref)	0.91 (0.85, 0.97)	0.94 (0.80, 1.09)	0.65 (0.53, 0.78)	0.62 (0.47, 0.82)	<0.0001
IRR (95% CI)[b]	1.00 (ref)	0.95 (0.87, 1.03)	1.03 (0.87, 1.21)	0.70 (0.57, 0.85)	0.76 (0.58, 1.01)	0.001

Table continues

prior to diagnosis and 87% reported that their condition came to clinical attention because they sought treatment for symptoms or because a tumor was palpable during a routine pelvic examination. There were no appreciable differences between cases who did and did not release medical records with respect to risk factors for uterine leiomyomata (47).

Diet. A validation study of the 1995 FFQ was conducted in 1996–1998 (46). Approximately 400 Black Women's Health Study participants provided 3 nonconsecutive 24-hour telephone recall interviews and one 3-day food record over a 1-year period. Energy-adjusted and deattenuated Pearson correlations comparing nutrient estimates from the FFQ with averages from the combined recall/record data ranged from 0.5 to 0.8 (46). The correlation for calcium comparing FFQ with combined recall/record data was 0.6 (95% CI: 0.2, 0.9). In separate analyses, food group servings were compared with those estimated from the average of 3 dietary recalls (48). Mean servings per day for the ''dairy'' group were 1.0 (standard deviation, 1.3) for the FFQ and 1.1 (standard deviation, 1.0) for the dietary recalls.

Restriction criteria

Follow-up began in 1997 because method of uterine leiomyomata diagnosis was first included on the 1999 questionnaire. Of the 53,153 respondents to the 1997 questionnaire, we excluded postmenopausal women ($n = 16{,}594$) in whom

Table 2. Continued

	<1/Week	1–3/Week	4–6/Week	7–13/Week	≥14/Week	*P*-Trend
Low-fat milk						
No. of cases	3,606	1,277	396	376	216	
No. of person-years	99,476	35,216	10,502	11,540	7,623	
IRR (95% CI)[a]	1.00 (ref)	0.99 (0.93, 1.06)	1.04 (0.94, 1.16)	0.90 (0.81, 1.00)	0.79 (0.69, 0.91)	0.001
IRR (95% CI)[b]	1.00 (ref)	0.98 (0.92, 1.05)	1.02 (0.92, 1.13)	0.88 (0.79, 0.98)	0.80 (0.70, 0.92)	0.001
	<1/Week	**1–3/Week**	**4–6/Week**	**≥7/Week**		
Cheese						
No. of cases	3,451	2,052	243	125		
No. of person-years	96,141	57,120	7,248	3,848		
IRR (95% CI)[a]	1.00 (ref)	1.02 (0.96, 1.08)	0.99 (0.86, 1.13)	0.97 (0.81, 1.17)		0.95
IRR (95% CI)[b]	1.00 (ref)	1.02 (0.97, 1.08)	0.98 (0.86, 1.12)	0.97 (0.81, 1.16)		0.90
Ice cream						
No. of cases	4,429	1,198	158	86		
No. of person-years	123,452	33,708	4,864	2,335		
IRR (95% CI)[a]	1.00 (ref)	1.02 (0.95, 1.09)	0.94 (0.80, 1.10)	1.07 (0.86, 1.33)		0.88
IRR (95% CI)[b]	1.00 (ref)	1.02 (0.96, 1.09)	0.94 (0.80, 1.10)	1.05 (0.85, 1.31)		0.95
Yogurt (regular or frozen)						
No. of cases	3,912	1,505	313	141		
No. of person-years	111,165	40,272	8,369	4,551		
IRR (95% CI)[a]	1.00 (ref)	1.07 (1.01, 1.14)	1.08 (0.96, 1.22)	0.89 (0.75, 1.06)		0.57
IRR (95% CI)[b]	1.00 (ref)	1.04 (0.98, 1.11)	1.02 (0.91, 1.15)	0.85 (0.72, 1.01)		0.52
Butter						
No. of cases	4,815	889	99	68		
No. of person-years	134,155	25,910	2,284	2,009		
IRR (95% CI)[a]	1.00 (ref)	0.95 (0.89, 1.02)	1.21 (0.99, 1.48)	0.95 (0.75, 1.22)		0.92
IRR (95% CI)[b]	1.00 (ref)	0.97 (0.90, 1.04)	1.25 (1.02, 1.53)	1.00 (0.79, 1.27)		0.45

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref, referent.
[a] Adjusted for age at start of questionnaire cycle, time period, and energy intake.
[b] 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 contraceptives use, vigorous exercise, smoking, alcohol intake, body mass index, diabetes, education, occupation, income, marital status, and geographic region.

uterine leiomyomata are rare (3); women with a history of uterine leiomyomata ($n = 10{,}626$); women lost to follow-up after 1997 ($n = 980$); cases without data on diagnosis year ($n = 125$) or method ($n = 120$); and women with missing covariate data ($n = 582$), implausible energy intakes (<500 or $\geq 3{,}800$ kcal/day), or 10 or more missing items on the baseline FFQ ($n = 2{,}006$), leaving 22,120 women followed up from 1997 through 2007. Those excluded were less educated than those included, but they were similar with respect to parity, age at menarche, and other uterine leiomyomata risk factors.

Data analysis

Cases were women who reported a first diagnosis of uterine leiomyomata confirmed by ultrasound or surgery. Person-years were calculated from March 1997 until uterine leiomyomata diagnosis, menopause, death, loss to follow-up, or March 2007 (end of follow-up), whichever occurred first. Age- and period-stratified Cox regression was used to estimate incidence rate ratios and 95% confidence intervals for the associations of interest.

Foods were categorized on the basis of their frequency distributions within the analytic sample. Nutrients were categorized into quintiles after adjustment for total energy intake by using the nutrient residual method (49). Because the average of 2 or more FFQs may provide a more valid assessment of long-term dietary intake (50), we assessed 1995 diet in relation to uterine leiomyomata diagnosed through 2001 (1997–2001) and the average of 1995 and 2001 FFQs in relation to uterine leiomyomata diagnosed through 2007 (2001–2007). Participants with missing or implausible data

Table 3. Risk of Uterine Leiomyomata in Relation to Soy Food Intake, Black Women's Health Study, United States, 2001–2007

	Category of Intake, No. of Servings				*P*-Trend
	<1/Week	1–3/Week	4–6/Week	≥7/Week	
Total soy foods					
No. of cases	1,614	144	54	59	
No. of person-years	46,051	4,349	1,313	1,779	
IRR (95% CI)[a]	1.00 (ref)	0.95 (0.80, 1.13)	1.17 (0.89, 1.54)	0.98 (0.75, 1.27)	0.86
IRR (95% CI)[b]	1.00 (ref)	0.90 (0.76, 1.07)	1.11 (0.84, 1.46)	0.95 (0.73, 1.24)	0.80
Soy milk					
No. of cases	1,709	97	25	40	
No. of person-years	48,842	2,818	673	1,160	
IRR (95% CI)[a]	1.00 (ref)	1.00 (0.81, 1.22)	1.06 (0.71, 1.58)	1.00 (0.73, 1.37)	0.91
IRR (95% CI)[b]	1.00 (ref)	0.93 (0.75, 1.14)	1.00 (0.67, 1.49)	1.00 (0.73, 1.37)	0.79
	<1/Week	1–2/Week	≥3/Week		
Tofu					
No. of cases	1,797	38	36		
No. of person-years	51,488	1,068	936		
IRR (95% CI)[a]	1.00 (ref)	1.08 (0.78, 1.49)	1.13 (0.81, 1.57)		0.42
IRR (95% CI)[b]	1.00 (ref)	1.04 (0.75, 1.43)	1.09 (0.78, 1.53)		0.57
Soy/veggie burgers					
No. of cases	1,776	72	23		
No. of person-years	50,884	1,820	789		
IRR (95% CI)[a]	1.00 (ref)	1.16 (0.91, 1.46)	0.85 (0.56, 1.29)		0.99
IRR (95% CI)[b]	1.00 (ref)	1.13 (0.89, 1.43)	0.81 (0.54, 1.23)		0.75

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref, referent.
[a] Adjusted for age at start of questionnaire cycle, time period, and energy intake.
[b] 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 contraceptives use, vigorous exercise, smoking, alcohol intake, body mass index, diabetes, education, occupation, income, marital status, geographic region, and total dairy intake.

for the 2001 FFQ ($n = 6,563$) were assigned their 1995 FFQ data for 1997–2007.

A covariate was included in multivariable analyses if it was either an established risk factor for uterine leiomyomata (based on the literature) or a potential risk factor for uterine leiomyomata associated with exposure at baseline (Table 1). On the basis of these criteria, we constructed 2 sets of multivariable models: one that controlled for age (1-year intervals), time period (1997–1999, 1999–2001, 2001–2003, 2003–2005, 2005–2007), and energy intake (quintiles); and one that additionally controlled for reproductive and hormonal factors (51), including age at menarche (years), parity (0, ≥1 births), age at first birth (years), years since last birth (<5, 5–9, 10–14, 15–19, ≥20), oral contraceptive use (ever, never), and age at first oral contraceptive use (years), as well as the following lifestyle and socioeconomic factors (52–54): body mass index (<20, 20–24, 25–29, 30–34, ≥35 kg/m^2), vigorous exercise (hours/week), smoking (current, past, never), current alcohol intake (<1, 1–6, ≥7 drinks/week), education (≤12, 13–15, 16, ≥17 years), marital status (married/partnered, divorced/separated/widowed, single), occupation (white collar, non-white-collar, unemployed, missing), household income (≤$25,000, $25,001–50,000, $50,001–100,000, >$100,000, missing), geographic region (South, Northeast, Midwest, and West), and diabetes (no, yes).

Tests for trend were conducted by modeling a continuous version of the exposure variable assigned the median value of each category (55). To examine whether diet–uterine leiomyomata associations were modified by body mass index (<25, 25–29, ≥30 kg/m^2), total fat intake (tertiles), education (<16, ≥16 years), income (≤$50,000, >$50,000), or use of multivitamins and other supplements, we stratified by these factors. *P* values from interaction tests were obtained by using the likelihood ratio test comparing models with and without cross-product terms between the covariate and dietary factor. Departures from proportional hazards were evaluated in the same manner by using cross-product terms between each dietary factor and age (<35, ≥35 years) and time period (1997–2001, 2001–2007). Analyses were performed with SAS statistical software, version 9.1 (56).

RESULTS

Sample characteristics according to dairy and soy intake are shown in Table 1. High-fat dairy intake was positively associated with current smoking, non-white-collar occupations, energy intake, parity, and living in the Northeast and was inversely associated with exercise and income. Low-fat dairy intake was positively associated with body mass index, exercise, education, diabetes, supplement use, energy intake, and living in the Midwest and was inversely associated with current smoking and living in the South. Soy intake was positively associated with exercise, education, income, supplement use, and living in the Northeast and West and was inversely associated with body mass index, parity, diabetes, and living in the Midwest. Soy intake was inversely associated with high-fat dairy and positively associated with low-fat dairy intake.

During 164,358 person-years, 5,871 incident cases of uterine leiomyomata diagnosed by ultrasound ($n = 3,964$) or surgery ($n = 1,907$) were reported. Dairy intake was inversely associated with uterine leiomyomata risk (Table 2). Multivariable incidence rate ratios comparing 1, 2, 3, and ≥4 servings/day with <1 serving/day of total dairy were 0.94 (95% CI: 0.88, 1.00), 0.87 (95% CI: 0.78, 0.98), 0.84 (95% CI: 0.70, 1.01), and 0.70 (95% CI: 0.58, 0.86), respectively (*P*-trend <0.001). Multivariable incidence rate ratios comparing the highest with lowest intake categories of high-fat and low-fat dairy were nearly identical. Further control for total dairy intake in each of these models (to estimate the effect of substituting high-fat for low-fat dairy, and vice versa) attenuated the dairy-specific incidence rate ratios (data not shown), suggesting that any dairy food, regardless of fat content, was protective. Inclusion of butter as a high-fat dairy food made little difference in the incidence rate ratios (data not shown).

Milk accounted for 49% of mean total dairy consumption. Milk intake was inversely associated with uterine leiomyomata risk (≥14 vs. <1 serving/week: incidence rate ratio (IRR) = 0.78, 95% CI: 0.68, 0.89; *P*-trend <0.0001), and associations were similar for high-fat and low-fat milk. Intakes of cheese, ice cream, and butter were not materially associated with uterine leiomyomata, but yogurt showed a weak inverse association (Table 2). Soy intake was not associated with uterine leiomyomata with or without adjustment for total dairy (Table 3).

We examined vitamins, minerals, and fatty acids commonly found in dairy foods, including calcium, phosphorus, vitamin D, and butyric acid (Tables 4 and 5). Incidence rate ratios comparing the highest with the lowest quintiles of dietary calcium and phosphorus were 0.93 and 0.96, respectively, before adjustment for total dairy intake (Table 4). The association between uterine leiomyomata and calcium-to-phosphorus ratio, a measure of bioavailable calcium, was stronger than for each of these nutrients alone (IRR = 0.88, 95% CI: 0.81, 0.96; *P*-trend <0.001). Control for total dairy intake attenuated the incidence rate ratios for each of these nutrients. Dietary vitamin D was not associated with uterine leiomyomata risk (Table 5). Butyric acid, a fatty acid found predominantly in high-fat dairy foods, was inversely associated with uterine leiomyomata before adjustment for total dairy intake.

In multivariable models without dietary factors, incidence rate ratios for calcium supplements, calcium with vitamin D, and multivitamins were all close to 1.0 in the overall sample (IRR = 1.03, 95% CI: 0.96, 1.11; IRR = 1.03, 95% CI: 0.94, 1.13; and IRR = 1.04, 95% CI: 0.98, 1.10; respectively) and among women consuming <1 serving/day of total dairy (IRR = 1.01, 95% CI: 0.92, 1.11; IRR = 1.00, 95% CI: 0.89, 1.12; and IRR = 1.02, 95% CI: 0.95, 1.10, respectively). Results were similar when we 1) restricted our sample to the 5,828 women (26.4%) not using any supplements (IRRs for total dairy intake comparing 1, 2, 3, ≥4 vs. <1 servings/day = 0.86, 0.82, 0.65, and 0.65, respectively; *P*-trend = 0.003); 2) controlled for all 3 supplements when assessing the effects of total dairy and dietary calcium; and 3) controlled for multivitamins and calcium with vitamin D when assessing the effect of dietary vitamin D (data not shown).

Incidence rate ratios did not vary appreciably by case definition (ultrasound vs. surgery), body mass index, total fat intake, education, income, or recency of pelvic examination (data not shown). Associations for total dairy intake persisted among women aged <35 years, for whom uterine leiomyomata misclassification is lower (12): incidence rate ratios comparing 1, 2, 3, and ≥4 servings/day with <1 serving/day of total dairy were 0.94 (95% CI: 0.85, 1.05), 0.82 (95% CI: 0.67, 0.99), 0.71 (95% CI: 0.51, 0.98), and 0.69 (95% CI: 0.50, 0.96), respectively (*P*-trend = 0.001). Finally, use of a simple update method (i.e., using the 2001 FFQ for 2001–2007 instead of averaging the 1995 and 2001 FFQs) produced incidence rate ratios similar to those using the cumulative-average method (data not shown).

DISCUSSION

In the present study, both high-fat and low-fat dairy intakes were inversely associated with uterine leiomyomata risk among black women. Two components of dairy, calcium-to-phosphorus ratio and butyric acid, were also inversely associated with risk. However, control for total dairy intake attenuated the incidence rate ratios for these individual nutrients, suggesting that the inverse associations were operating through dairy intake.

Our results conflict with those from the sole study known to have examined dairy consumption and uterine leiomyomata, a case-control study (17) in which neither milk nor cheese consumption was related to risk of surgically diagnosed uterine leiomyomata. Our study differs from that one in that we collected prospective dietary data, thereby avoiding recall bias; we used a validated FFQ; and we controlled for energy intake, which can account for unmeasured confounding (57) and reduce measurement error (58).

A protective effect of dairy consumption on uterine leiomyomata risk is plausible. Calcium, a major component of dairy foods, may reduce fat-induced cell proliferation by maintaining intracellular calcium concentrations (59, 60). Because phosphorus and calcium compete for absorption in the intestine, a low dietary calcium-to-phosphorus ratio decreases calcium bioavailability (61). Therefore, the inverse association observed for calcium-to-phosphorus ratio

Table 4. Risk of Uterine Leiomyomata in Relation to Dietary Calcium and Phosphorus Intake, Black Women's Health Study, United States, 1997–2007

	Quintile of Intake					*P*-Trend
	1	2	3	4	5	
Calcium, mg/day						
Median	284.6	386.7	481.7	595.0	808.1	
No. of cases	1,183	1,272	1,139	1,167	1,055	
No. of person-years	32,443	32,355	32,365	32,391	32,510	
IRR (95% CI)[a]	1.00 (ref)	1.12 (1.03, 1.21)	1.01 (0.93, 1.10)	1.04 (0.96, 1.13)	0.94 (0.87, 1.02)	0.007
IRR (95% CI)[b]	1.00 (ref)	1.10 (1.02, 1.19)	1.00 (0.92, 1.08)	1.03 (0.95, 1.12)	0.93 (0.86, 1.02)	0.005
IRR (95% CI)[c]	1.00 (ref)	1.11 (1.03, 1.21)	1.03 (0.94, 1.12)	1.09 (0.99, 1.19)	1.04 (0.93, 1.16)	0.76
Phosphorus, mg/day						
Median	668.5	801.6	897.8	1000.4	1184.4	
No. of cases	1,176	1,258	1,144	1,185	1,100	
No. of person-years	32,796	32,694	32,791	32,746	32,835	
IRR (95% CI)[a]	1.00 (ref)	1.09 (1.01, 1.19)	1.00 (0.92, 1.08)	1.05 (0.96, 1.13)	0.97 (0.89, 1.05)	0.16
IRR (95% CI)[b]	1.00 (ref)	1.09 (1.01, 1.18)	1.00 (0.92, 1.08)	1.04 (0.96, 1.13)	0.96 (0.88, 1.04)	0.11
IRR (95% CI)[c]	1.00 (ref)	1.11 (1.03, 1.20)	1.03 (0.95, 1.12)	1.10 (1.01, 1.20)	1.06 (0.96, 1.17)	0.43
Calcium-to-phosphorus ratio						
Median	0.38	0.48	0.55	0.63	0.74	
No. of cases	1,237	1,193	1,250	1,093	1,043	
No. of person-years	32,398	32,400	32,292	32,448	32,521	
IRR (95% CI)[a]	1.00 (ref)	1.00 (0.92, 1.08)	1.05 (0.97, 1.14)	0.93 (0.86, 1.01)	0.89 (0.82, 0.96)	0.001
IRR (95% CI)[b]	1.00 (ref)	0.98 (0.91, 1.06)	1.04 (0.96, 1.12)	0.92 (0.84, 0.99)	0.88 (0.81, 0.96)	<0.001
IRR (95% CI)[c]	1.00 (ref)	0.99 (0.91, 1.07)	1.06 (0.98, 1.15)	0.95 (0.87, 1.04)	0.95 (0.85, 1.05)	0.05

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref, referent.
[a] Adjusted for age at start of questionnaire cycle, time period, and energy intake.
[b] 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 contraceptives use, vigorous exercise, smoking, alcohol intake, body mass index, diabetes, education, occupation, income, marital status, and geographic region.
[c] Additionally adjusted for total dairy foods.

supports the hypothesis that calcium protects against uterine leiomyomata. Butyric acid, present in milk fat, is a potent antitumorigenic agent that induces differentiation and apoptosis, and it inhibits proliferation and angiogenesis (25). The inverse, albeit weaker, association between butyric acid and uterine leiomyomata suggests another mechanism by which dairy foods might exert a protective effect. The lack of effect for dietary vitamin D is not entirely surprising because the largest sources of bioavailable vitamin D are derived from sun exposure and vitamin supplements (62).

We found no association between soy intake and uterine leiomyomata risk, but soy intake in US populations is low relative to that in countries such as Japan (19, 63) and is substantially lower than dairy intake (64). Soy is a primary source of phytoestrogens, specifically isoflavones (65), which may act as antiestrogens by competing with estrogen for receptor binding, possibly decreasing the bioavailability of estrogens (66, 67) or altering estrogen biosynthesis (68, 69). In vitro studies suggest that high levels of genistein, a soy-derived phytoestrogen, inhibit proliferation of cultured uterine leiomyomata cells (70, 71). Conversely, phytoestrogens can mimic estrogen activity (69). Although a case-control study found that urinary excretion of lignans (found in soybeans) was inversely associated with uterine leiomyomata (18), no association was found with urinary isoflavones. Likewise, a cross-sectional study found no association between intake of soy isoflavones and uterine leiomyomata (19).

Strengths of our study include the prospective design and use of validated measures for key variables. With prospective data collection, error in the reporting of diet is likely random, which generally biases results toward the null. Averaging diet measured at 2 time periods may reduce measurement error (50). We adjusted for multiple uterine leiomyomata risk factors and socioeconomic status measures associated with diet (72). High cohort retention, which decreases the potential for selection bias, is an additional strength. When we compared active participants with those lost to follow-up, minimal differences were found according to dairy intake or uterine leiomyomata risk factors.

A potential limitation of our study is that some uterine leiomyomata cases were likely missed, particularly those with asymptomatic disease. Although self-report was confirmed for almost all participants from whom we obtained

Table 5. Risk of Uterine Leiomyomata in Relation to Dietary Vitamin D and Butyric Acid Intake, Black Women's Health Study, United States, 2001–2007

	Quintile of Intake					*P*-Trend
	1	2	3	4	5	
Vitamin D, mcg/day						
Median	1.65	2.50	3.30	4.29	6.40	
No. of cases	358	379	380	356	375	
No. of person-years	10,531	10,525	10,533	10,536	10,546	
IRR (95% CI)[a]	1.00 (ref)	1.06 (0.92, 1.22)	1.07 (0.93, 1.23)	1.00 (0.87, 1.16)	1.06 (0.92, 1.23)	0.75
IRR (95% CI)[b]	1.00 (ref)	1.07 (0.93, 1.23)	1.11 (0.96, 1.28)	1.01 (0.88, 1.17)	1.08 (0.94, 1.25)	0.58
IRR (95% CI)[c]	1.00 (ref)	1.08 (0.93, 1.24)	1.13 (0.98, 1.30)	1.05 (0.91, 1.21)	1.15 (0.99, 1.33)	0.14
Among nonusers of multivitamins in 2001						
No. of cases	187	207	184	159	163	
IRR (95% CI)[a]	1.00 (ref)	1.13 (0.93, 1.37)	1.06 (0.86, 1.29)	0.92 (0.74, 1.13)	1.05 (0.85, 1.29)	0.79
IRR (95% CI)[b]	1.00 (ref)	1.16 (0.96, 1.40)	1.06 (0.87, 1.29)	0.96 (0.79, 1.17)	1.07 (0.87, 1.30)	0.97
IRR (95% CI)[c]	1.00 (ref)	1.17 (0.97, 1.42)	1.09 (0.89, 1.32)	1.00 (0.82, 1.23)	1.15 (0.94, 1.42)	0.30
Among users of multivitamins in 2001						
No. of cases	171	172	196	197	212	
IRR (95% CI)[a]	1.00 (ref)	0.99 (0.80, 1.22)	1.08 (0.88, 1.32)	1.07 (0.88, 1.31)	1.08 (0.89, 1.32)	0.48
IRR (95% CI)[b]	1.00 (ref)	0.96 (0.77, 1.20)	1.17 (0.95, 1.45)	1.08 (0.87, 1.33)	1.12 (0.91, 1.38)	0.36
IRR (95% CI)[c]	1.00 (ref)	0.97 (0.78, 1.20)	1.19 (0.96, 1.47)	1.10 (0.89, 1.36)	1.16 (0.94, 1.44)	0.24
Butyric acid (fatty acid 4:0), g/day						
Median	0.14	0.23	0.31	0.42	0.59	
No. of cases	391	409	364	362	325	
No. of person-years	10,525	10,522	10,562	10,559	10,601	
IRR (95% CI)[a]	1.00 (ref)	1.06 (0.92, 1.21)	0.94 (0.81, 1.08)	0.93 (0.81, 1.08)	0.83 (0.72, 0.96)	0.001
IRR (95% CI)[b]	1.00 (ref)	1.06 (0.93, 1.22)	0.96 (0.83, 1.11)	0.97 (0.84, 1.12)	0.88 (0.76, 1.02)	0.02
IRR (95% CI)[c]	1.00 (ref)	1.07 (0.94, 1.23)	0.98 (0.85, 1.13)	1.00 (0.86, 1.16)	0.92 (0.79, 1.07)	0.13

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref, referent.

[a] Adjusted for age at start of questionnaire cycle, time period, and energy intake.

[b] 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 contraceptives use, vigorous exercise, smoking, alcohol intake, body mass index, diabetes, education, occupation, income, marital status, and geographic region.

[c] Additionally adjusted for total dairy foods.

medical records, not all participants were screened. This concern was partly addressed by our observation of similar associations for dairy intake among women with a recent pelvic examination and younger women, for whom uterine leiomyomata misclassification is reduced (12). Our inability to directly assess vitamin D status through blood levels is another limitation, precluding us from examining its role as a mediator of the dairy effect. We were also unable to assess the role of lactose intolerance in explaining our dairy intake–uterine leiomyomata association. Although dairy intakes vary substantially among people who test positive for lactose intolerance (39, 73), there could be common or related genetic factors associated with dairy intake and uterine leiomyomata.

The Black Women's Health Study, although based on a large national cohort, is a self-selected sample of women with higher levels of education than the general black population. Nevertheless, prevalence estimates of uterine leiomyomata risk factors, such as age at menarche and parity, are similar to those found in national studies (74). In addition, FFQ estimates for dairy foods are consistent with national data on adult female African Americans (20, 21). Because the association between dairy intake and uterine leiomyomata did not vary appreciably by other factors, we expect our findings to extend to the general population of black women.

In summary, we found that high dairy intake was inversely associated with uterine leiomyomata risk among black women. Because dairy intake is appreciably lower among US black women than white women, differences in dairy intake may contribute to the racial discrepancy in rates of uterine leiomyomata. Future studies including black women and white women could test this hypothesis directly. Our case group likely represents women with symptomatic disease given that most validation study cases reported symptoms, a low percentage were detected incidentally, and uterine leiomyomata rates were similar to rates based on hospital-discharge data (47). Symptomatic disease has the greatest impact on a woman's quality of life and health care utilization (6). Confirmation of these findings is therefore a high priority.

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