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Soy-Based Infant Formula Feeding and Uterine Fibroid Development in a Prospective Ultrasound Study of Black/African-American Women

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Background: Uterine fibroids are highly prevalent, benign tumors. They are the leading indication for hysterectomy, and Black women are disproportionally burdened. Soy-based infant formula contains phytoestrogens, and exposure during sensitive developmental windows may adversely affect the developing uterus; early phytoestrogen treatment in rodent studies led to detrimental uterine effects, including increased fibroid risk in Eker rats. Limited epidemiological studies also have suggested increased fibroid development with soy formula infant feeding.

Objective: The goal of this study was to examine the association between soy formula feeding in infancy and fibroid development in adulthood.

Methods: We evaluated this association among 1,610 Black/African-American women age 23–35 y in the Study of Environment, Lifestyle & Fibroids (SELF). Soy formula feeding data was gathered directly from the participants' mothers (89%). A standardized ultrasound examination was conducted during 4 clinic visits over 5 y to detect fibroids ≥0.5 cm in diameter. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between soy formula feeding and incident fibroids adjusted for early-life and adult factors. Fibroid growth was calculated as change in log-volume for fibroids matched at successive visits.

Results: Of 1,121 fibroid-free participants at baseline, 150 (13%) were ever fed soy formula as infants, and 269 (24%) developed incident fibroids. We did not observe an association between ever being fed soy formula and incident fibroid risk (HR = 1.08; 95% CI: 0.75, 1.54). However, participants fed soy formula within 2 months of birth and for >6 months ($n = 53$) had an elevated risk of fibroid incidence in comparison with those never fed soy formula (HR = 1.56; 95% CI: 0.92, 2.65). Fibroid growth rates did not differ.

Discussion: Adding support to limited human data, this prospective fibroid study found that soy-based formula feeding during infancy was associated with a suggestive increase in risk of ultrasound-identified incident fibroids in adulthood. https://doi.org/10.1289/EHP11089

Introduction

Uterine fibroids are noncancerous tumors of the myometrium that develop in over 70% of women of reproductive age.[1] Symptomatic fibroids may cause heavy menstrual bleeding, pelvic pain, and urinary incontinence, and they are the leading cause of hysterectomy in the United States.[2,3] African-American women experience fibroid onset an estimated 10 y earlier than U.S. White women[4] and have a disproportionate health burden from fibroids.[5,6]

Phytoestrogens are compounds produced by plants that can act as estrogens by binding to estrogen receptors.[7] Isoflavones, a subgroup of phytoestrogens found primarily in legumes and soybeans, provide antioxidant and anti-inflammatory benefits; however, they can also act as endocrine disruptors, leading to adverse health conditions.[7,8] Researchers hypothesize that exposure to these estrogen-like compounds during sensitive developmental windows can have detrimental effects on reproductive systems.[9,10] Two of the most well-characterized phytoestrogens are the isoflavones daidzein and genistein that have chemical structures that resemble 17-β estradiol and are commonly found in soy-based infant formula.[7,8,11] Multiple laboratory animal studies have demonstrated that early exposure to phytoestrogens adversely affects reproductive tract development, including the uterus (reviewed in Suen et al.[9]). Female mice postnatally exposed to genistein exhibit posteriorization of the uterus that persists into adulthood and are infertile.[12–14] Eker rats treated with genistein postnatally exhibit epigenetic alterations in the myometrium and have increased fibroid incidence as adults.[15]

Though studies in humans are few, soy formula feeding during infancy has been linked to uterine fibroids in adulthood,[16–19] as well as to other female reproductive conditions including early and late menarche,[20,21] menstrual irregularities,[22,23] and endometriosis.[24] In the Infant Feeding and Early Development (IFED) Study that examined the postnatal development of estrogen-responsive tissues during the first 9 months of life, the uterine volume of girls fed soy formula decreased more slowly in comparison with the uterine volume of girls who were fed cow's milk formula, and vaginal tissue of the soy-fed infants was proliferative, indicating estrogenization.[25]

Medical indications for soy-based infant formula include use in term infants with congenital galactosemia or hereditary lactase deficiency, in families following a strict vegan diet, and for secondary lactose intolerance from acute gastroenteritis.[26,27] Despite indications that apply to a small percentage of infants,[27] soy formula is consumed by 12% of U.S. infants in the first year of life, with close to 16% of infants from higher-income households consuming soy-based formulas.[28] This widespread use of soy-based formula is likely due to other conditions, including cows' milk allergy or intolerance and desires to have relief of gas, fussiness, or colic symptoms.[25,29] In addition, because soy food consumption is beneficial for a variety of health outcomes,[30] some parents may believe that soy formula feeding in infancy protects against development of diseases later in life.[31] In the U.S., most infants are fed infant formula by 2 months of life or earlier, despite recommendations for exclusive breastfeeding for the first 6 months of an infant's life.[27,32] These patterns of infant feeding result in many infants exposed to soy formula during a sensitive developmental window.[33] Therefore, we assessed the association between soy formula feeding in infancy and fibroid development in adulthood in our cohort of young Black/African-American women, the group who develop the highest fibroid burden.[5,6] The Study of Environment, Lifestyle & Fibroids

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(SELF) followed fibroid development with standardized ultrasound examinations at 20-month intervals over 5 y, and most of our soy formula data were collected from participants' mothers.

Methods

Study Population

SELF is a prospective cohort study designed to evaluate risk factors for incidence and growth of uterine fibroids among young women with no prior clinical diagnosis of fibroids.[34] Established in 2010–2012, study recruitment was implemented in collaboration with the Henry Ford Health System (HFHS) in Detroit, Michigan. SELF enrollment was limited to women who self-identified as "Black or African American" among a list of racial and ethnic categories from which they were instructed to choose all that applied. Of 3,200 women screened, 89% met eligibility criteria, and 1,693 women ages 23–35 y attended an orientation and completed all additional enrollment activities. To assess fibroids, a transvaginal ultrasound examination was conducted at the enrollment clinic visit and during three subsequent clinic visits at approximately 20-month intervals through 2018. Self-reported medical history and health-related behaviors, such as pregnancy history, use of hormonal contraception, and smoking status were collected at each visit via computer-assisted telephone interviews, web-based questionnaires, and hard-copy questionnaires. Participants who missed a visit were invited to attend the next study visit. Ninety-five percent of enrolled participants attended at least two visits, 79% attended all four study visits, and over 90% attended the final visit. SELF was approved by the institutional review boards of the National Institute of Environmental Health Sciences and HFHS. All participants provided informed consent as part of the enrollment process.

Assessment of Soy-Based Formula Feeding during Infancy

Exposure to soy-based infant formula was assessed via an early-life questionnaire given out at time of enrollment. Two versions of the early-life questionnaire were created with the same questions. Participants who reported being able to speak with their mother were given a version designed in an interview format so the questions could be systematically asked of mothers. Remaining participants were given a version that simply listed the questions, and they were instructed to get help answering the questions from relatives and family friends who were present during their infancy and childhood. The early-life questionnaire was completed by 1,628 participants (96%), of whom 89% got answers from their mothers.

Participants were asked if they were ever fed soy formula as an infant with response options of "yes," "no," or "do not know." For those who answered yes, they were asked about how many months they were fed soy formula with the following response options: "<1 month," "1 to 3 months," "4 to 6 months," ">6 months," or "do not know." Participants fed soy formula were also asked whether they were started on soy formula within the first 2 months of their life, with response options of "yes," "no," or "do not know."

Using these data, we created the following four exposure variables: dichotomous exposure of soy formula feeding in infancy (ever or never), timing of soy formula initiation (never fed, within first 2 months after birth, or more than 2 months after birth), soy formula feeding duration (never fed, ≤6 months, or >6 months), and a composite variable combining timing of initiation and duration of soy formula feeding (never fed, initiated within 2 months after birth and >6 months duration, or initiated more than 2 months after birth or ≤6 months duration).

Assessment of Fibroids

The methods for assessing fibroid incidence and growth in the SELF cohort have been previously documented in detail.[34,35] Briefly, transvaginal ultrasounds were conducted by experienced and trained sonographers using 2-D equipment at each clinic visit. A standardized protocol was followed to detect, measure, and document fibroids ≥0.5 cm in diameter. The largest six fibroids were measured in three perpendicular planes at three separate times during the examination. Fibroid volume was calculated from each of the three fibroid measurements based on the ellipsoid formula, and these calculations were averaged to estimate the volume of each fibroid. Video and still images were archived, and an 8% sample for each sonographer per month, oversampled for fibroid cases, was reviewed by the lead sonographer for quality-control purposes.

Our overall sample of 1,610 participants who returned for one or more follow-up ultrasound visit (Figure 1) included 23% ($n = 364$) who had fibroids detected at enrollment[35] and who were excluded from the incidence analysis. Also excluded were five participants who had a hysterectomy for nonfibroid indications prior to their first follow-up visit. Last, 9 participants were excluded due to factors that impeded ultrasound visualization, resulting in a total of 1,232 participants available for analysis of incidence. Incident fibroid cases were defined as participants who were fibroid-free at the initial ultrasound but had fibroids detected at a subsequent ultrasound.

Fibroids included in the growth analysis were matched across two consecutive clinic visits by the lead sonographer and principal investigator using archived images and fibroid location. A total of 399 participants were included in the growth analysis, of which 245 had prevalent fibroids detected at enrollment and 154 had fibroids that were detected over the course of follow-up. There were 1,259 interval growth measurements from successive visits. The median interval length was 19 months (25th–75th percentiles: 18–21).

Covariates

Characteristics of each participant's mother during pregnancy with the participant and early-life characteristics of each participant were ascertained on the early-life questionnaire. Prepregnancy

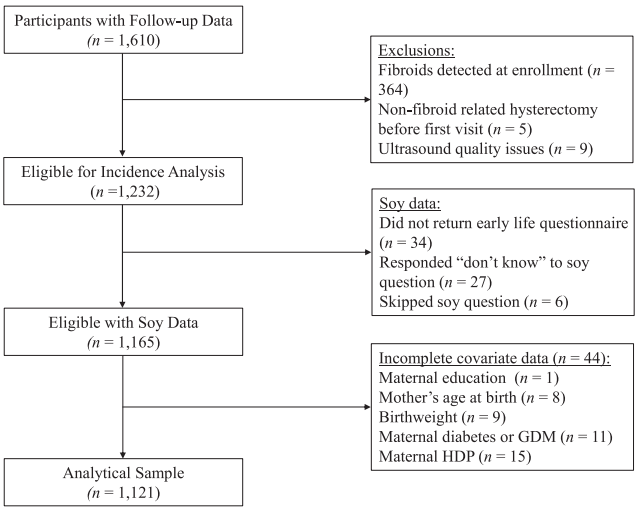

Figure 1. Flowchart of participant selection for incidence analysis, Study of Environment, Lifestyle & Fibroids (SELF), 2010–2018. Of the 1,610 participants at baseline with follow-up data available, a total of 1,121 were included in the analytical sample for incident fibroids ($n = 269$).

and gestational diabetes (GDM) were assessed separately by asking whether the participant's mother had diabetes or "sugar" before or during the pregnancy of the participant. Maternal hypertensive disorders of pregnancy (HDP) were assessed by asking whether the mother developed preeclampsia, eclampsia, or toxemia during the relevant pregnancy, and a separate question asked whether the mother developed pregnancy-related high blood pressure. Mother's age at the time of the participant's birth and participant's birth weight were also assessed on the early-life questionnaire. Participants were asked in a separate questionnaire to report the highest year or level of school completed by their mothers or primary caregivers when they were ~10 y old. Other factors of interest were asked of the participant at enrollment and at each follow-up visit by computer-assisted questionnaires and telephone interviews. These time-varying factors included participant age, hormonal contraception history, pregnancy history, current cigarette use, and household income. Body mass index (BMI), also a time-varying factor, was calculated using height measured at enrollment and weight measured at each clinic visit.

Statistical Analyses

Maternal pregnancy factors, early-life factors, and adult characteristics of participants were descriptively examined according to ever vs. never soy-based formula feeding during infancy. To examine the association between infant soy formula feeding and fibroid incidence, we used Cox proportional hazard regression, with age as the time scale to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). When fitting Cox models, we assigned fibroid incidence at the time when a fibroid was first seen on ultrasound among those fibroid-free at enrollment. Participants contributed follow-up time from the enrollment clinic visit until they had an incident fibroid detected at a study visit, nonfibroid-related hysterectomy, loss to follow-up, or their final study visit, whichever came first.

To identify important covariates for adjustment, we examined the literature on indications for soy formula feeding,[27] risk factors for fibroids,[2,36] and studies that examined the association of the two.[16–19] Given the lack of consistent findings to identify causal risk factors for fibroid development, we conducted the analyses considering three models for adjustment using factors with support from prior studies, or associations in our data. We completed three models: minimal adjustment for age by using age as the time scale (Model 1), adjustment for early-life factors only (Model 2), and adjustment for both early-life factors and time-varying participant adult factors (Model 3). The early-life factors were maternal prepregnancy diabetes or GDM (no or yes), maternal HDP (no or yes), mother's age at participant's birth (<20, 20–29, or ≥30 y), highest education level of participant's mother at age 10 (≤high school/GED or some college/college degree), and birth weight (<2,500 or ≥2,500 grams). We used birth weight as a surrogate for preterm birth because low birth weight is a result of preterm birth or intrauterine growth restriction[37] and our data on gestational age were incomplete.[38] These early-life factors might have influenced choice of soy formula feeding and have been associated with fibroid prevalence, though the studies are few, and data are limited. Maternal fibroid history was assessed as a potential confounder, but it did not affect observed associations between soy formula feeding and fibroid development, so it was not included in final models. Participant adult factors were time since last injectable depot medroxyprogesterone acetate (DMPA) use (never, <2 y, or ≥2 y since last use), parity (0, 1–2, or ≥3 births), time since last birth (<3 or ≥3 y ago including no births), current smoking (no or yes), BMI (<25.0, 25.0–<30.0, 30.0–<35.0, 35.0–<40.0, or ≥40.0 kg/m^2), and household income (<USD $20,000 or ≥USD $20,000 per year). All participant adult factors were included as time-varying covariates in the models. Because these factors were associated with fibroid incidence and/or growth in our sample, adjusting for them could increase precision of the association of interest and improve model fit. We ran complete case analysis on all models. After excluding participants missing data on soy formula feeding during infancy ($n=67$) and those missing any covariate data ($n=44$), our final analytical data set for incidence comprised 1,121 participants (Figure 1). We tested proportionality of hazards based on a test of interaction between our composite soy formula feeding variable and age in our fully adjusted model. Tests of proportionality of hazards did not indicate violation of model assumptions ($p=0.84$).

Fibroid growth was calculated as the difference in the natural logarithm of the volumes, and this volume change was scaled to a growth rate over 18 months. Factors affecting growth were analyzed using a mixed model [GLIMMIX procedure in SAS (version 9.4; SAS Institute Inc.)].[35,39] The random effects portion of our mixed models accounted for correlation among fibroids from the same participant and for correlation over time for the same fibroid as well as greater variability among our volume measures for small vs. large fibroids.[35] For ease of interpretation, the logarithmic growth rate scale was back transformed to estimate percent difference between exposed and unexposed in volume change per 18 months. When examining fibroid growth, all models were adjusted for fibroid volume, number of fibroids, and age,[35] as well as for covariates considered in the three models for adjustment as described for the incidence analyses (minimal adjustment, additional adjustment for early-life factors, and further adjustment for adult factors).

We conducted several sensitivity analyses. First, we restricted the incidence and growth analyses to only those participants whose mothers directly provided data on maternal and early-life exposures, excluding participants who completed the questionnaire with help from others. This restriction allowed us to evaluate the sensitivity of the findings to potential misclassification based on use of reports from relatives and family friends. Second, to account for varying infant feeding patterns, we repeated the incidence analyses, adjusting for whether participants were breastfed during their infancy. Third, we tested the robustness of our incidence findings by moving the time of incidence to the midpoint of each interval instead of the end. Last, we examined the extent to which results from our growth analyses might be influenced by outliers by excluding fibroids that had residuals for growth >3 standard deviations from the mean as had been done in prior fibroid growth analyses.[35,39]

All statistical analyses were conducted with SAS (version 9.4; SAS Institute Inc.).

Results

Maternal, early-life, and enrollment characteristics for the 1,610 participants who had one or more follow-up visits and by exposure to soy-based infant formula for the incidence ($n=1,121$) and growth ($n=399$) analytical samples are shown in Table 1. Mothers of soy formula–exposed participants in comparison with nonexposed tended to be older at the time of the participant's birth and more educated. Participants ever fed soy formula were more likely to have been breastfed and to have come from a pregnancy complicated by hypertension. At time of enrollment in SELF, participants ever fed soy formula as infants tended to be younger and have higher household incomes in comparison with those who were unexposed. In adulthood, parity, smoking, and

Table 1. Maternal, early-life, and enrollment characteristics of 1,610 participants by soy-based formula feeding during infancy, Study of Environment, Lifestyle & Fibroids (SELF), 2010–2018.

Characteristic	Overall cohort	Incidence analysis sample		Growth analysis sample	
	Overall ($n = 1,610$) *n* (%)	Never fed soy formula ($n = 971$) *n* (%)	Ever fed soy formula ($n = 150$) *n* (%)	Never fed soy formula ($n = 355$) *n* (%)	Ever fed soy formula ($n = 44$) *n* (%)
Pregnancy and demographic factors of participant's mother					
Prepregnancy or gestational diabetes[a]					
No	1,441 (95)	921 (95)	137 (91)	340 (96)	42 (95)
Yes	80 (5)	50 (5)	13 (9)	15 (4)	2 (5)
Don't know response/missing	28	0	0	0	0
Hypertensive disorders of pregnancy[a]					
No	1,313 (87)	866 (89)	116 (77)	309 (87)	35 (80)
Yes	193 (13)	105 (11)	34 (23)	46 (13)	9 (20)
Don't know response/missing	43	0	0	0	0
Smoked during pregnancy[a]					
No	1,154 (76)	729 (76)	117 (78)	271 (77)	35 (80)
Yes	366 (24)	234 (24)	33 (22)	83 (23)	9 (20)
Don't know response/missing	29	8	0	1	0
Age at participant's birth (y)[a]					
<20	328 (21)	217 (22)	30 (20)	74 (21)	5 (11)
20–29	906 (59)	575 (59)	81 (54)	210 (59)	29 (66)
≥30	303 (20)	179 (19)	39 (26)	71 (20)	10 (23)
Missing	12	0	0	0	0
Highest education at age 10 y of participant[b]					
≤High school/GED	742 (46)	463 (48)	56 (37)	165 (46)	13 (30)
Some college or associate/technical degree	672 (42)	414 (42)	69 (46)	141 (40)	22 (50)
Bachelor/master/doctoral degree	194 (12)	94 (10)	25 (17)	49 (14)	9 (20)
Missing	2	0	0	0	0
Early life factors of participant					
Participant's birth weight (g)[a]					
<2,500	204 (13)	135 (14)	19 (13)	43 (12)	4 (9)
≥2,500	1,327 (87)	836 (86)	131 (87)	312 (88)	40 (91)
Don't know response/missing	18	0	0	0	0
Breastfed during infancy[a]					
Never breastfed	1,039 (68)	685 (71)	72 (48)	254 (72)	24 (55)
Breastfed	488 (32)	283 (29)	78 (52)	100 (28)	20 (45)
Don't know response/missing	22	3	0	1	0
Duration, among those breastfed:					
≤6 months	320 (70)	176 (67)	58 (78)	59 (63)	19 (95)
>6 months	138 (30)	88 (33)	16 (22)	34 (37)	1 (5)
Don't know response/missing	30	19	4	7	0
Fed soy formula during infancy[a]					
Never fed soy formula	1,313 (87)	971 (100)	0 (0)	355 (100)	0 (0)
Ever fed soy formula	196 (13)	0 (0)	150 (100)	0 (0)	44 (100)
Don't know response/missing	40	0	0	0	0
Timing of initiation, among those ever fed soy formula:					
Started within first 2 months after birth	105 (57)	0 (0)	81 (58)	0 (0)	29 (66)
Started later than 2 months after birth	79 (43)	0 (0)	59 (42)	0 (0)	15 (34)
Don't know response/missing	12	0	10	0	0
Duration, among those ever fed soy formula:					
≤6 months	89 (48)	0 (0)	65 (45)	0 (0)	19 (43)
>6 months	97 (52)	0 (0)	78 (55)	0 (0)	25 (57)
Don't know response/missing	10	0	7	0	0
Initiation and duration, among those ever fed soy formula:					
Initiated within 2 months after birth and >6-month duration	66 (36)	0 (0)	53 (38)	0 (0)	21 (48)
Initiated more than 2 months after birth or ≤6-month duration	115 (64)	0 (0)	85 (62)	0 (0)	23 (52)
Don't know response/missing	15	0	12	0	0
Participant characteristics at enrollment					
Age at ultrasound (y)					
23–25	362 (22)	243 (25)	50 (33)	47 (13)	3 (7)
26–28	395 (25)	249 (26)	37 (25)	80 (23)	14 (32)
29–31	442 (27)	254 (26)	41 (27)	113 (32)	13 (29)
32–35	411 (26)	225 (23)	22 (15)	115 (32)	14 (32)
Yearly household income of participant (USD)					
<$20,000	734 (46)	441 (46)	63 (43)	141 (40)	13 (30)
$20,000 – $50,000	590 (37)	377 (39)	58 (39)	131 (37)	19 (43)
>$50,000	275 (17)	145 (15)	27 (18)	81 (23)	12 (27)
Don't know response/missing	11	8	2	2	0
Parity					
0 births	626 (39)	348 (36)	65 (43)	173 (49)	21 (48)
1–2 births	708 (44)	441 (45)	60 (40)	141 (40)	19 (43)
≥3 births	276 (17)	182 (19)	25 (17)	41 (11)	4 (9)

Table 1. (*Continued.*)

Characteristic	Overall cohort	Incidence analysis sample		Growth analysis sample	
	Overall ($n = 1{,}610$) *n* (%)	Never fed soy formula ($n = 971$) *n* (%)	Ever fed soy formula ($n = 150$) *n* (%)	Never fed soy formula ($n = 355$) *n* (%)	Ever fed soy formula ($n = 44$) *n* (%)
Time since last birth					
Within 3 y	365 (23)	246 (25)	36 (24)	58 (16)	5 (11)
≥3 y ago, or no births	1,245 (77)	725 (75)	114 (76)	297 (84)	39 (89)
Smoking status					
Non/former	1,296 (80)	781 (80)	130 (87)	293 (83)	37 (84)
Current	314 (20)	190 (20)	20 (13)	62 (17)	7 (16)
Body mass index (kg/m^2)					
<25.0	322 (20)	197 (20)	25 (17)	66 (19)	7 (16)
25.0 to <30.0	341 (21)	203 (21)	34 (22)	72 (20)	8 (18)
30.0 to <35.0	307 (19)	182 (19)	31 (21)	72 (20)	14 (32)
35.0 to <40.0	268 (17)	168 (17)	22 (15)	68 (19)	4 (9)
≥40.0	372 (23)	221 (23)	38 (25)	77 (22)	11 (25)
DMPA use					
Never used	918 (57)	502 (52)	87 (58)	238 (67)	28 (64)
<2 y since last use	188 (12)	105 (11)	17 (11)	28 (8)	3 (7)
≥2 y since last use	503 (31)	364 (37)	46 (31)	89 (25)	13 (29)
Missing	1	0	0	0	0

Note: DMPA, depot medroxyprogesterone acetate; GED, high school equivalency diploma.
[a]Frequencies and percentages for the overall cohort are based on a total of 1,549 participants because 61 participants did not complete the early-life questionnaire.
[b]Maternal education data were collected from all participants on the enrollment questionnaire.

use of DMPA were similar for those ever and never fed soy formula as infants.

During 4,841 person-years of follow-up, participants had an average 3.8 (±0.5) study visits and a median length of study participation of 4.7 y (25th–75th percentiles: 4.6–4.9). Five participants (0.4%) were censored due to hysterectomy for nonfibroid indications and 269 participants (24%) had incident fibroids detected; median volume at detection was 0.6 cm^3 (25th–75th percentiles: 0.2–1.4 cm^3). In this sample of young women, with no clinical diagnosis of fibroids before enrollment, most of the fibroids followed for growth were also small (median volume, 3.3 cm^3, 25th–75th percentiles: 0.8–13.7 cm^3; average diameter, 1.8 cm).

In analyses adjusted for age (Table 2, Model 1), we did not observe an association between ever being fed soy formula as an infant and incident fibroid risk (HR = 1.03; 95% CI: 0.73, 1.47). However, our data showed that participants fed soy formula within 2 months of birth in comparison with those never fed soy formula had a 24% increased risk of incident fibroids (HR = 1.24; 95% CI: 0.81, 1.91). Similarly, participants exposed to soy formula feeding for more than 6 months in infancy in comparison with those never fed soy formula had increased fibroid incidence (HR = 1.21; 95% CI: 0.77, 1.90). Considering both the timing and duration of soy formula feeding, soy formula feeding within 2 months of birth and for >6 months′ duration (vs. never fed soy formula) was associated with a 37% increased risk of incident fibroids (HR = 1.37; 95% CI: 0.82, 2.29). The magnitudes of the associations were stronger in models additionally adjusted for early-life characteristics (Model 2) and both early-life and time-varying adult characteristics (Model 3), except for models that examined duration of soy formula feeding ≤6 months, where the

Table 2. Association between soy-based formula feeding in infancy and fibroid incidence in adulthood among 1,121 participants in Study of Environment, Lifestyle & Fibroids (SELF), 2010–2018.

Exposure	No. exposed	Incident cases	Person-years	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
Soy formula feeding						
Never fed[d]	971	233	4,178	Ref	Ref	Ref
Ever fed	150	36	663	1.03 (0.73, 1.47)	1.05 (0.74, 1.51)	1.08 (0.75, 1.54)
Timing of soy formula feeding initiation[e]						
Within 2 months after birth	81	23	351	1.24 (0.81, 1.91)	1.32 (0.85, 2.04)	1.36 (0.88, 2.12)
More than 2 months after birth	59	12	265	0.86 (0.48, 1.53)	0.84 (0.47, 1.51)	0.81 (0.45, 1.46)
Duration of soy formula feeding[e]						
≤6 months	65	14	290	0.88 (0.51, 1.51)	0.90 (0.52, 1.54)	0.91 (0.52, 1.56)
>6 months	78	21	341	1.21 (0.77, 1.90)	1.24 (0.79, 1.96)	1.28 (0.81, 2.03)
Initiation and duration of soy formula feeding[e]						
Initiated within 2 months after birth and >6-month duration	53	16	227	1.37 (0.82, 2.29)	1.44 (0.86, 2.42)	1.56 (0.92, 2.65)
Initiated more than 2 months after birth or ≤6-month duration	85	19	379	0.94 (0.59, 1.49)	0.95 (0.59, 1.52)	0.92 (0.57, 1.47)

Note: CI, confidence interval; DMPA, depot medroxyprogesterone acetate; GED, high school equivalency diploma; HR, hazard ratio; Ref, referent.
[a]Cox model with age as the time scale and no additional covariate adjustment.
[b]Adjusted for early-life factors of maternal prepregnancy or gestational diabetes (no or yes), maternal hypertensive disorders of pregnancy (no or yes), mother's age at participant's birth (<20, 20–29, or ≥30 y), birth weight (<2,500 or ≥2,500 grams), and highest education of mother at age 10 y (≤high school/GED or some college/college degree).
[c]Adjusted for early-life factors as well as time-varying adult factors of time since last DMPA use (never, <2 y, or ≥2 y since last use), parity (0, 1–2, or ≥3 births), time since last birth (<3 or ≥3 y ago including no births), current smoking (no or yes), body mass index (<25.0, 25.0 to <30.0, 30.0 to <35.0, 35.0 to <40.0, or ≥40.0 kg/m^2), and household income (<USD $20,000 or ≥USD $20,000 per year).
[d]Never fed is referent for all exposure categories.
[e]Numbers of exposed do not sum to 150 because of missing data: timing of soy formula initiation ($n = 10$), duration of soy formula feeding ($n = 7$), or combination of initiation and duration of soy formula feeding ($n = 12$).

Table 3. Association between soy-based formula feeding in infancy and fibroid growth over 18 months in adulthood among 399 participants in Study of Environment, Lifestyle & Fibroids (SELF), 2010–2018.

Exposure	Growth intervals[a]	Model 1[b]	Model 2[c]	Model 3[d]
		Estimated percentage difference in growth (95% CI)		
Soy formula feeding				
Never fed[e]	1,109	Ref	Ref	Ref
Ever fed	150	−3.1 (−16.4, 12.4)	−2.9 (−16.4, 12.8)	−1.3 (−14.0, 13.4)
Timing of soy formula feeding initiation				
Within 2 months after birth	96	−0.6 (−17.0, 18.9)	−0.5 (−17.1, 19.3)	1.5 (−14.3, 20.2)
More than 2 months after birth	54	−7.4 (−27.1, 17.7)	−7.1 (−27.1, 18.4)	−5.9 (−24.5, 17.3)
Duration of soy formula feeding				
≤6 months	78	−6.2 (−23.4, 14.9)	−6.3 (−23.8, 15.2)	−3.1 (−19.7, 17.0)
>6 months	72	0.2 (−18.2, 22.7)	0.5 (−18.0, 23.3)	0.6 (−17.1, 22.2)
Initiation and duration of soy formula feeding				
Initiated within 2 months after birth and >6-month duration	55	2.6 (−18.1, 28.5)	2.0 (−18.7, 27.9)	4.7 (−15.7, 30.1)
Initiated more than 2 months after birth or ≤6-month duration	95	−6.6 (−22.4, 12.5)	−6.0 (−22.2, 13.5)	−4.7 (−19.7, 13.0)

Note: CI, confidence interval; DMPA, depot medroxyprogesterone acetate; GED, high school equivalency diploma; Ref, referent.
[a]Growth analyses were conducted among fibroids that could be matched across successive visits. This includes fibroids from 399 participants with 1,259 interval growth measurements. Participants could contribute multiple fibroids and fibroids could be followed across multiple intervals.
[b]Adjusted for fibroid characteristics of volume of fibroid (<0.5 cm^3, 0.5 to <4.2 cm^3, 4.2 to <14.1 cm^3, or ≥14.1 cm^3), number of fibroids (ordinal; 1, 2, 3, or ≥4), and age (continuous).
[c]Adjusted for fibroid characteristics and age as well as early-life factors of maternal prepregnancy or gestational diabetes (no or yes), maternal hypertensive disorders of pregnancy (no or yes), mother's age at participant's birth (<20, 20–29, or ≥30 y), birth weight (<2,500 or ≥2,500 grams), and highest education of mother at age 10 y (≤high school/GED or some college/college degree).
[d]Adjusted for fibroid characteristics, age, early-life factors, and time-varying adult factors of time since last DMPA use (never, <2 y, or ≥2 y since last use), parity (0, 1–2, or ≥3 births), time since last birth (<3 or ≥3 years ago including no births), current smoking (no or yes), body mass index (<25.0, 25.0 to <30.0, 30.0 to <35.0, 35.0 to <40.0, or ≥40.0 kg/m^2), and household income (<USD $20,000 or ≥USD $20,000).
[e]Never fed is referent for all exposure categories.

estimates were slightly attenuated or fluctuated. For example, considering soy formula feeding initiated within 2 months after birth and >6 months in duration, after adjustment for early-life factors (Model 2), the aHR was 1.44 (95% CI: 0.86, 2.42), and after adjustment for both early-life and adult factors (Model 3), the aHR was 1.56 (95% CI: 0.92, 2.65).

Fibroid growth rates did not differ based on exposure to soy formula in infancy (Table 3). In comparison with an estimated measure of 69% growth per 18 months for all fibroids in our analytical dataset, the estimated difference in growth rate over 18 months comparing participants ever and never fed soy formula as infants was small and accompanied by a wide CI (−3.1%; 95% CI: −16.4%, 12.4%). Estimated differences between participants ever and never fed soy formula as infants were similarly of small magnitude after adjustment for early-life and adult factors, and growth rates did not differ when initiation and duration of soy formula feeding were considered (Table 3, Models 2 and 3).

In our sensitivity analyses restricting the study population to participants whose mothers completed or helped complete the early-life questionnaire, estimates for risk of incidence fibroids (Table S1) and differences in fibroid growth (Table S2) were similar to the estimates obtained in our main analyses. When we adjusted for breastfeeding during the participants' infancies, our estimates for the association between soy formula feeding and fibroid incidence were slightly strengthened (Table S3), and assigning fibroid onset to the midpoint of the interval did not substantively alter the estimates of association (Table S4). Outlier analysis identified 16 fibroids with residuals for growth >3 standard deviations from the mean. After exclusion of these outliers estimated growth difference by soy formula exposure remained of small magnitude (Table S5).

Discussion

In this community-based sample of young Black/African-American women, soy-based formula feeding during infancy was associated with a suggestive increased risk of ultrasound-identified incident fibroids in adulthood. The strongest association was observed for participants who were fed soy-based formula soon after birth and for a duration longer than 6 months. However, fibroid growth rates did not differ based on exposure to soy-based infant formula. Our incidence findings are consistent with that observed in an animal model of Eker rats: Genistein exposure on postnatal days 10 to 12 increased uterine fibroid incidence in adulthood to 93% in genistein-exposed rats vs. a 65% spontaneous tumor incidence observed in control rats.[15] We are unable to compare our growth findings to fibroid development in the treated Eker rats because data pertaining to fibroid growth was not reported.

Overall, our findings align with previous epidemiological studies that examined the association between soy formula feeding in infancy and fibroid development in adulthood. A recent meta-analysis reports that soy formula feeding in infancy increased the risk of uterine fibroids by 19% in adulthood.[40] Consistent with our findings, the Sister Study reported increased risk of early onset fibroids for Black women diagnosed at ≤30 y of age [relative risk (RR) = 1.26; 95% CI: 0.83, 1.89] and White women diagnosed at ≤35 y of age (RR = 1.33; 95% CI: 1.08, 1.64) who were fed soy formula during their infancy when compared with those who were not, and these associations were further strengthened when feeding within the first 2 months of infancy was considered [relative risk (RR) = 1.48 (95% CI: 0.84, 2.63) and RR = 1.43 (95% CI: 1.10, 1.86) for Black and White women, respectively].[18] Although sample sizes were large (n = 3,201 and n = 27,048 for Black and White women, respectively), the Sister Study was limited by a cross-sectional analysis that relied on retrospective self-report of fibroid diagnosis data. In a prospective analysis that examined self-reported new clinical diagnoses of uterine fibroids among 23,505 participants age 23–50 y in the Black Women's Health Study, risk was increased for women diagnosed at <30 y of age [incidence rate ratio (IRR) = 1.28; 95% CI: 0.91, 1.79] but not women diagnosed at ≥30 y of age (IRR = 0.99; 95% CI: 0.87, 1.13; p for interaction = 0.19).[19] A cross-sectional assessment in the baseline SELF cohort found no association for prevalent fibroid at baseline with soy formula feeding in infancy, but among participants with fibroids detected, those exposed to soy formula had larger fibroids in comparison with unexposed participants, consistent with earlier onset.[16] Despite similarity to previous findings, our results must be interpreted with caution because exposure numbers were small, leading to imprecise estimates with wide CIs, especially among those exposed early in infancy and for a duration longer than 6 months (n = 53). Nonetheless, our study notably extends prior analyses by capturing soy formula

feeding data directly from mothers for most participants, restricting the analytical sample to participants who were fibroid-free at study entry and by using standardized ultrasound imaging for the detection of incident fibroids over a 5-y follow-up period.

Our study has limitations, but also important strengths. Although the composition of soy infant formula has varied since the product was first introduced to the U.S. food supply over 100 y ago, all soy formulas on the market throughout the birth years of SELF participants (1975–1989) contained isolated soy protein,[41,42] the component that has high concentrations of isoflavones.[43] Although the SELF population is young, information pertaining to the pregnancy characteristics of the participants' births and feeding patterns during their infancies was gathered from mothers approximately 25–35 y after the participants were born. Validation studies examining the long-term maternal recall of pregnancy characteristics have shown that mothers are able to recall their child's birth weight with reasonable accuracy[44,45]; however, maternal recall of GDM[46,47] and HDP[48,49] is less consistent. A systematic review of 10 validation studies of maternal recall of HDP found sensitivity estimates ranged from 57% to 87% for preeclampsia and from 31% to 100% for gestational hypertension.[50] Furthermore, most studies of maternal recall have been conducted among predominately White, highly educated individuals[49,51]; thus, future validation studies in more diverse populations are needed. To our knowledge, mothers' recall of soy formula feeding during their children's infancy has not been assessed, but validation studies have demonstrated short- and long-term recall of other infant feeding histories to be fairly accurate. When recalling infant formula feeding after 10 y, 94% of mothers recalled feeding formula to their babies and 65% recalled the exact brand.[52] Among a cohort of 374 Norwegian mothers, breastfeeding duration recorded during infancy and recalled 20 y later was found to be strongly correlated [intraclass correlation coefficient (ICC) = 0.82, $p < 0.001$].[53] Nonetheless, the potential for recall error is an important limitation of this study. Yet, 89% of participants were able to gather infant feeding patterns directly from their mothers. Moreover, prevalence of soy formula feeding among SELF participants (13%) was similar to prevalence in the most recent report of soy-based formula consumption (12%)[28] and to prevalence during the birth years of our participants (11%).[16,42] More accurate exposure and covariate data could be available in the future from follow-up of pregnancy and childhood studies that collected such data at or near the time of pregnancy/infancy. Bias due to unmeasured confounders is a risk inherent with all observational studies,[54] but we have a rich database of covariates, and we used the available literature and prior analyses in the SELF cohort to identify potential confounders. To our knowledge, this study was the first large epidemiological study to assess incident fibroids via prospective ultrasound imaging, providing the best data on fibroid incidence available.

Experimental animal studies clearly show adverse reproductive effects from postnatal exposure to phytoestrogens at exposure levels comparable to levels that infants fed soy formula experience (reviewed in Suen et al.[9]). The human data are limited. Our findings, based on exposure data collected primarily from mothers and outcome data from prospectively assessed fibroids, add to the human data that have suggested possible grounds for concern. The early months after birth when there is transient activation of the hypothalamic-pituitary-gonadal axis may be a particularly susceptible window for exogenous estrogen exposure.[33,55] Currently, expert panels deem soy-based infant formula safe for the growth and development of term infants,[55,56] yet the associated risk of adverse health outcomes later in life are not well understood nor are they factored into current recommendations.[9,31,57–59] Well-designed prospective studies are needed to accurately capture both exposure and outcome data. Future studies that build on prospective birth cohorts that recorded infant feeding patterns from birth and follow participants into adulthood with gynecological ultrasound could provide further critical data on the long-term effects of early-life estrogenic exposures.

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