JOURNAL OF WOMEN'S HEALTH
Volume 24, Number 11, 2015

DOI: 10.1089/jwh.2015.5277

A Prospective, Ultrasound-Based Study to Evaluate Risk Factors for Uterine Fibroid Incidence and Growth: Methods and Results of Recruitment

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Abstract

Background: Uterine fibroids are common, benign, smooth-muscle tumors that can cause major morbidity for reproductive-age women, often requiring invasive treatment. Despite this personal and public health burden, no prior study has attempted to periodically screen fibroid-free women with ultrasound to detect incident disease and identify risk factors.

Methods: We designed a study to prospectively investigate development of fibroids by enrolling women without a clinical diagnosis of fibroids and screening for fibroids with ultrasound at baseline. Enrollment procedures included extensive questionnaires and specimen collection (blood, urine, vaginal swabs). The cohort is followed at approximately 20-month intervals. At each follow-up there are updates to the questionnaire data, further specimen collection, and an ultrasound examination. We identify incident disease and measure tumor growth. The two exposures of primary interest are vitamin D insufficiency and reproductive tract infections. This manuscript provides a detailed description of the study methods, recruitment results, and participant characteristics.

Results: The Study of Environment, Lifestyle and Fibroids enrolled 1,696 African American women aged 23–34 years. ''Family and friends'' was a leading recruitment source. More than 95% of participants contributed all the requested biological specimens at baseline. Study ultrasound examinations revealed undiagnosed fibroids in 378 women (22% of participants). The retention rate for the first follow-up was 87%.

Conclusions: Study design aspects likely to be important for long-term studies in young African Americans include personalized recruitment, multiple steps to the enrollment process that rely on the initiative of the participant, and methods for tracing highly mobile study subjects.

Introduction

UTERINE FIBROIDS DEVELOP in the majority of reproductive-age women[1] and are the leading cause of hysterectomy in the United States,[2,3] at a cost of up to $34 billion per year.[4] Though this condition rarely is a cause of death, it is a major cause of morbidity. The primary symptoms are excessive menstrual bleeding and pelvic pain. The bleeding can lead to chronic anemia and severely reduced quality of life.[5] This benign tumor of the muscle layer of the uterus is hormonally dependent, developing after puberty and tending to shrink after menopause.[6,7] The factors that initiate tumorigenesis are not known, but both estrogen and progesterone are important for growth (reviewed by Bulun[8]). The tumors are usually monoclonal, with the tissue characterized by excessive extracellular matrix (reviewed by Flake et al.[7]). In the United States, the risk of developing symptomatic disease that requires treatment is greater for African American women than for white women.[9,10] Ultrasound studies indicate that tumor onset begins 10 or more years earlier for African American than for white women.[11,12]

Despite the morbidity and health care costs associated with uterine fibroids, there have been very few studies to identify risk factors and possible strategies for prevention. The only well-replicated risk factors are increased age (up to age of menopause), African American ethnicity, earlier age of

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menarche, and nulliparity.[12] The prospective investigations of new clinical diagnoses of fibroids in the Nurses' Health Study[13] and the Black Women's Health Study[14] have both contributed important epidemiologic information (reviewed by Laughlin et al.[12] and Wise and Laughlin-Tommaso[15]), but the disease outcome in those studies is clinical diagnosis of fibroids. The actual time of disease onset is unknown because tumors may be present for years before they are clinically diagnosed. These studies identify associations for clinically recognized fibroids, so results may be biased by factors related to clinical detection (e.g., access to clinical care, indications for ultrasound examination such as pregnancy, and perceived symptomatology). Five studies have used ultrasound to screen for fibroids.[1,11,16–18] These studies identify prevalent fibroids that have not yet been clinically recognized, but the actual time of disease onset for these undiagnosed fibroids is also unknown. No previous study used ultrasound to follow fibroid-free women prospectively to detect new fibroid development and monitor tumor growth.

The Study of Environment, Lifestyle, and Fibroids (SELF) was initiated to fill this critical information gap. The study is designed to monitor fibroid development and growth and to identify risk factors for these fibroid outcomes. The purpose of this paper is to describe the study methods including design, recruitment, and the enrollment/follow-up procedures. We also present baseline characteristics of the enrolled participants including the prevalence and characteristics of fibroids found at the baseline ultrasound.

Materials and Methods

Study design

Women were eligible if they reported no prior clinical diagnosis of fibroids. At enrollment they were screened for fibroids with ultrasound. Both those with and without fibroids at this baseline ultrasound are followed for 5 years with re-examination at approximately 20-month intervals to detect new fibroids and measure growth of existing fibroids. This prospective study was designed to test two environmental hypotheses:

(1) Increasing vitamin D is associated with reduced risk of fibroid development. Protection from fibroid development is biologically plausible given the anti-proliferative and anti-fibrotic activities of the active metabolite of vitamin D.[19] The hypothesis also follows empirically from both laboratory and epidemiologic findings indicating a possible role for vitamin D in preventing fibroid development.[20–28] A large ultrasound-based epidemiologic study found reduced risk of fibroids with increasing 25-hydroxy-vitamin D [25(OH)D] in both black and white women.[24] Furthermore, the magnitudes of the associations were very similar in the two ethnic groups.

(2) Reproductive tract infections are a risk factor for fibroids. This hypothesis was discussed as early as the 1930s,[29] but has never been carefully tested.[12] Recent suggestions that fibroid pathogenesis mimicks abnormal wound healing,[30] and possible involvement of inflammation[31] provides impetus for trying to carefully evaluate this hypothesis.

In addition to the primary environmental hypotheses, this large cohort study will provide the opportunity to carefully examine associations for which there are conflicting data in the literature (e.g., body mass index, oral contraceptive use) or for which little data are available (e.g., exercise, dietary factors, stress). We are also collecting DNA so that genetic and epigenetic susceptibility to fibroids can be evaluated.

Participants

The study enrolled African American women, ages 23–34, who lived in the Detroit, Michigan area. We focused on this ethnic group because of their greater risk of disease.[1,11,32] In addition, there are methodologic reasons for focusing on a single ethnic group. Because of the apparent 10-year earlier age of disease onset for black women compared with white women in the U.S.,[12] an efficient prospective study of both black and white participants would need to enroll a different age distribution of women in the two groups. This would likely result in differential recall of early life events, making it difficult to compare ethnic groups. Initial power calculations indicated a desired sample size of 1,600 African American women.

Eligibility criteria

The primary inclusion criteria were age (23–34 years) and self-identified ethnicity (black, African American, or part African American). Women reporting a prior diagnosis of uterine fibroids were excluded. Women who reported that they were pregnant at the time of recruitment had their enrollment delayed until after the pregnancy in order to assure optimum ultrasound imaging. All inclusion and exclusion criteria are listed in Table 1.

Recruitment and enrollment procedures

Recruitment was designed to saturate the Detroit, Michigan area with information about the study. We began by sending

Table 1. Eligibility Criteria for the Study of Environment, Lifestyle, and Fibroids

Inclusion criteria
Age 23–34 years at time of recruitment
Self-identify as African American, black, or partly African American
Intact uterus (i.e., no previous hysterectomy)
Residence in the United States
Ability to attend clinic visits in Detroit, MI
Stated commitment to remain in study for 5 years
Willing to provide contact information for tracing (contact information for three persons who could be asked about their whereabouts, or their social security number and contact information for 1 person who would know their whereabouts).
Exclusion criteria
Any prior diagnosis of uterine fibroids
Any prior diagnosis of cancer that required radiation or chemotherapy
Any prior diagnosis of lupus, Grave's disease, Sjogren's, scleroderma, or multiple sclerosis that required medication
Delayed entry
Any woman who was pregnant at recruitment had enrollment delayed until 3 months after the pregnancy ended.

letters describing the study to African American women aged 23–34 years who had been seen in the past year at the Henry Ford Health System (HFHS), a large integrated health system in the Detroit area and a collaborating institution. We then expanded recruitment to the entire Detroit area with a website (detroitself.org); fliers, brochures at health care clinics (all obstetrics and gynecology clinics were contacted and, if willing to participate, were sent brochures to display); local radio, television, newspaper, and magazine advertisements; and information booths at community events. The HFHS patient sample that was sent letters was selected with stratification by age to help maintain equal recruitment across the eligible age range. Older African American women (35–65 years) who had sought care at HFHS in the previous 6 months were also sent letters informing them of the study and asking them to tell eligible women they might know about the study.

The enrollment process was designed to select for women motivated and able to continue in a long-term study. Women had to initiate the enrollment process (i.e., women who heard about the study and were interested in learning more about it phoned the study number). Enrollment required several steps: (1) a telephone eligibility screening; (2) completion of orientation—a detailed 30–60 minute description of the study procedures that could be done as a group activity at HFHS or individually by telephone; (3) completion of a self-administered ''Pre-enrollment Questionnaire'' that included questions about family history of fibroids, participant's current health status, a checklist of medical conditions to identify prior health problems, and physical activity in the past 7 days;[33] (4) provision of contact information for themselves and information to facilitate tracing if they could not be located; (5) signing the informed consent form; (6) scheduling and attending a clinic visit; and (7) completing three questionnaires either before or during the clinic visit (in rare instances after the visit). The computer-assisted telephone interview (CATI) lasted approximately 60 minutes. The computer-assisted web interview (CAWI) required approximately 45 minutes. The Block 2005 Food Frequency Questionnaire (FFQ)[34] that was adapted to a web format (www.nutritionquest.com) lasted approximately 40 minutes. Enrollment was not complete until the clinic visit and the four questionnaires (CATI, CAWI, FFQ, and self-administered Pre-enrollment Questionnaire) were completed. Monetary compensation was provided (see Supplementary Materials available online at www.liebertpub.com/jwh).

At the clinic visit a transvaginal ultrasound examination was conducted to assess fibroids using the Muram criteria[35] extended to small lesions (0.5 cm in diameter or larger). Study sonographers had extensive experience and extra training for the study to assure consistency in differential diagnoses,[36–39] measurement, and documentation. The uterus and up to six fibroids were measured in three perpendicular planes. The uterus was measured at two separate times during the ultrasound examination and each fibroid three times. The uterine location of each fibroid was recorded (see Supplementary Materials for details of the fibroid assessment). For analysis, a volume for each of the three replicates was calculated based on the ellipsoid formula, and these were averaged to estimate the volume of each fibroid. The size of the largest fibroid was ascertained based on the maximum fibroid diameter (using the average of the maximum dimension from each of the three replicate measures).

In addition to the vaginal ultrasound, the clinic visit included measurements of height, weight, skin reflectance, and blood pressure as well as collection of urine, nonfasting blood samples, and vaginal swabs (see Supplementary Materials for details of clinic measures and processing and storage of biological specimens). For urine, a collection cup was sent before the clinic visit for the participant to collect a first-morning urine sample on her visit day. She was instructed to start collecting with the initial drops (not a clean catch) and keep the specimen cold until delivery at the clinic (ice packs provided). If no first-morning urine sample was brought to the clinic, the volume was <30 mL, or the returned sample was frozen, a spot urine sample was collected at the visit. Information on exposures within the last 24 hours (medication, selected personal care products, environmental toxins) and exposures within the last month (antibiotics, hormonal birth control, specific supplements) was recorded. Participants were instructed to bring any prescription or over-the-counter medications, supplements, and vitamins they had taken in the last 4 weeks. These were recorded and whether the medications/supplements were brought to the clinic (or just reported) was noted on the data form.

The CATI and CAWI were designed to limit the number of missing responses. For the CATI, interviewers were trained to probe for participants' best answers. For the CAWI, the options for answering a question rarely included ''don't know.'' If a question was left blank, a second nearly identical screen was presented asking the participant to pick the best answer with the additional response choice, ''prefer not to answer.''

Before leaving the clinic, women were given a Menstrual Diary Form and an Early-Life Questionnaire to complete and mail back. The menstrual diary was designed to collect prospective data about the subsequent menstrual period (spotting, bleeding, and pain) including the date the period began. The dates are used (along with the self-report at the clinic visit of start of last menstrual period) to obtain a measure of cycle length and to help retrospectively assign clinic specimens into follicular or luteal phase categories. The Early-Life Questionnaire was formatted for the participant to ask her mother about prenatal and early life exposures that the participant might not be able to answer by herself (e.g., ''Was I fed soy formula as an infant?''). For participants who reported that they were unable to interview their mother, a modified form was given instead. The modified version elicited the same information, but the participant was encouraged to ask for assistance from relatives and family friends who would be familiar with her early life history.

The participants were given results for height, weight, and blood pressure at the clinic visit. A letter was sent to each woman after the clinic visit with information on her hemoglobin level and a summary of her dietary intake (generated by the food frequency program). At the clinic visit, study staff asked participants if they wanted information on their fibroid status at ultrasound. If they wanted fibroid information, the letter also included information on whether or not fibroids had been detected and if so, the number, and size of the largest.

Follow-up procedures

Time windows for scheduling three subsequent clinic visits at approximately 20-month intervals were calculated at intervals of 18–26 months from the baseline clinic visit.

Women who miss a given follow-up visit can still participate in the next. For each of the subsequent follow-up visits, participants return for an ultrasound examination, which is conducted with the same data collection methods as at baseline and without reference to previous ultrasound findings. Weight and blood pressure are measured and specimens (urine, blood, vaginal swabs) are collected again with the same procedures. Each follow-up includes another CATI, CAWI, menstrual diary, and sometimes additional self-administered questionnaire(s) to update baseline information and to expand the information base. At each follow-up, women who report any medical procedure involving the uterus since the last study visit (not counting pregnancy-related procedures) are asked to give signed permission to obtain medical records related to the procedure(s). The records are retrieved by mail or fax from the designated medical facilities.

Special activities in subsets of women

1. Extra 6-month blood draw. An extra blood sample was taken 6 months after enrollment (baseline) from a subset of women to evaluate the short-term retention rate and check for reliability of the vitamin D biomarker, 25(OH)D. Reliability over time has not been studied in young African American women. The first 242 participants who enrolled were asked to return for the additional blood draw. Of the 233 scheduled for the extra blood draw, 209 attended, of which 207 (86% of those approached) provided blood samples.

2. Time-outside diary. Diary data will be used to evaluate the validity of the CATI questions about time spent outside. The first 121 participants who had their clinic visits in summer months were asked if they would be willing to complete the 7-day time-outside diary. Eleven refused, 2 never completed it, and 108 returned a completed diary.

Prospective data analysis plan

Survivorship analyses will be used to evaluate the relationship between exposure (vitamin D for the first hypothesis and reproductive tract infections for the second hypothesis) and fibroid incidence. At each follow-up, fibroid incidence will be evaluated in two ways. Case group 1 will constitute women with a newly detected fibroid among those who were previously fibroid free. Case group 2 will constitute women with any newly detected fibroid (case group 1 plus women with more fibroids than were detected at their last ultrasound). For analysis, the timing of fibroid onset will be estimated by the midpoint of the interval between ultrasound examinations.

Survivorship analysis (time to development of a first fibroid or an additional fibroid) allows for estimation of the exposure-related relative risk (hazard ratio) for incident fibroids. Baseline data as well as data collected with each follow-up will be used in the multivariate modeling (Cox proportional hazards analysis with time-dependent covariates). Women who have a hysterectomy or menopause before they develop fibroids will be censored at time of event. Age is an *a priori* confounder. Other likely confounders will include age of menarche, and parity, but other potential confounders will be investigated including education, exercise, alcohol, and hormone use.

For analysis of fibroid growth, we will first use a dichotomous measure of growth at each follow-up. Women with ''growing fibroids'' will be those with at least one fibroid showing a >50% increase in volume over a 20-month interval. A less stringent growth criterion will be used if too few women show any growing fibroids by this criterion, but we expect the lower limit to be 30% because measurement error can be large enough to mimic a nearly 30% volume increase.[40] We will formally investigate factors associated with growth (fibroid characteristics including fibroid size, location, and number in uterus and woman-specific exposures including vitamin D and reproductive tract infections) by using average growth data (volume change) across measurement intervals for all individual fibroids as done previously.[41] Mixed effects models will be used to statistically adjust for the correlation among tumors within a woman and adjust for potential confounders. Confounders will need to be empirically determined given the lack of prior studies on fibroid growth. If there are sufficient data, we will also estimate a fibroid growth curve for the early growth phase. We anticipate that new methods may need to be developed for studying the growth curve dynamics and the effects of exposures on those dynamics.

Power calculations

Power calculations indicate that we have an adequate sample size (1,696 enrolled participants of whom 378 had fibroids at the enrollment (baseline) ultrasound) to test our two primary environmental hypotheses in SELF. The calculations for examining incident fibroid cases (case group 1) are based on the simplified outcome of cumulative 5-year incidence of new fibroid cases (i.e., the percentage of fibroid-free women that develop tumors by the 5-year follow-up). The minimal detectable associations for exposure prevalences of 10%, 25%, and 50% will be 1.5, 1.4, and 1.3, respectively (assuming 80% power, a two-sided alpha of 0.05, a 25% cumulative incidence in the unexposed,[12] and at least a 70% study retention rate). The power to detect associations with case group 2 (i.e., a new fibroid regardless of prior number of fibroids) will be greater. For the growth analyses, we estimate that we will be able to detect a 33% or greater increase in growth (with 80% power and a two-sided alpha of 0.05, given 25% exposed), assuming one fibroid per woman and growth data for at least one follow-up interval on at least 80% of the fibroid cases. This estimate is based on unpublished data from the Fibroid Growth Study (Peddada et al., 2008[41]) (12% mean annual fibroid growth rate with standard deviation of 16% for unexposed). We estimate that at least 441 women will contribute growth data.

Results

Recruitment

From November 2010 to December 2012, we screened 3200 women, and 89% were found to be eligible for the study. Though nearly all those eligible agreed to participate, a substantial number did not attend an orientation (29%). Women had the option of either a telephone or in-person orientation, and both were chosen about equally. However, the women who attended an in-person orientation were more likely to complete enrollment than women who did the orientation over the phone (95% of those attending an in-person orientation enrolled, while only 74% of those who chose the

Table 2. The Recruitment Sources for All Women Who Were Screened for the Study, the Subset Who Were Ineligible, and the Subset Enrolled

	Total screened N = *3178*[a]		*Ineligible* N = *392*		*Women who enrolled* N = *1696*[b]	
Recruitment source	n	%	n	%	n	%
Family/friend	1247	33.5	199	50.8	644	38.0
HFHS letter	1242	33.4	120	30.6	645	38.0
Flier/brochure	362	9.7	30	7.7	222	13.1
Radio station	49	1.3	10	2.6	23	1.4
Magazine/newspaper	47	1.3	5	1.3	27	1.6
Email	24	0.6	2	0.5	14	0.8
Television	14	0.4	6	1.5	6	0.4
Postcard	12	0.3	2	0.5	7	0.4
SELF website	12	0.3	3	0.8	6	0.4
Other website	13	0.3	0	0.0	5	0.3
Newsletter	8	0.2	0	0.0	7	0.4
SELF recruiter	2	0.1	0	0.0	0	0.0
Other	146	3.9	15	3.8	90	5.3

[a]Includes women who were eligible to participate, but (1) immediately refused ($n = 33$; separate data not shown); (2) were undecided at the end of enrollment ($n = 50$; separate data not shown); (3) on hold at the end of enrollment ($n = 25$; separate data not shown); (4) women who agreed but failed to complete enrollment activities ($n = 973$; separate data not shown); and (5) women who enrolled but were later found to be ineligible or unable to complete activities ($n = 9$; separate data not shown), as well as the ineligible at screening (shown) and the enrolled (shown).

[b]Excludes 9 women who were enrolled but found to be ineligible or unable to complete activities.

HFHS, Henry Ford Health System; SELF, The Study of Environment, Lifestyle, and Fibroids.

phone orientation proceeded to enrollment). Hence, we enrolled 1705 participants for fibroid follow-up (53% of those who called to be screened for eligibility). We excluded 9 enrollees after they had been enrolled because they were found to be ineligible or to have not been able to complete critical components of the data collection. Thus, the final number of participants in the SELF cohort was 1696.

Women who enrolled could have learned about the study from several sources, but when asked at their initial phone call about where they heard of the study, the most frequently reported sources of information were ''family or friends'' (38%) and ''letter from HFHS'' (38%). The distribution of reported recruitment source for the women who initially called about the study is similar to that for those who completed enrollment (Table 2).

Description of SELF cohort at baseline

Table 3 shows baseline characteristics for the 1696 participants enrolled in SELF. They were fairly evenly distributed across the eligible ages of 23–34 years. Most had more than a high school education (78%), with 28% having completed college. Incomes were low, reflecting the economic situation in the Detroit area. Early and late age of menarche (≤age 10 and ≥age 14 years) were equally frequent: 18%. The majority of women had been pregnant and had given birth, but percent parous was substantially lower than percent gravid (61% vs. 73%), with about half the women having at least one prior induced abortion. The majority had used some form of hormonal contraception in the past, the most common being oral contraceptives (71% ever users, 12% current users) and Depo Provera (43% ever users, 7% current users). The majority of women were overweight or obese. Prior diagnoses of hypertension and diabetes were 10% and 3%, respectively. Prior diagnosis of a sexually transmitted disease was common with chlamydia being most frequently reported (37%). Only 26% reported ever smoking, but 41% reported a history of alcohol intake consistent with binge or heavy drinking.

Several early life exposures were reported frequently enough to investigate including exposure to maternal smoking in utero (26%), infant soy formula (13%), being breastfed (32%), and childhood chemical hair treatment around age 10 years (15% with treatment five or more times per year). The number of women with missing data on most of these factors was small (<1% for the data collected with CATI or CAWI). There were more missing data for the Early Life Questionnaire that involved consultation with the participant's mother or others who could provide relevant information and required them to mail it back to the study center. There are 5.8% of participants with no Early Life Questionnaire data (74 women have not returned it, and 24 women, 1.4% of total sample, were not given a form because they reported having no mother or other person(s) to provide the data).

Ultrasound data revealed that 378 women (22%) had at least one fibroid ≥0.5 cm in diameter at the baseline ultrasound. Of these women 63% had a single fibroid, and for the majority (62%) the largest fibroid was <2 cm in diameter. The prevalence of fibroids increased with age from 10% for 23–25 year olds to 32% for 32–35 year olds (Table S5).

Completeness of enrollment (baseline) specimen collection

Of the 1696 participants in the SELF study, at least some blood was collected for 98% of the participants ($n = 1662$), and the full set of tubes was collected for 96.9% ($n = 1643$). The first-morning urine sample was collected and returned to the clinic at the enrollment visit by 97.5% of the participants ($n = 1654$). An additional 2.4% ($n = 41$) provided a spot urine

Table 3. Characteristics of SELF Participants at Time of Enrollment

Characteristic	n *(%)* (N = 1696)
Participant age at ultrasound (years)	
23–25	378 (22)
26–28	424 (25)
29–31	459 (27)
32–35	435 (26)
Education	
≤High school or GED	370 (22)
Some college or associate/technical degree	850 (50)
Bachelor's, master's, or doctoral degree	475 (28)
Missing	1
Total annual household income (USD)	
<20,000	768 (46)
20,000–50,000	629 (37)
>50,000	287 (17)
Missing	12
Age at menarche (years)	
≤10	310 (18)
11	334 (20)
12	459 (27)
13	287 (17)
≥14	306 (18)
Gravidity	
Ever pregnant	1244 (73)
Never pregnant	452 (27)
Parity (number of births)	
0	663 (39)
1	433 (26)
2	313 (18)
≥3	287 (17)
Number of miscarriages (among gravid)	
0	926 (75)
1	240 (19)
≥2	72 (6)
Missing[a]	6
Number of induced abortions (among gravid)	
0	570 (46)
1	345 (28)
≥2	324 (26)
Missing[b]	5
History of hormonal contraception[c]	
None	237 (14)
Oral contraceptives	1200 (71)
Depo-Provera	722 (43)
Hormone patch	304 (18)
Vaginal ring	227 (13)
Mirena IUD	191 (11)
Hormone implant	42 (2)
Body mass index (kg/m^2)	
<25.0	336 (20)
25.0 to <30.0	350 (21)
30.0 to <35.0	329 (19)
≥35.0	681 (40)
Prior diagnosis of:	
Hypertension	
Yes	168 (10)
No	1510 (90)
Missing	18
Diabetes	
Yes	57 (3)
No	1627 (97)
Missing	12
Asthma	
Yes	331 (20)
No	1348 (80)
Missing	17
Chlamydia	
Yes	632 (37)
No	1062 (63)
Missing	2
Gonorrhea	
Yes	324 (19)
No	1371 (81)
Missing	1
Smoking status	
Never	1247 (74)
Past	125 (7)
Current	324 (19)
Alcohol use (at time when drinking the most)[d]	
Low/never	450 (27)
Moderate	554 (33)
Heavy	692 (41)
Early life exposures	
Maternal smoking (in utero exposure)	
No	1252 (74)
Yes	444 (26)
Born a week or more before due date[e]	
No	1145 (76)
Yes, born 1–2 weeks early	212 (14)
Yes, born ≥3 weeks early	148 (10)
Missing	191
Fed soy formula as infant[e]	
No	1355 (87)
Yes	198 (13)
Missing	143
Breastfed as infant[e]	
No	1076 (68)
Yes	496 (32)
Missing	124
Frequency of childhood hair treatment with chemical products, including hair straighteners, around age 10 years	
Rarely/never	939 (55)
Once a year	183 (11)
2 to 4 times a year	331 (20)
5 to 9 times a year	196 (12)
10 or more times a year	45 (3)
Missing	2
Uterine fibroids at baseline ultrasound[f]	
No	1318 (78)
Yes	378 (22)
Number of fibroids (among those with fibroids)	
1	240 (63)
2	56 (15)
≥3	82 (22)

(*continued*)

TABLE 3. (CONTINUED)

Characteristic	n *(%)* (N = 1696)
Size of largest fibroid[g] (cm) (among those with fibroids)	
<2	234 (62)
2–3.9	93 (25)
≥4	51 (13)
Fibroid type (among those with fibroids)	
Any submucosal	34 (9)
Any intramural	313 (83)
Any subserosal	104 (28)
Fibroid location (among those with fibroids)	
Any fundal	174 (46)
Any corpus	273 (72)
Any lower uterine segment	30 (8)

[a] Missing includes 2 women with one or two miscarriages and 2 women with up to two miscarriages with the possibility of none.

[b]Missing includes 2 women with one or two abortions and 3 women with up to two abortions with the possibility of none.

[c]Women often had used more than one form of hormonal birth control.

[d]Low/moderate drinkers never drank more than 10 drinks in a year. Heavy drinkers usually drank six or more drinks on days when they drank or drank four or more drinks per sitting at least two to three times a month. Moderate drinkers were everyone else.

[e]Data from the Early Life Questionnaire has more missing data because it involved consultation with mother or others who knew of participant's early life and had to be mailed back to study center ($n = 74$ not yet returned). Also, 24 participants were not given a form because they had no one to ask.

[f]Includes six questionable fibroids that could not be seen in all three dimensions. Each was the single fibroid detected.

[g]Based on maximum diameter measured.

GED, General Educational Development test (high school equivalency); IUD, intrauterine device.

at the clinic for a total of 99.9%. One participant did not provide a urine sample. Two vaginal swabs were collected by 100% of the participants. One was for assessment of chlamydia, mycoplasma, *Neisseria gonorrhoeae* and Trichomonas infection (Gen-Probe Aptima swab), the other for assessment of bacterial vaginosis (Epicentre Catch-All Sample Collection Swabs).

First follow-up retention

Eighty-seven percent of participants returned for their first follow-up. Those who miss any given follow-up are still eligible to complete subsequent follow-up activities, so we anticipate >90% of the women will have at least one follow-up visit.

Discussion

SELF was able to recruit the desired number of young African American women within the planned time frame. The recruitment sources that yielded the most participants were those personally known by the respondents (family and friends or letters from HFHS). Using ''known'' recruitment sources may be important for enrolling African Americans in research studies, given the research abuse that has occurred in the past. We selected for women who were likely to remain in the study, and as expected, our sample is on average more educated than U.S. black women overall [78% with more than a high school degree vs. 60% in 25- to 34-year-old black women in the U.S.; 28% vs. 23% with college degrees (www.census.gov/hhes/socdemo/education/data/cps/2011/tables.html)]. This increased education level of participants was also seen among participants in the Black Women's Health Study, another cohort study that aimed to enroll women who would remain with the study.[42] As hoped, the follow-up rate (87% for the first follow-up) appears to be adequate.

The data collection that was designed to limit missing data was very successful and could be implemented in other studies. As a result, we have a very rich database. Given the broad scope of questionnaire data (demographic, reproductive, medical, lifestyle) and the collection of biological specimens in this large sample of young African American women, there are opportunities for a wide range of novel supplemental investigations. Most importantly, we have detailed ultrasound data with uterine and fibroid measurements as well as the uterine location of detected fibroids.

Conclusions

Study design aspects likely to be important for long-term studies in young African Americans include personalized recruitment, multiple steps to the enrollment process that rely on the initiative of the participant, and methods for tracing highly mobile study subjects.

Acknowledgments

We thank the participants for sharing their valuable information and taking time to complete the numerous study activities. Drs. Gordon Flake and Anne Marie Jukic reviewed an earlier version of the manuscript. We also thank the following study team members without whom the recruitment and retention of study participants, day-to-day operations, and data and specimen collection would not be possible: at Social and Scientific Systems, Inc., Taylor Abernathy, Jackie Allison, Thomasina Austin, Ans Bilhorn, Deborah Cousins, Carrissa Dixon, Suzie Dollar, Judith Fontanelle, Elizabeth Ganze, Irina Khodush, Jason Langfahl, Christina Makarushka, Carol Messler, Naomi Piserchia, Ellen Revak, Tina Richmond, Diana Smith, Nick Verna, Terri Young (Westat), Fikri Yucel, and the Telephone Research Center staff; and at HFHS, Kyra Jones, Karen Bourgeois, Louise Brennan, Tangi Dargin, Vickie Gaines, Wanda Greene, Yolanda Harris, Cynthia Hill, Melissa Houston, Darine Joumaa, LaSalle McKenzie, Dojna Mototolea, Rita Norman, Debbie Williams, Evangeline Griesemer, and LaToya Allen. This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences, and, in part, by funds allocated for health research by the American Recovery and Reinvestment Act.

Author Disclosure Statement

No competing financial interests exist.

References

1. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: Ultrasound evidence. Am J Obstet Gynecol 2003;188:100–107.
2. Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990–1997. Obstet Gynecol 2002;99:229–234.
3. Merrill RM. Hysterectomy surveillance in the United States, 1997 through 2005. Med Sci Monit 2008;14:CR24–31.
4. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol 2012;206:211 e211–219.
5. Perez-Lopez FR, Ornat L, Ceausu I, et al. EMAS position statement: Management of uterine fibroids. Maturitas 2014; 79:106–116.
6. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990;94:435–438.
7. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: A review. Environ Health Perspect 2003;111:1037–1054.
8. Bulun SE. Uterine fibroids. N Engl J Med 2013;369:1344–1355.
9. Velebil P, Wingo PA, Xia Z, Wilcox LS, Peterson HB. Rate of hospitalization for gynecologic disorders among reproductive-age women in the United States. Obstet Gynecol 1995;86:764–769.
10. Becker ER. National trends and determinants of hospitalization costs and lengths-of-stay for uterine fibroids procedures. J Health Care Finance 2007;33:1–16.
11. Laughlin SK, Baird DD, Savitz DA, Herring AH, Hartmann KE. Prevalence of uterine leiomyomas in the first trimester of pregnancy: An ultrasound-screening study. Obstet Gynecol 2009;113:630–635.
12. Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Semin Reprod Med 2010;28:204–217.
13. 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;90:967–973.
14. Wise LA, Palmer JR, Stewart EA, Rosenberg L. Age-specific incidence rates for self-reported uterine leiomyomata in the Black Women's Health Study. Obstet Gynecol 2005;105: 563–568.
15. Wise LA, Laughlin-Tommaso SK. Chapter 19 - Uterine Leiomyomata. In: Goldman MB, Troisi R, Rexrode KM, eds. Women and health, 2nd ed. San Diego: Academic Press; 2013:285–305.
16. Borgfeldt C, Andolf E. Transvaginal ultrasonographic findings in the uterus and the endometrium: Low prevalence of leiomyoma in a random sample of women age 25–40 years. Acta Obstet Gynecol Scand 2000;79:202–207.
17. Bower JK, Schreiner PJ, Sternfeld B, Lewis CE. Black–white differences in hysterectomy prevalence: The CARDIA study. Am J Public Health 2009;99:300–307.
18. Eskenazi B, Warner M, Samuels S, et al. Serum dioxin concentrations and risk of uterine leiomyoma in the Seveso Women's Health Study. Am J Epidemiol 2007;166:79–87.
19. Rosen CJ. Clinical practice. Vitamin D insufficiency. N Engl J Med 2011;364:248–254.
20. Blauer M, Rovio PH, Ylikomi T, Heinonen PK. Vitamin D inhibits myometrial and leiomyoma cell proliferation in vitro. Fertil Steril 2008.
21. Halder SK, Goodwin JS, Al-Hendy A. 1,25-Dihydroxyvitamin D3 reduces TGF-beta3-induced fibrosis-related gene expression in human uterine leiomyoma cells. J Clin Endocrinol Metab 2011;96:E754–762.
22. Halder SK, Sharan C, Al-Hendy A. 1,25-dihydroxyvitamin D3 treatment shrinks uterine leiomyoma tumors in the Eker rat model. Biol Reprod 2012;86:116.
23. Sharan C, Halder SK, Thota C, Jaleel T, Nair S, Al-Hendy A. Vitamin D inhibits proliferation of human uterine leiomyoma cells via catechol-O-methyltransferase. Fertil Steril 2010;95:247–253.
24. Baird DD, Hill MC, Schectman JM, Hollis BW. Vitamin d and the risk of uterine fibroids. Epidemiology 2013;24:447–453.
25. Halder SK, Osteen KG, Al-Hendy A. Vitamin D3 inhibits expression and activities of matrix metalloproteinase-2 and -9 in human uterine fibroid cells. Hum Reprod 2013;28:2407–2416.
26. Sabry M, Halder SK, Allah AS, Roshdy E, Rajaratnam V, Al-Hendy A. Serum vitamin D3 level inversely correlates with uterine fibroid volume in different ethnic groups: A cross-sectional observational study. Int J Womens Health 2013;5:93–100.
27. Al-Hendy A, Diamond MP, El-Sohemy A, Halder SK. 1, 25-dihydroxyvitamin D3 Regulates Expression of Sex Steroid Receptors in Human Uterine Fibroid Cells. J Clin Endocrinol Metab 2015:jc20144011.
28. Halder SK, Osteen KG, Al-Hendy A. 1,25-dihydroxyvitamin d3 reduces extracellular matrix-associated protein expression in human uterine fibroid cells. Biol Reprod 2013;89:150.
29. Witherspoon JT, Butler VW. The etiology of uterine fibroids with special reference to the frequency of their occurrence in the Negro: An hypothesis. Surg Gynecol Obstet 1934;58: 57–61.
30. Leppert PC, Catherino WH, Segars JH. A new hypothesis about the origin of uterine fibroids based on gene expression profiling with microarrays. Am J Obstet Gynecol 2006;195:415–420.
31. Wegienka G. Are uterine leiomyoma a consequence of a chronically inflammatory immune system? Med Hypotheses 2012;79:226–231.
32. Kjerulff KH, Langenberg P, Seidman JD, Stolley PD, Guzinski GM. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med 1996;41:483–490.
33. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–1395.
34. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–469.
35. Muram D, Gillieson M, Walters JH. Myomas of the uterus in pregnancy: Ultrasonographic follow-up. Am J Obstet Gynecol 1980;138:16–19.
36. Fedele L, Bianchi S, Dorta M, Brioschi D, Zanotti F, Vercellini P. Transvaginal ultrasonography versus hysteroscopy in the diagnosis of uterine submucous myomas. Obstet Gynecol 1991;77:745–748.
37. Kupfer MC, Schiller VL, Hansen GC, Tessler FN. Transvaginal sonographic evaluation of endometrial polyps. J Ultrasound Med 1994;13:535–539.
38. Reinhold C, Tafazoli F, Wang L. Imaging features of adenomyosis. Hum Reprod Update 1998;4:337–349.
39. Wilde S, Scott-Barrett S. Radiological appearances of uterine fibroids. Indian J Radiol Imaging 2009;19:222–231.

40. Moshesh M, Peddada SD, Cooper T, Baird D. Intraobserver variability in fibroid size measurements: Estimated effects on assessing fibroid growth. J Ultrasound Med 2014;33: 1217–1224.
41. Peddada SD, Laughlin SK, Miner K, et al. Growth of uterine leiomyomata among premenopausal black and white women. Proc Natl Acad Sci U S A 2008;105:19887–19892.
42. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: A follow-up study for causes and preventions of illness. J Am Med Womens Assoc 1995;50: 56–58.

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