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Reproductive Factors, Hormonal Contraception, and Risk of Uterine Leiomyomata in African-American Women: A Prospective Study

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Abstract

The authors assessed the risk of uterine leiomyomata in relation to reproductive factors and hormonal contraception in a prospective cohort study of US Black women. From March 1997 through March 2001, the authors followed 22,895 premenopausal women with intact uteri and no prior self-reported diagnosis of uterine leiomyomata. The authors used age- and time-stratified Cox regression models to estimate incidence rate ratios for self-reported uterine leiomyomata, confirmed by ultrasound or hysterectomy, in association with selected reproductive and hormonal factors. During 76,711 person-years of follow-up, 2,279 new cases of ultrasound- or hysterectomy-confirmed uterine leiomyomata were self-reported. After adjustment for age, body mass index, smoking, alcohol intake, and other reproductive covariates, the risk of ultrasound- or hysterectomy-confirmed leiomyomata was inversely associated with age at menarche, parity, and age at first birth and positively associated with years since last birth. Overweight or obesity appeared to attenuate the inverse association between parity and uterine leiomyomata. Current use of progestin-only injectables was inversely associated with risk. No consistent patterns were observed for other forms of hormonal contraception. Reproductive history is an important determinant of leiomyomata risk in premenopausal US Black women. Progestin-only injectables may reduce risk.

Keywords

Blacks; contraceptives; oral; female; leiomyoma; premenopause; prospective studies; reproduction; uterine neoplasms

Uterine leiomyomata (fibroids) are clinically recognized in about 30 percent of reproductive-age women (1) and are a major source of gynecologic morbidity. Symptoms include pelvic pain, reproductive dysfunction, and heavy menstrual bleeding (2,3). Uterine leiomyomata are

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the fifth leading cause of hospitalizations for gynecologic conditions unrelated to pregnancy in women aged 15–44 years (4) and the primary indication for hysterectomy among women of all ages in the United States (5,6). Clinical diagnoses of uterine leiomyomata are from two to three times more common in Black women than White women (5,7–9), and Black women have an earlier age at first diagnosis (7,9,10) and more numerous and symptomatic tumors than do White women (9,10).

Although the etiology of uterine leiomyomata remains poorly understood, growth of these tumors is thought to depend on ovarian hormones (1,11). Epidemiologic studies conducted in predominantly White populations suggest that risk is inversely associated with age at menarche, parity, and age at first birth and positively associated with years since last term birth (12–20). Findings on oral contraceptives are inconsistent (12–19,21) but tend toward an inverse association, particularly for preparations with a higher dose of progestin (14). The present study uses prospective data from a nationwide cohort of African-American women to evaluate risk of uterine leiomyomata in relation to reproductive factors and hormonal contraception. We expand on the scope of existing research by examining different constituents of oral contraceptives.

MATERIALS AND METHODS

Study population

The Black Women's Health Study is an ongoing prospective cohort study designed to examine risk factors for major illnesses in African-American women. In 1995, 64,500 participants aged 21–69 years were enrolled through questionnaires mailed to subscribers of *Essence* magazine, members of Black professional organizations, and friends and relatives of respondents (22). The baseline questionnaire in 1995 elicited information on demographic and behavioral characteristics, reproductive and contraceptive histories, health care utilization, and medical conditions. Updated information is obtained by postal questionnaire every 2 years. After a run-in phase, the cohort comprised 59,000 women. Follow-up of this cohort has exceeded 80 percent in each questionnaire cycle.

Follow-up for the present analysis began in March 1997, the start of the second questionnaire cycle, because data on the method of confirmation for leiomyomata were first obtained on the 1999 follow-up questionnaire. Starting with the 53,322 women who completed the 1997 questionnaire, we restricted our sample to premenopausal women with intact uteri because leiomyomata are rare after menopause (3). We therefore excluded women who reported natural menopause (n = 5,143), hysterectomy (n = 6,625), bilateral oophorectomy (n = 4,175), medical menopause (n = 218), or unknown menopausal status (n = 522) at the start of follow-up. We further excluded women who reported a diagnosis of leiomyomata before 1997 (n = 10,450), who completed neither 1999 nor 2001 follow-up questionnaires (n = 2,193), or who provided no information about year of diagnosis (n = 99) or confirmation type (n = 208). Finally, analyses excluded women with incomplete exposure or covariate information (n = 789). The remaining 22,895 women were followed for incidence of leiomyomata in the subsequent 4 years. The proportion of women with missing data did not vary appreciably by any of the reproductive factors examined.

Assessment of outcome

The diagnosis of leiomyomata is often suspected when an enlarged irregular uterine contour is palpable on pelvic examination. Ultrasound examination is the primary noninvasive standard used to confirm diagnoses. Although histologic evidence is the "gold standard" (3), histologically confirmed cases represent only 10–30 percent of cases for whom ultrasound evidence is available (7,23). Studies limited to histologic cases may spuriously identify risk

factors associated with large tumor size, symptoms, or treatment preference (23). Therefore, our outcome definition included confirmation by hysterectomy or ultrasound. Ultrasound has been shown to have high sensitivity (99 percent), specificity (91 percent), and positive predictive value (96 percent) relative to histologic evidence (24,25).

On the 1999 and 2001 follow-up questionnaires, women were asked if they had been diagnosed with "fibroids" in the previous 2-year interval and if "yes," the calendar year in which they were first diagnosed and whether their diagnosis was confirmed by "pelvic exam" and/or by "ultrasound/hysterectomy." A diagnosis was classified as "hysterectomy-confirmed" if the participant reported hysterectomy in the same questionnaire cycle under a separate question.

Incident cases were defined as women who reported on the 1999 or 2001 questionnaire a first diagnosis of "fibroids" confirmed by ultrasound or hysterectomy. The index date for each case was defined as the midpoint of the reported calendar year in which the diagnosis was confirmed. Women with diagnoses confirmed only by pelvic examination ($n = 412$) were not included as cases in primary analyses because their diagnoses may represent other pathology (7,26).

We assessed the accuracy of self-reported leiomyomata in a random sample of 248 ultrasound- or hysterectomy-confirmed cases. These women were mailed supplemental questionnaires regarding their initial date of diagnosis, method of confirmation, symptoms, and treatment, and they were asked for permission to review their medical records. We obtained medical records for 122 of the 128 women who gave us permission and confirmed the self-report in 117 women (96 percent). The proportion of women reporting on the supplemental questionnaire that their diagnosis was first confirmed at ultrasound or hysterectomy did not differ among those who did ($n = 128$) and did not ($n = 50$) release their medical record (98 percent vs. 98 percent). Likewise, the proportion of women reporting the presence of symptoms prior to the detection of leiomyomata did not differ materially among those who did and did not release their medical record (73 percent vs. 60 percent). Among the 178 cases who completed the supplemental survey, 70 percent reported symptoms of uterine leiomyomata prior to diagnosis of the condition. Moreover, 55 percent were diagnosed after seeking medical care for the condition; most of the remaining cases were detected by "routine physical exam" (32 percent).

Assessment of reproductive factors and hormone use

On the 1995 survey, information was obtained on age at menarche, number of livebirths and stillbirths (parity), age at each birth, total duration of lactation, and number of spontaneous or induced abortions. We also asked about history of infertility, defined as "trying to become pregnant for at least one year without success," age at which it first occurred, and its causes. A complete history of oral contraceptive use was obtained in 1995. For each year from age 13 years to age at baseline, the duration of oral contraceptive use in three categories (<6, 6–9, >9 months) was recorded. We calculated the duration of each reported interval (taking the midpoint of each category) and then summed all of the intervals from the baseline and follow-up questionnaires to ascertain the total duration of oral contraceptive use.

Information on oral contraceptive brand was obtained on follow-up questionnaires and was used to categorize oral contraceptive use in terms of type, dose, biologic potency of estrogen and progestin, and formulation (monophasic, multiphasic, or progestin-only "minipills") (27, 28). We used Dickey's method (27), based on the entire formulation of the oral contraceptive, to classify oral contraceptives into three categories of estrogenic potency (low: <30 mg; medium: 30–39 mg; and high: ≥40 mg) in ethinyl estradiol equivalents per tablet and three categories of progestational activity (low: <1 mg; medium: 1 mg; and high: >1 mg) in norethindrone equivalents per day. Oral contraceptive progestins were classified as either estranes (norethindrone group) or the biologically more potent gonanes (norgestrel group)

(28). Women who had used oral contraceptives for 6 or more months were classified as ever users.

Norplant (Population Council, New York, New York) and Depo-Provera (Pharmacia-Upjohn, Kalamazoo, Michigan) are long-acting, progestin-only contraceptives, the former being a subdermal implant releasing levonorgestrel at a constant rate over 5 years and the latter given as a 150-mg dose of depot medroxyprogesterone acetate (DMPA) by deep intramuscular injection every 90 days. Current use of progestin-only implants and injectables was ascertained on the baseline and follow-up questionnaires.

Data analysis

Each participant contributed person-time from March 1997 until the diagnosis of uterine leiomyomata, menopause, loss to follow-up, death, or March 2001 (end of follow-up), whichever came first. Age- and time-stratified Cox regression models were used to estimate incidence rate ratios and 95 percent confidence intervals for leiomyomata associated with reproductive exposures of interest (29). To control for age, calendar time, and any two-way interactions between these two time scales, we stratified our analyses jointly by age in 1-year intervals at the start of follow-up and calendar year of the current questionnaire cycle (30). Time-varying covariates were reassigned after 2 years according to the updated exposure values reported on the 1997 and 1999 questionnaires, with the exception of infertility and lactation, which were measured in 1995 only. The Anderson-Gill data structure was used to update all time-varying covariates (31), and “exact” methods were used to handle tied event times.

To qualitatively assess the linearity of continuous variables, we categorized variables into equally spaced categories and plotted the midpoint of each category versus the log hazard. We also performed likelihood ratio tests that compared the best-fitting restricted cubic spline model for the data (using stepwise selection techniques from a richly parameterized 10-knot initial model) with the linear model nested within it (32). Variables that did not satisfy these assessments of linearity were modeled nonparametrically using restricted cubic splines (32).

A covariate was included in multivariate analyses if the literature supported its role as a risk factor or if adding the covariate to a model containing all other predictors of leiomyomata changed the incidence rate ratio by 10 percent or more (33). Tests for trend across categories of variables were calculated by including a single ordinal variable coded as the category of exposure (34); the “unexposed” category (e.g., nulliparous) was excluded from dose-response assessment.

Multivariate models controlled for age at menarche, parity, age at first birth, years since last birth, lactation, oral contraceptive use, body mass index, smoking, current alcohol consumption, and education. Departures from the proportional hazards assumption were tested by the likelihood ratio test comparing models with and without interaction terms for covariates versus age. In this same manner, we evaluated effect modification by education, body mass index (35), smoking, and alcohol intake on the main associations of interest (36).

RESULTS

The median age at menarche among Black Women’s Health Study participants was 12 years (table 1). Parous women had on average two births, with a median age at first birth of 22 years and a median time since last birth of 9 years. Forty-three percent of parous women reported having breastfed for 3 or more months. The majority of women had used oral contraceptives at some point in their lives, and 23 percent were currently using them. The prevalence of progestin-only injectable use was 3 percent. In 1995, 11 percent of women reported a history

of infertility. Among the 68 percent whose cause was investigated, the most commonly reported causes were the following: "not found" (34 percent), tubal blockage (23 percent), and ovulatory disorder (15 percent).

During 76,711 person-years of follow-up, 2,279 new cases of uterine leiomyomata confirmed by ultrasound ($n = 2,006$) or hysterectomy ($n = 273$) were reported. Based on all cases of uterine leiomyomata (ultrasound or hysterectomy confirmed), risk was inversely related to age at menarche after adjustment for potential confounders (table 2). The multivariate incidence rate ratio for women with an age at menarche of 15 or more years versus less than 11 years was 0.7 (95 percent confidence interval (CI): 0.5, 0.8), and a dose-response relation was apparent. Results were similar when hysterectomy-confirmed cases were considered separately.

Parity was associated with a 30 percent lower risk of leiomyomata (table 2). There was no evidence of a dose-response reduction in risk with each additional birth. Since previous research has shown a positive association between infertility and leiomyomata (14,17), especially at earlier ages (12,16), we were concerned that use of a nulliparous referent group could have yielded a spurious inverse association with parity if it contained a large proportion of infertile women. However, the inverse association for parity remained after the exclusion of women with a history of infertility (data not shown). Although infertility was not an independent risk factor for leiomyomata overall, we observed an inverse association for age at first occurrence (^{P}trend = 0.01). Spontaneous and induced abortions were unrelated to risk (table 2). All results were similar for hysterectomy-confirmed cases, with the exception of parity: The multivariate incidence rate ratio comparing parous with nulliparous women was 1.4 (95 percent CI: 1.0, 2.0).

Risk of leiomyomata was inversely related to age at first birth, independent of years since last birth and other covariates (table 2). The multivariate incidence rate ratio for women with an age at first birth of 30 or more years versus less than 20 years was 0.6 (95 percent CI: 0.4, 0.9), and there was evidence of a dose-response relation. Findings were similar for hysterectomy-confirmed cases. In an attempt to replicate findings from a recent National Institute of Environmental Health Sciences (NIEHS) study (37), we repeated the analyses among nulliparous and primiparous women and controlled for a history of infertility. Contrary to the j-shaped pattern observed in the NIEHS study, we found the same inverse linear pattern produced by our main model based on all cases. Compared with nulliparous women, the multivariate incidence rate ratios for parous women with an age at first birth of less than 25, 25–29, 30–34, and 35 or more years were 0.9 (95 percent CI: 0.8, 1.0), 0.6 (95 percent CI: 0.5, 0.7), 0.4 (95 percent CI: 0.3, 0.5), and 0.3 (95 percent CI: 0.2, 0.5), respectively.

Time since most recent birth was positively related to the risk of leiomyomata among parous women, independent of age at first birth and other covariates (table 2). Women who had a birth in the past 5 years had less than half the risk of leiomyomata compared with women whose last birth was 5 or more years ago. This pattern of risk was uniform within categories of age at first birth (data not shown). Duration of lactation was not associated with risk of uterine leiomyomata. Results were similar for hysterectomy-confirmed cases.

Relative to noncurrent use of hormonal contraception, current use of oral contraceptives was not associated with risk of leiomyomata (table 3), while current use of progestin-only injectables was associated with a 40 percent reduction in risk (95 percent CI: 0.4, 0.9). When past users of injectables were excluded, the inverse association remained. While weakly elevated risks were found for initiation of oral contraceptive use at younger ages, no pattern of increased risk was found for past or current oral contraceptive use, duration or recency of use (table 3), hormonal potency, classification of progestin, or formulation of oral contraceptive (table 4). Mutual control for estrogenic and progestational potency did not materially influence

these findings. Among hysterectomy-confirmed cases, either results were null (table 3) or numbers were too small to examine oral contraceptive characteristics separately (table 4).

We did not observe any effect modification by age, alcohol consumption, smoking, or education on the main associations of interest. The association with parity appeared to vary by body mass index (Pinteraction = 0.01). Among women with a body mass index below 27 (the median), the incidence rate ratio for parous relative to nulliparous women was 0.6 (95 percent CI: 0.5, 0.6); among women with a body mass index of 27 or above, the incidence rate ratio for parous relative to nulliparous women was 0.8 (95 percent CI: 0.7, 0.9).

Restriction of our analytical sample to women who reported a Papanicolaou smear in the past 2 years yielded analogous findings to those based on the original sample (data not shown). Moreover, results were similar when cases confirmed by pelvic examination (n = 404) were included as part of the outcome definition, censored at the time of diagnosis, or classified as noncases as presented in this paper.

DISCUSSION

The present results are the first prospective data on risk factors for uterine leiomyomata in Black women. The Nurses' Health Study II published prospective data on uterine leiomyomata (17), but their case group comprised only 5 percent Black women, and the results on reproductive factors were not stratified by race. The rate ratios observed in the present study are consistent with those found in studies of White women. Risk was inversely associated with age at menarche, parity, age at first birth, and current use of injectables and positively associated with years since last birth. While age at first oral contraceptive use was weakly inversely associated with risk, null associations were found for duration and recency of use, hormonal potency, classification of progestin, and formulation of oral contraceptive.

Epidemiologic studies on age at menarche in relation to uterine leiomyomata have shown an inverse association (13,16–20). The inverse association found in the Black Women's Health Study and other studies supports the hypothesis that women with an early age at menarche have, on average, increased menstrual cycling and greater lifelong exposure to bioavailable estrogens, which are thought to promote growth of uterine leiomyomata. Early age at menarche has been correlated with higher levels of estradiol (38) and estrone and lower levels of sex hormone binding globulin (39,40).

The decreased risk of leiomyomata in parous compared with nulliparous women is consistent with results from previous research (12,14,17,18), although our study did not confirm the dose-response reduction in risk for parity that has been shown in some (12,14,18), but not all (17), studies. The lack of an association for spontaneous or induced abortion agrees with findings from other studies (12,41) and suggests that the protection conferred by pregnancy may relate to full-term pregnancy only. Inverse associations for parity remained after the exclusion of women reporting a history of infertility and after accounting for lifetime lactation. Although lactation is thought to suppress ovarian hormones (37), our study does not support an association with leiomyomata, in accord with the two other studies that have examined lactation (18,19). Excess body weight appeared to weaken the inverse association observed for parity, as women with a body mass index above the median had only half the parity-related reduction in risk of women below the median.

Hormonal and nonhormonal mechanisms may explain the inverse association with parity. First, higher parity reflects a decrease in menstrual cycling. Second, a full-term pregnancy induces significant long-term changes in levels of ovarian hormones and growth factors (42–46), including lower levels of plasma and urinary estradiol (38,44), higher levels of sex hormone binding globulin (44), and long-term decreases in basal levels of prolactin (46,47). Third, full-

term pregnancy may cause a reduction in estrogen receptor levels in myometrial tissue, which could reduce the sensitivity of leiomyomata to hormonal stimuli (48). Fourth, extensive uterine tissue degradation and remodeling occurs both during and after full-term pregnancy (49). Collagenases and other tissue-degrading enzymes induce apoptosis and may inhibit the growth of preneoplastic or neoplastic cells (49).

In line with other studies (12,16,17), the risk of uterine leiomyomata in the Black Women's Health Study increased with increasing time since last birth. The time-risk relation between parity and risk of leiomyomata is similar for uterine cancer (50), which supports the hypothesis that the protection conferred by parity may be related to pregnancy-related hormonal changes or the mechanical shedding of transformed myometrial cells. A recent NIEHS study demonstrated that a first birth occurring in the mid-reproductive years (ages 25–29 years) was most protective against leiomyomata, while births at other ages showed no association with risk (37). Our study did not replicate these findings but, rather, showed an inverse linear relation with age at first birth, regardless of whether analyses included primiparous or all parous women.

There was no clear association between oral contraceptives and risk of uterine leiomyomata in the Black Women's Health Study. While two studies found that ever users of oral contraceptives were at reduced risk (14,16,18), others found little or no association (12,13, 19) or increased risk (21). Only one study found a reduction in risk as the number of years of oral contraceptive use increased (14). Our finding of an increased risk associated with early age at first oral contraceptive use is consistent with that of one other study (17). In contrast to a study that found a reduction in risk associated with increasing dose of progestin (14), we found no association with progestational potency or progestin classification. Although the validity and clinical relevance of potency information have been questioned (51), we carried out these analyses because other diseases, such as breast cancer (52), ovarian cancer (53), and vulvar vestibulitis (54), have been linked to oral contraceptive potency.

Current use of progestin-only injectables was associated with a decreased risk of uterine leiomyomata relative to nonuse of hormonal contraception. A Thai study showed a similar inverse relation between the use of DMPA, an injectable progestin, and surgically confirmed leiomyomata (18). In that study, the reduction in risk was most pronounced for women using DMPA for 5 or more years and for current users. In the Black Women's Health Study, the inverse association for use of progestin-only injectables remained unchanged after excluding past users. This suggests that the inverse association was not influenced by the inclusion of women with subclinical leiomyomata who may have discontinued DMPA because of irregular bleeding.

Use of DMPA has been associated with an increase in gonadotropin-releasing hormone pulse frequency, modification of the endometrial lining, suppression of gonadotropins, and reduced secretion of estradiol (55,56) and progesterone. Progestins may also downregulate the estrogen receptor in leiomyomata (57). Estradiol concentrations in DMPA users resemble postmenopausal levels, and the degree of estradiol suppression may increase with longer use (55). Findings for progestin-only oral contraceptives and implants were uninformative because of small numbers.

In the Black Women's Health Study, information on reproductive and contraceptive histories was collected before the diagnosis and confirmation of leiomyomata. This prospective design eliminates the potential for recall bias because cases reported their exposures prior to their diagnosis of leiomyomata. Although it is still possible that leiomyomata developed years before their clinical diagnosis, it is unlikely that women would have modified their lifestyle without the experience of symptoms or the clinical diagnosis of the condition.

We validated self-reported uterine leiomyomata through a detailed supplementary questionnaire and review of medical records. We were able to confirm the diagnosis in 96 percent of the cases for whom we obtained medical records. We cannot rule out the possibility that women who released their records reported with greater accuracy than those who did not. Results based on the most secure case definition, hysterectomy-confirmed leiomyomata, were similar to those based on the larger group that included ultrasound-confirmed cases. The one exception was that parity was not inversely associated with risk in the hysterectomy group. Differences between ultrasound- and hysterectomy-confirmed cases may be related to factors associated with patient or physician preference regarding the choice of treatment rather than the true incidence of leiomyomata (23). For example, if cases who had completed childbearing were more likely to choose hysterectomy as a form of contraception than cases who had not finished childbearing, then our association for parity would have been upwardly biased.

As in most other large-scale epidemiologic studies (7,16), Black Women's Health Study participants were not systematically screened for uterine leiomyomata. Because of the high incidence of these tumors and their tendency to be asymptomatic, some cases were undoubtedly misclassified as noncases. In a recent NIEHS study that screened randomly selected women aged 35–49 years from an urban health plan, 59 percent of premenopausal Black women who had not reported a previous diagnosis of leiomyomata showed ultrasound evidence of the condition (9). The degree of misclassification increased with age (9). In the Black Women's Health Study, if misclassification was unrelated to any of the reproductive factors examined, the observed incidence rate ratios would have been biased toward the null. However, among women aged less than 35 years, a "low-risk" group in which misclassified cases would have constituted a smaller proportion of true noncases, findings were similar to those for the entire study group.

If any reproductive factor influenced the detection of leiomyomata, over- or underestimation of the incidence rate ratio could have occurred. For example, women who visited a physician for any factor that increased their likelihood of pelvic examination (e.g., prenatal care) would have been more likely to have an incidental diagnosis of leiomyomata, which would have upwardly biased the incidence rate ratio for parity. Given that parity was inversely associated with leiomyomata in the Black Women's Health Study, we would expect the true association to be even stronger than what we observed. Likewise, the observed incidence rate ratios for oral contraceptive use may have been inflated because of detection bias. Data from our validation study show that a high proportion of cases (70 percent) had symptoms prior to the detection of uterine leiomyomata and that 55 percent of cases sought medical care for symptoms prior to detection of the condition. While this leaves room for detection bias, restriction of the sample to women reporting a Papanicolaou smear within the previous 2 years did not appreciably change our results, suggesting that detection bias played a minor role.

Findings generated from a follow-up study can be compromised if response is low within each cycle of follow-up and there is permanent loss to follow-up. The Black Women's Health Study response of over 80 percent reduces the potential for selection bias. Length of follow-up did not differ significantly by parity, oral contraceptive use, body mass index, or age at menarche, but significant differences were noted for education. In a comparison of women with less than 12 years versus 17 or more years of education, the mean length of follow-up was 37.1 months and 39.8 months ($p < 0.001$). When we used Robins' method of inverse probability of censoring weighting (58) to account for differential loss to follow-up—a method that weights women who were not lost to follow-up more heavily to account for women who were, given the same covariate history—our results did not change materially.

Black Women's Health Study participants may differ from the general population of US Black women in ways that may affect the generalizability of our findings. However, the median ages

at menarche, age at first birth, and body mass index in the cohort were similar to those documented in nationwide representative studies of Black women (59–61). Moreover, we did not find any effect modification by education, smoking, or alcohol consumption on the main associations of interest. Therefore, the present findings are likely to extend to other US Black women.

Reproductive history is an important determinant of uterine leiomyomata in US Black women. Several national studies show that Black girls have an earlier mean age at menarche than White girls (59,60,62,63) and that Black women are more likely to begin and end childbearing at earlier ages (61). However, evidence from studies including Black women and White women, combined with the modest associations found in the Black Women's Health Study, suggests that reproductive factors explain only a small fraction of the Black-White difference in rates of uterine leiomyomata (16,17).

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Abbreviations

CI
: confidence interval

DMPA
: depot medroxyprogesterone acetate

NIEHS
: National Institute of Environmental Health Sciences

TABLE 1

Baseline characteristics of 22,895 participants in the Black Women's Health Study, 1997

	Median or %	IQR*
Demographic and lifestyle factors		
Age (median years)	34	29–40
Body mass index (median kg/m^2)	26	23–31
Education (median years)	15	14–16
Smoking history		
Current (%)	14	
Former (%)	13	
Alcohol consumption, ≥1 drink/day (%)	3	
Papanicolaou smear within past 2 years (%)	91	
Reproductive factors		
Age at menarche (median years)	12	11–13
Parous (%)	57	
Age at first birth (median years)	22	19–27
Time since last birth (median years)	9	4–15
Duration of lactation, ≥3 months (%)	43	
History of infertility (%)	11	
Age at first occurrence of infertility (median years)	25	22–29
Hormonal contraceptive use		
Oral contraceptives, ever (%)	81	
Oral contraceptives, current (%)	23	
Progestin-only implants, current (%)	0.5	
Progestin-only injectables, current (%)	3	

* IQR, interquartile range (25th–75th percentile).

TABLE 2

Incidence rate ratios for uterine leiomyomata according to selected reproductive factors, Black Women's Health Study, 1997–2001

Reproductive characteristic	Person-years (no.)	All cases				Hysterectomy-confirmed cases			
		Cases (no.)	Age-adjusted IRR,*†	Multivariate IRR‡	95% CI*	Cases (no.)	Age-adjusted IRR†	Multivariate IRR‡	95% CI
Age at menarche (years)									
<11	8,247	284	1.0	1.0	Referent	27	1.0	1.0	Referent
11	12,875	414	0.9	0.9	0.8, 1.1	47	1.1	1.2	0.7, 1.9
12–13	41,165	1,202	0.8	0.8	0.7, 0.9	149	1.0	1.1	0.7, 1.6
14	7,745	217	0.8	0.8	0.6, 0.9	30	1.0	1.0	0.6, 1.7
≥15	6,679	162	0.6	0.7	0.5, 0.8	20	0.7	0.8	0.4, 1.4
p_{trend}					<0.001				0.31
Nulliparous	32,805	1,071	1.0	1.0	Referent	53	1.0	1.0	Referent
Parous	43,906	1,208	0.6	0.7§	0.6, 0.8	220	1.6	1.4§	1.0, 2.0
No. of births									
1	17,955	460	1.0	1.0	Referent	55	1.0	1.0	Referent
2	15,733	453	1.0	0.9	0.8, 1.1	96	1.5	1.3	0.9, 2.0
3	7,011	198	0.9	0.8	0.6, 1.0	43	1.4	1.1	0.7, 1.9
≥4	3,207	97	1.0	0.9	0.6, 1.2	26	1.8	1.4	0.7, 2.7
p_{trend}					0.18				0.53
Age at first birth (years)									
<20	12,014	398	1.0	1.0	Referent	88	1.0	1.0	Referent
20–24	14,528	439	0.9	0.9	0.8, 1.1	73	0.8	0.8	0.6, 1.1
25–29	11,189	262	0.7	0.8	0.6, 0.9	49	0.7	0.8	0.5, 1.3
≥30	6,175	109	0.5	0.6	0.4, 0.9	10	0.2	0.4	0.2, 0.8
p_{trend}					0.002				0.03
Years since last birth									
<5	12,377	122	1.0	1.0	Referent	11	1.0	1.0	Referent
5–9	11,165	269	2.2	2.0	1.6, 2.5	31	2.0	1.5	0.8, 3.1
10–14	8,295	341	3.5	2.8	2.2, 3.7	72	4.6	2.9	1.4, 5.8
15–19	6,275	261	3.5	2.6	1.9, 3.5	65	4.6	2.5	1.2, 5.4
≥20	5,794	215	3.4	2.2	1.4, 3.2	41	3.2	1.4	0.6, 3.5
p_{trend}					<0.001¶				0.001¶
Duration of lactation (months)									
<1	21,282	635	1.0	1.0	Referent	123	1.0	1.0	Referent
1–11	13,432	394	1.0	1.1	0.9, 1.2	76	1.0	1.1	0.8, 1.6
12–23	3,184	91	0.9	1.0	0.8, 1.3	10	0.5	0.6	0.3, 1.1
≥24	1,591	46	0.9	1.0	0.7, 1.4	8	0.7	0.8	0.4, 1.7
p_{trend}					0.51				0.41
History of infertility (1995)									
Never#	68,873	2,051	1.0	1.0	Referent	231	1.0	1.0	Referent
Ever	7,839	228	0.9	0.9	0.8, 1.1	42	1.2	1.3	0.9, 1.8
Age at first occurrence									
<25 years	3,076	102	1.1	1.2	0.9, 1.4	23	2.0	1.9	1.2, 2.9
25–29 years	2,507	67	0.8	0.8	0.7, 1.1	12	1.1	1.2	0.7, 2.1
≥30 years	1,780	47	0.7	0.8	0.6, 1.0	5	0.4	0.6	0.2, 1.4
p_{trend}					0.03				0.01
No. of spontaneous abortions									
0	62,976	1,873	1.0	1.0	Referent	215	1.0	1.0	Referent
1	10,614	316	0.9	1.0	0.9, 1.2	47	1.1	1.0	0.7, 1.3
2	2,182	65	0.9	1.1	0.8, 1.4	6	0.6	0.6	0.3, 1.3
≥3	940	25	0.8	0.9	0.6, 1.4	5	1.1	1.1	0.5, 2.7
p_{trend}					0.57				0.51
No. of induced abortions									

Reproductive characteristic	Person-years (no.)	All cases				Hysterectomy-confirmed cases			
		Cases (no.)	Age-adjusted IRR,*†	Multivariate IRR‡	95% CI*	Cases (no.)	Age-adjusted IRR†	Multivariate IRR‡	95% CI
0	44,783	1,345	1.0	1.0	Referent	160	1.0	1.0	Referent
1	17,181	500	0.9	0.9	0.9, 1.1	67	1.0	1.0	0.7, 1.3
2	8,276	268	1.0	1.1	0.9, 1.2	32	1.0	1.0	0.7, 1.4
≥3	6,472	166	0.8	0.8	0.7, 1.0	14	0.6	0.5	0.3, 0.9
p_{trend}					0.24				0.08

*IRR, incidence rate ratio; CI, confidence interval.

†Adjusts for age (1-year intervals) and time period (1997–1999, 1999–2001).

‡Adjusts for age, time period, age at menarche (years), parity (0, 1, 2, 3, ≥4 births), months of lactation (<1, 1–11, 12–23, ≥24), age at first birth (years), years since last birth (four-knot restricted cubic spline), years of oral contraceptive use (<5, 5–9, ≥10), body mass index (kg/m^2, four-knot restricted cubic spline), smoking (current, past, never), current alcohol consumption (<1, 1–6, ≥7 drinks/week), and education (<13, 13–15, 16, ≥17 years).

§Adjusts for all covariates listed above except age at first birth and years since last birth.

¶Likelihood ratio test for nonlinearity comparing model with a four-knot restricted cubic spline with linear model nested within it.

#Omits 12 cases (two hysterectomy confirmed) and 476 person-years with missing data on age at infertility.

TABLE 3

Incidence rate ratios for uterine leiomyomata according to hormonal contraceptive use, Black Women's Health Study, 1997–2001

Hormonal contraceptive use	Person-years (no.)	All cases				Hysterectomy-confirmed cases			
		Cases (no.)	Age-adjusted IRR,[*†]	Multivariate IRR[‡]	95% CI[*]	Cases (no.)	Age-adjusted IRR[†]	Multivariate IRR[‡]	95% CI
Current use									
None	56,666	1,771	1.0	1.0	Referent	247	1.0	1.0	Referent
Progestin-only injectables	1,903	26	0.5	0.6	0.4, 0.9	3	0.8	0.8	0.3, 2.6
Progestin-only implants	264	3	0.4	0.5	0.2, 1.5	0	—[§]	—	—
Progestin-only oral contraceptives	177	4	0.8	1.1	0.4, 3.0	0	—	—	—
	17,702	475	1.0	1.0	0.9, 1.1	23	0.7	0.7	0.5, 1.2
Combined oral contraceptives									
Oral contraceptive use									
Never[¶]	13,918	386	1.0	1.0	Referent	52	1.0	1.0	Referent
Past	42,748	1,385	1.0	1.1	1.0, 1.3	195	1.0	1.0	0.7, 1.3
Current	17,879	479	1.1	1.1	0.9, 1.2	23	0.6	0.7	0.4, 1.2
Years of oral contraceptive use (ever users)									
<5	31,863	945	1.0	1.1	0.9, 1.2	120	1.0	0.9	0.7, 1.3
5–9	16,722	512	1.1	1.2	1.0, 1.3	58	1.1	1.1	0.8, 1.6
≥10	12,041	407	1.0	1.1	0.9, 1.3	40	0.7	0.8	0.5, 1.3
p_{trend}					0.60				0.99
Years since last oral contraceptive use (past users)									
<5	12,768	331	1.0	1.1	0.9, 1.3	27	0.9	1.1	0.7, 1.7
5–9	9,444	284	1.0	1.1	0.9, 1.3	22	0.7	0.8	0.5, 1.3
≥10	20,536	770	1.1	1.1	1.0, 1.3	146	1.1	1.0	0.7, 1.4
p_{trend}					0.65				0.28
Age at first oral contraceptive use (ever users)[#]									
<17	11,915	360	1.1	1.2	1.0, 1.4	37	1.1	1.0	0.6, 1.5
17–20	33,595	1,078	1.1	1.2	1.0, 1.3	125	0.9	1.0	0.7, 1.4
21–24	11,047	318	1.0	1.0	0.9, 1.2	47	1.0	1.1	0.8, 1.7
≥25	4,071	108	0.9	0.9	0.7, 1.1	9	0.6	0.7	0.3, 1.3
p_{trend}					0.005				0.72

[*] IRR, incidence rate ratio; CI, confidence interval.

[†] Adjusts for age (1-year intervals) and time period (1997–1999, 1999–2001).

[‡] Adjusts for age, time period, age at menarche (years), parity (0, 1, 2, 3, ≥4 births), age at first birth (years), years since last birth (four-knot restricted cubic spline), years of oral contraceptive use (<5, 5–9, ≥10), body mass index (kg/m^2, four-knot restricted cubic spline), smoking (current, past, never), current alcohol consumption (<1, 1–6, ≥7 drinks/week), and education (<13, 13–15, 16, ≥17 years).

[§] Insufficient number of cases to estimate the incidence rate ratio.

[¶] Reference category for all comparisons of oral contraceptive use. All analyses of oral contraceptive use (except current use) adjust for past use and exclude current users of progestin-only injectables and implants (29 cases; 2,167 person-years).

[#] Additionally adjusts for years of oral contraceptive use (continuous).

TABLE 4

Incidence rate ratios for uterine leiomyomata according to estrogenic potency, progestational potency, progestin classification, and formulation of oral contraceptives, Black Women's Health Study, 1997–2001

Hormonal contraceptive use	Person-years (no.)	All cases			
		Cases (no.)	Age-adjusted IRR,*†	Multivariate IRR‡	95% CI*
Never users§	13,918	386	1.0	1.0	Referent
Estrogenic potency¶					
Low (<30 μg)	6,278	175	1.1	1.1	0.9, 1.3
Medium (30–39 μg)	4,663	119	1.1	1.0	0.8, 1.3
High (≥40 μg)	3,767	108	1.2	1.2	0.9, 1.5
p_{trend}					0.90
Progestational potency#					
Low (<1 mg)	10,489	272	1.1	1.1	0.9, 1.2
Medium (1 mg)	1,432	46	1.2	1.2	0.9, 1.6
High (>1 mg)	2,787	84	1.2	1.2	0.9, 1.5
p_{trend}					0.31
Classification of progestin**					
Gonane	7,798	195	1.0	1.0	0.9, 1.2
Levonorgestrel, norgestrel	4,519	119	1.0	1.1	0.9, 1.3
Desogestrel	1,157	30	1.1	1.1	0.7, 1.5
Norgestimate	2,122	46	0.9	0.9	0.7, 1.2
Estrane	8,301	250	1.1	1.2	0.9, 1.4
	7,734	226	1.1	1.1	0.9, 1.3
Norethindrone, norethindrone acetate					
Ethynodiol diacetate	567	24	1.7	1.6	1.1, 2.5
Estrogen formulation#					
Monophasic	9,398	276	1.1	1.1	0.9, 1.3
Biphasic or triphasic	6,524	165	1.1	1.1	0.9, 1.3

*IRR, incidence rate ratios; CI, confidence interval.

†Adjusts for age (1-year intervals) and time period (1997–1999, 1999–2001).

‡Adjusts for age, time period, age at menarche, parity, age at first birth, years since last birth, body mass index, smoking, alcohol, and education.

§Reference category for all comparisons. All analyses exclude current users of progestin-only injectables and implants (29 cases; 2,167 person-years).

¶In ethinyl estradiol equivalents per day. Estrogenic activity of entire tablet, as measured by mouse uterine assay (27). Omits 106 cases and 5,338 person-years with missing information on oral contraceptive dose.

#In norethindrone equivalents per day: 1 mg of norethindrone = 1 mg of norethindrone acetate = 1 mg of ethynodiol diacetate = 0.2 mg of norgestrel = 0.1 mg of levonorgestrel (27). Omits 106 cases and 5,338 person-years with missing information on oral contraceptive dose.

**Omits 34 cases and 1,780 person-years with missing information on oral contraceptive brand.