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Evaluating risk factors for differences in fibroid size and number using a large electronic health record population

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ABSTRACT

Objective: To evaluate individual characteristics of women with fibroids in relation to fibroid size and number.
Methods: This cross-sectional study involved 2302 women (black and white, age range 18–87) with image- or surgery-confirmed fibroids from the Synthetic Derivative, a database of de-identified demographic and clinical information from patient electronic health records (EHRs) from the Vanderbilt University Medical Center. We performed multivariate regression analyses on the following outcomes: volume of largest fibroid, largest dimension of all fibroids, and number of fibroids (single vs multiple). Candidate risk factors included age at diagnosis, body mass index (BMI), race, type 2 diabetes status, and number of living children (a proxy for parity). We assessed potential effect measure modification by race and both age and BMI using a likelihood ratio test.
Results: Black race was strongly associated with having multiple fibroids (adjusted odds ratio [aOR]: 1.83, 95% confidence interval [CI]: 1.49, 2.24) and larger fibroid volume (adjusted beta: 1.77, 95% CI: 1.38, 2.27) and greater largest dimension (adjusted beta: 1.28, 95% CI: 1.18, 1.38). Having multiple fibroids was most strongly associated with ages 43–47 (aOR = 3.37, 95% CI: 2.55, 4.46) compared with the youngest age group (ages 18–36). Having a larger number of living children was associated with having single a fibroid (aOR: 0.88, 95% CI: 0.78, 0.99).
Conclusions: Our findings suggest that different underlying etiologies are involved for women developing single versus multiple fibroids and small versus large fibroids. Studies are needed of the mechanisms by which these characteristics influence fibroid formation and growth.

1. Introduction

The majority of women in the United States have at least one uterine fibroid by the age of menopause [1]. Fibroids are a major cause of hysterectomies [2], which are primarily done to manage symptoms [3] and cost the U.S. up to $34.4 billion annually in healthcare, treatment, and time lost from work [4]. Fibroids vary in size and number between women, leading to a range of symptoms including: pressure of the abdomen, chronic pelvic pain, and heavy or painful periods [5]. In addition, presence of multiple fibroids has associated with preterm birth and cesarean delivery, while large fibroids have associated with preterm premature rupture of membranes [6]. Increasing body mass index (BMI; kg/m^2) [7], nulliparity [8,9], and being African American (compared to being white) [10–13] have previously been associated with fibroid risk. In contrast, women with type 2 diabetes are less likely to develop fibroids [14,15].

Although fibroid risk factors have been well-documented [7,8,10–13], few studies have examined factors associated with fibroid size and number. One potential reason for the lack of studies on fibroid characteristics is that fibroid size and number can only be assessed by imaging or surgical procedures (such as ultrasounds or hysterectomies). As a result, few studies have examined risk factors for fibroid characteristics. In a study by our group, we found an inverse relationship between age at menarche and fibroid number and size using the *Right From the Start* (2001–2010) cohort, confirming reproductive hormonal exposure is a significant factor influencing fibroids [16]. A cross-

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sectional study of 988 women (630 cases) who had ultrasound results from the *National Institute of Environmental Health Sciences Uterine Fibroid Study* reported that decreased levels of insulin-like growth factor-I were associated with having small- (< 2 cm) and medium- (≥2 to < 4 cm) sized fibroid in white women, and decreased insulin levels were associated with having a large fibroid (≥4 cm), especially in black women [17]. In another cross-sectional study from the *Prospective Research on Ovarian Function Study*, fibroid characteristics, abstracted from pathology and operative notes, and key risk factors were compared between black and white women (N = 360) undergoing hysterectomies [18]. The authors found that black women, on average, had larger and more numerous fibroids than white women [18]. The authors also found that nulligravid black and white women were more likely to have larger fibroids, and nulligravid white women were more likely to have multiple fibroids than white women with one or more pregnancies [18].

Individual characteristics of a woman may put her at risk of developing single versus multiple fibroids or a small versus large fibroid. Knowing which of these characteristics is strongly associated with fibroid size and number might allow for better understanding of the mechanisms underlying individual variation in fibroid size and number. Our objective was to identify individual characteristics of a woman associated with fibroid size or number. We examined the association of fibroid volume, largest fibroid dimension, and fibroid number with candidate risk factors using a clinical population of 2302 women identified from electronic health records (EHRs).

2. Materials and methods

2.1. Study population–the Synthetic Derivative

We conducted our analyses using subjects from the Synthetic Derivative, a clinical population at Vanderbilt University Medical Center [19] consisting of de-identified demographic and clinical information from patient EHRs. We used a previously validated phenotyping algorithm with a positive predictive value of 96% to identify fibroid cases [20]. The algorithm included black and white women who were 18 years or older, had at least one International Classification of Diseases, 9th Revision (ICD-9) or current procedure terminology (CPT) code for pelvic imaging, and had at least one ICD-9 or CPT code indicating a fibroid diagnosis. Fibroid status for 2302 cases was manually validated by examining image or surgical reports from patient EHRs. We manually extracted dimensions for each reported fibroid, number of fibroids, and relevant demographic information from pelvic imaging reports, including ultrasound, magnetic resonance imaging, and computed tomography scans or surgical reports from myomectomies and hysterectomies. Precedence for recording patient information was given to the first image report mentioning fibroids. If a patient's EHR lacked an image report citing fibroids, we entered patient data from the first surgical report describing their fibroids.

We abstracted fibroid number (single vs. multiple), volume of largest fibroid (cm^3), and largest dimension (cm) of all reported fibroids. The following formula for volume of an ellipsoid was used to calculate fibroid volume: length × width × height × 0.523. The largest fibroid dimension and volume measurements were $\log_{10}$-transformed to accommodate the assumption of normally distributed residuals for linear regression. For individuals with two recorded dimensions of their largest fibroid (35.6% of cases), we assigned the last measurement by averaging the initial two to calculate fibroid volume. For individuals with data for number of fibroids, some EHRs (18.6%) noted the presence of many fibroids but gave no specific number. Because of this limitation, we coded fibroid number as one versus multiple fibroids.

Abstracted clinical characteristics included age at diagnosis, BMI (continuous), self-reported or clinically identified race, type 2 diabetes status, and number of living children. We used previously published programming algorithms to abstract type 2 diabetes from EHRs [21]. Number of living children was chosen as a proxy for parity. In addition, we abstracted indication for imaging and fibroid location. This study was evaluated and approved by the Vanderbilt University Medical Center Institutional Review Board (IRB).

2.2. Statistical analyses

We performed univariate and multivariate regression analyses for the following outcomes: volume of largest fibroid, largest dimension of all fibroids, and number of fibroids (single vs. multiple). Exposures included age at diagnosis, BMI, race, type 2 diabetes status, and number of living children (numbered 0 through 5 and 6 or more grouped together) as covariates. All multivariate regression analyses included age, BMI, and race as covariates. Age and BMI were not normally distributed and had nonlinear effect sizes; therefore, analyses were performed by grouping age into quintiles and BMI into World Health Organization (WHO) categories [22]. Too few underweight individuals were in our dataset (underweight N = 27), so we combined individuals from the underweight and normal weight categories. We assessed potential effect measure modification by race across age quintiles and BMI categories using a likelihood ratio test (LRT). A likelihood ratio test p-value of 0.10 or less was considered an interaction.

In secondary analyses, multiple imputation was performed for missing data (number of living children) for each outcome to determine if missingness in this exposure affected our analyses. All exposures in the multivariate regression model and outcome were included in each multiple imputation data model. Each dataset was imputed ten times. To ensure consistency in multiple imputation analyses, the random number generation functions were seeded with the number 12,345. Multiple imputation analyses were largely consistent with effect sizes estimated from non-imputed data; therefore, we present and discuss results herein using non-imputed missing data. Stata/SE 13 (College Station, Texas) was used for all statistical analyses.

3. Results

Our study population included 2302 individuals with fibroids (Table 1). Their mean age (± SD) was 45.5 years ± 12, and the majority were overweight (29%) or obese (44%). The average BMI (± SD) was 30.4 kg/m^2. The mean volume (± SD) of largest fibroid and mean largest fibroid dimension (± SD) were 71.4 cm^3 ± 202 cm^3 and 3.7 cm ± 3 cm, respectively. Fibroid number was dichotomized (single vs. multiple), and more women (52%) had multiple fibroids.

3.1. Fibroid number

Increasing age had a nonlinear association with having multiple fibroids (Table 2). The strongest association was observed when comparing ages 43–47 to the referent group (ages 18–36) (adjusted odds ratio [aOR]: 3.37, 95% confidence interval [CI]: 2.55, 4.46). Black race associated with having multiple fibroids (aOR: 1.83, 95% CI: 1.49, 2.24), while having a higher number of living children was associated with having fewer fibroids (aOR: 0.88, 95% CI: 0.78, 0.99). BMI and type 2 diabetes were not associate with fibroid number. We did not observe evidence of effect measure modification by race on age or BMI for analyses of fibroid number (age − LRT p = 0.739, BMI − LRT p = 0.632).

3.2. Fibroid size (volume and largest dimension)

Increasing age had a nonlinear association with both fibroid volume and largest fibroid dimension (Tables 3 and 4). The strongest effect of age on fibroid volume (adjusted beta: 1.57, 95% 1.12, 2.22) (Table 3) and dimension (adjusted beta: 1.19, 95% CI: 1.07, 1.32) (Table 4) was for women between 48 and 54 years of age. Black race also associated with increasing fibroid volume (adjusted beta: 1.77, 95% CI: 1.38, 2.27) and larger dimensions (adjusted beta: 1.28, 95% CI: 1.18, 1.38). BMI,