Growth of uterine leiomyomata among premenopausal black and white women

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Uterine leiomyomata (fibroids) are the leading cause of hysterectomy in the United States. Black women have a greater fibroid burden than whites, yet no study has systematically evaluated the growth of fibroids in blacks and whites. We prospectively tracked growth for 262 fibroids (size range: 1–13 cm in diameter) from 72 premenopausal participants (38 blacks and 34 whites). Fibroid volume was measured by computerized analysis of up to four MRI scans over 12 months. We used mixed effects models to identify factors that are associated with growth, and results were converted to percent change per 6 months for clinical relevance. The median growth rate was 9% (range: −89% to +138%). Seven percent of fibroids regressed (>20% shrinkage). Tumors from the same woman grew at different rates (within-woman component of variation was twice the component among women; both were significant, $P < 0.001$). Black and white women less than 35 years of age had similar fibroid growth rates. However, growth rates declined with age for whites but not for blacks ($P = 0.05$). The odds of a tumor growing more than 20% in 6 months also decreased with age for whites but not for blacks ($P < 0.01$). Growth rates were not influenced by tumor size, location, body mass index, or parity. We conclude that (*i*) spontaneous regression of fibroids occurs; (*ii*) fibroids from the same woman grow at different rates, despite a uniform hormonal milieu; (*iii*) fibroid size does not predict growth rate; and (*iv*) age-related differences in fibroid growth between blacks and whites may contribute to the higher symptom burden for black women.

ethnic | fibroid | MRI | tumor growth | longitudinal data

Uterine leiomyomata (fibroids) are the leading indication for hysterectomy in the United States (1). Myomectomy and uterine artery embolization are also common treatments, but hysterectomy may be required subsequently (2). Hartmann *et al.* (3) estimate a $4,600 excess health care cost during the year following each US woman's diagnosis of fibroids. National medical costs associated with fibroids exceed 2 billion dollars annually (4). African Americans have a higher fibroid incidence (5, 6), experience more severe symptoms (7), present with larger tumors (7), and have a threefold higher risk of hysterectomy (8) compared with whites. Symptoms increase with the size of fibroids (7, 9, 10). However, few studies have examined the growth of fibroids over time (11–13), and no study has systematically followed the growth of fibroids in black and white women.

The Fibroid Growth Study was designed to measure the growth of fibroids in black and white women with clinically relevant fibroids using MRI technology. We compare growth rates of individual tumors from the same woman; contrast fibroid growth in black and white women; and examine associations with age, parity, body mass index (BMI), and tumor characteristics.

Results

Study Participants. Characteristics of the 72 participants are shown in Table 1. Our cohort ranged in age from 24 to 54 years, and approximately half were African American. Nearly 60% were overweight or obese. More than half were diagnosed with fibroids within 2 years of study entry. Most had multiple fibroids, and approximately a third had more than eight. As expected from the criteria for entry, participants had enlarged uteri (range: 110–1,995 cm^3, with nearly a fifth greater than 1,000 cm^3). Fifteen of the 72 women opted for treatment during the study year. There were no statistically significant differences between black and white women with respect to these characteristics, but there was a tendency for blacks to be younger and to have higher BMIs. Women were recruited irrespective of symptoms. Although most (88%) reported problems with pelvic pain or bleeding, only 31% reported that these symptoms limited their activities.

Fibroid Characteristics at Enrollment. Fibroid size, type, and location are shown in Table 1. The initial volume of the 262 measured fibroids varied from 1.3 to 1098 cm^3 (1.4–12.8-cm diameter), with a median volume of 17.3 cm^3 (3.2-cm diameter). The 6 submucosal fibroids tended to be small, with a median size of 7.7 cm^3 (2.5-cm diameter).

Fibroid and Uterine Growth Rates. The 262 tumors varied widely in their growth rates; they ranged from shrinkage of 89% to growth of 138% per 6 months (Fig. 1). The median fibroid growth rate for both black and white women was 9% per 6 months. Eighty-eight tumors (34%) were rapidly growing (>20% increase in volume per 6 months), and 19 (7%) were spontaneously regressing (>20% decrease in volume per 6 months).

We next wanted to determine how fibroid growth was related to overall uterine growth. The median uterine growth rate was 6% per 6 months. Despite our only measuring a subset of fibroids for most women, those who had at least one measured fibroid that was rapidly growing had significantly increased uterine growth compared with those without a rapidly growing tumor ($P = 0.027$). Uterine growth rate averaged 14% higher for women with a measured rapidly growing tumor compared with women without.

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Table 1. Characteristics of the participants (n = 72) and their fibroids (n = 262), Fibroid Growth Study, enrollment 2001–2004

	Total n = 72 women, 262 fibroids		Black n = 38 women, 155 fibroids		White n = 34 women, 107 fibroids	
	n	%	n	%	n	%
Participant characteristic						
Age, yr						
<35	23	31.9	14	36.8	9	26.5
35–44	28	38.9	17	44.7	11	32.3
≥45	21	29.2	7	18.5	14	41.2
Parity						
0	43	59.7	21	55.3	22	64.7
≥1	29	40.3	17	44.7	12	35.3
BMI (kg/m^2)						
<25	30	41.6	12	31.6	18	53.0
25–29.9	21	29.2	13	34.2	8	23.5
≥30	21	29.2	13	34.2	8	23.5
Time since initial diagnosis of fibroids (yr)						
<1	25	34.7	10	26.3	15	44.1
1–2	17	23.6	10	26.3	7	20.6
3–5	8	11.1	6	15.8	2	5.9
5–9	12	16.7	7	18.4	5	14.7
≥10	8	11.1	5	13.2	3	8.8
missing	2	2.8	0	0.0	2	5.9
Uterine volume, cm^3						
<250	14	19.4	7	18.4	7	20.6
250–499	19	26.4	10	26.3	9	26.5
500–999	26	36.1	14	36.8	12	35.3
≥1,000	13	18.1	7	18.4	6	17.6
Number of fibroids						
1	5	6.9	1	2.6	4	11.8
2	11	15.3	5	13.2	6	17.6
3–8	27	37.5	15	39.5	12	35.3
>8	29	40.3	17	44.7	12	35.3
Treatment*						
None	57	79.1	28	73.7	29	85.3
Embolization	2	2.8	1	2.6	1	2.9
Myomectomy	7	9.7	6	15.8	1	2.9
Hysterectomy	6	8.3	3	7.9	3	8.8
Hormonal use						
None	52	72.2	27	71.1	25	73.5
Oral contraceptives	16	22.2	8	21.0	8	23.5
Other	4	5.6	3	7.9	1	3.0
Fibroid characteristics						
Initial fibroid volume (diameter†)						
<14.0 cm^3 (<3.0 cm)	121	46.1	75	48.5	46	43.0
14.0–64.9 cm^3 (3.0–4.9 cm)	82	31.3	52	33.6	30	28.0
≥65.0 cm^3 (≥5.0 cm)	59	22.5	28	18.1	31	29.0
Fibroid type						
Submucosal	6	2.3	6	3.9	0	0.0
Intramural	166	63.4	99	63.9	67	62.2
Subserosal	90	34.4	50	32.3	40	37.4
Fibroid location						
Corpus	147	56.1	85	54.8	62	57.9
Fundus	56	21.4	32	20.6	24	22.4
Lower segment	59	22.5	38	24.5	21	19.6

*Treated women had growth data censored at treatment (5 women had 4 MRI scans, but 3 were censored after 3 MRI scans, and 7 were censored after 2 MRI scans).

†Diameter calculated from measured volume based on ellipsoid formula.

Spontaneously Regressing Tumors. Nineteen tumors from 14 women showed spontaneous shrinkage. When examined descriptively, they were found to vary in size and location and to come from both blacks and whites aged 30–49 years [see supporting information (SI) Table S1]. We looked at the MRI scans showing these 19 tumors for lack of gadolinium enhancement, which would be consistent with loss of arterial blood flow and necrosis (14). By visual estimate, 7 tumors showed necrosis exceeding 50% of tumor volume and 2 others showed 20% to 40% necrosis. Tumors with more dramatic shrinkage tended to have greater

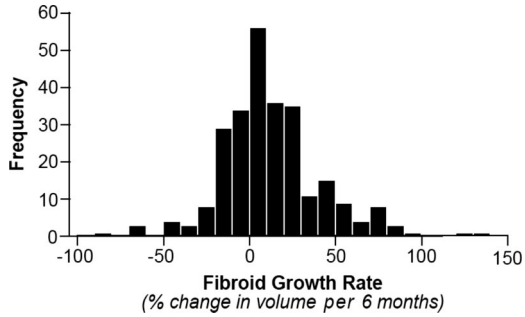

Fig. 1. Frequency distribution of growth rates for 262 fibroids from 72 premenopausal women, Fibroid Growth Study, enrollment 2001–2004.

necrosis (Spearman correlation = −0.56, $P = 0.013$; Table S1). In a comparison sample of 19 tumors randomly selected from the remaining 243, 1 tumor showed 20% necrosis and none showed greater than 20% necrosis.

Fibroids from the Same Woman Grow at Different Rates. Growth rates for each woman's tumors are shown in Fig. 2, with the 72 women ordered by the median growth rate of their tumors. The individual tumor growth rates are represented by the hatch marks on the vertical lines. These demonstrate the wide range of fibroid growth rates within a given woman. Seven women had both a rapidly growing and a spontaneously regressing tumor.

Fig. 2 also shows that despite the within-woman variability, some women tend to have tumors that grow rapidly, whereas other women tend to have stable or shrinking tumors. When the total variation in tumor growth rate was partitioned into a component for within-woman variation and a component for between-women variation using mixed model regression, both components were significant ($P < 0.001$). The variation of tumor growth within women was two times the variation between women.

Factors Related to Rate of Fibroid Growth. Fig. 3 shows the associations of fibroid growth with several characteristics, including ethnicity, age, number of fibroids, and size of the fibroid. The results are based on analysis of 258 fibroids from 72 women after excluding statistical outliers (the four most rapidly shrinking tumors; see *SI Text* for description of effects of the outliers). The mean tumor growth rate for blacks in the study was similar to that for whites (12% vs. 10% increase in volume per 6 months, respectively). However, when we compared tumors within age categories by ethnicity, the tumors from older white women (≥45

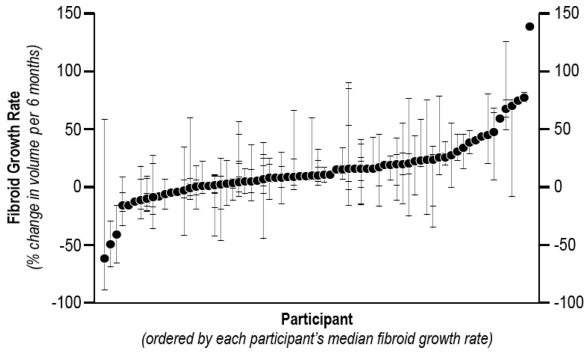

Fig. 2. Median (black circles) and range (vertical bars) of fibroid growth rates for each of 72 participants, ordered by each participant's median tumor growth rate. The horizontal hatch marks show the growth rate for each individual tumor, Fibroid Growth Study, enrollment 2001–2004.

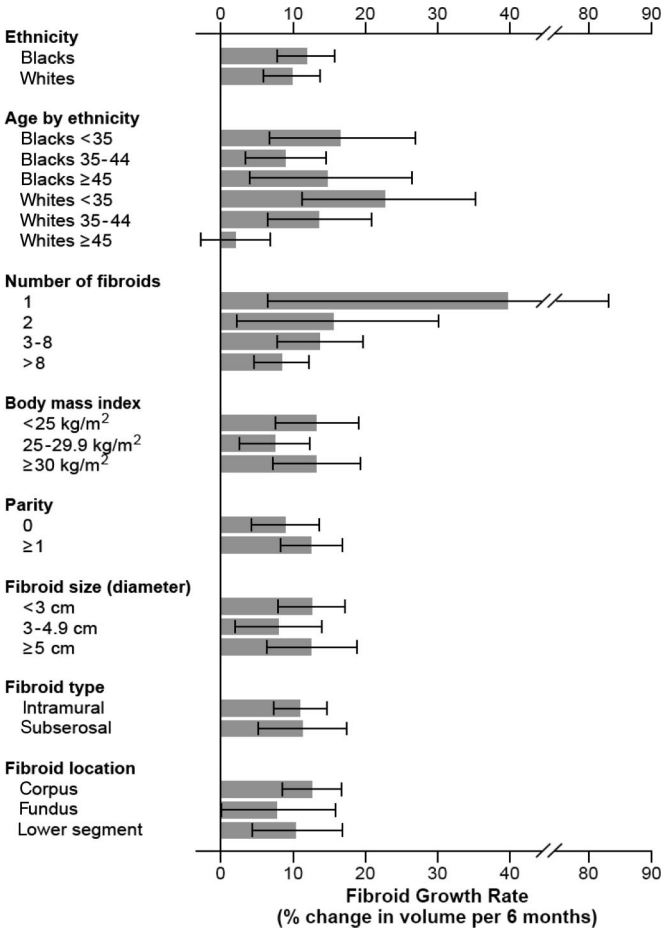

Fig. 3. Unadjusted mean fibroid growth rates by participant characteristics and fibroid characteristics, 258 fibroids (4 statistical outliers excluded) from 72 participants, Fibroid Growth Study, enrollment 2001–2004.

years) grew much more slowly than those from older black women (2% vs. 15% growth rate, respectively; Fig. 3). Adjusted analyses based on linear mixed effects models supported this association, demonstrating a significant decline in growth rate with age for tumors from whites but not from blacks ($P = 0.05$; Table 2). The pair-wise analysis shows a significant decrease in tumor growth rate for older whites when compared with younger whites ($P = 0.004$), and no such difference was found among blacks ($P = 0.67$). Furthermore, the chance of a tumor growing rapidly (>20% increase in volume per 6 months) depended on age for white women but not for black women ($P = 0.004$). The relative odds of rapid growth for younger whites was 17 times that of the older whites ($P < 0.001$). For blacks there was no significant difference by age ($P = 0.81$). These results are summarized in Table S2.

The only other factor affecting fibroid growth rate was the number of fibroids in the uterus. Single tumors grew much faster than fibroids that shared a uterus (Fig. 3, Table 2). Fibroid growth rates were not significantly associated with BMI or parity, or with tumor size, type, or location. The reader is referred to *SI Text* for sensitivity analyses (including dropping the six submucosal fibroids and dropping the five women with a single fibroid) that demonstrated robustness of results.

With the exception of the factors that we found to be important (age, ethnicity, and number of tumors), other characteristics were associated with <5% difference in growth rates. Although such differences would be statistically significant with extremely large sample sizes, they would likely not be viewed as

Table 2. Adjusted growth rate differences* associated with participant and fibroid characteristics, Fibroid Growth Study, enrollment 2001–2004

Factor	*P* value†	Adjusted differences in growth rate estimate (95% confidence interval)
Age by ethnicity, yr	0.05	
Blacks <35		Reference
Blacks 35–44		−7.05 (−17.62, 4.87)
Blacks ≥45		−3.38 (−17.31, 12.90)
Whites <35		Reference
Whites 35–44		−7.76 (−21.04, 7.74)
Whites ≥45		−19.57‡ (−30.48, −6.94)
Number of fibroids	0.06	
>8		Reference
3–8		5.69 (−2.89, 42.32)
2		0.72 (−13.73, 43.26)
1		33.75 (7.58, 61.17)
BMI	0.34	
<25		Reference
25–29.9		−4.81 (−13.79, 38.67)
≥30		2.40 (−7.30, 41.61)
Parity	0.43	
0		Reference
≥1		4.17 (−5.86, 42.41)
Initial fibroid volume (diameter§)	0.48	
<14.0 cm^3 (<3 cm)		Reference
14.0–64.9 cm^3 (3.0–4.9 cm)		−3.53 (−9.43. 37.80)
≥65 cm^3 (≥5.0 cm)		−3.10 (−9.96, 38.36)
Fibroid type¶	0.85	
Intramural		Reference
Subserosal		0.55 (−5.12, 39.20)
Fibroid location	0.64	
Corpus		Reference
Fundus		−3.25 (−9.67, 38.12)
Lower segment		−0.75 (−7.49, 39.17)

n = 258 fibroids from 72 women. Four statistical outliers (all shrinking >50% in volume per 6 months) were excluded, leaving 258 fibroids.

*Age by ethnicity differences are adjusted for number of fibroids; number of fibroid differences are adjusted for age by ethnicity; all other variables are adjusted for age by ethnicity and number of fibroids.

†*P* value for the overall importance of each factor for growth.

‡Pair-wise difference between ≥45 and <35 group is statistically significant at *P* = 0.004.

§Diameter calculated from measured volume based on ellipsoid formula.

¶Intramural group includes six submucosal fibroids.

clinically important. Using our variance estimates, we found that our study had 80% power to detect differences in growth rates of 14%.

Discussion

This longitudinal study of 262 uterine leiomyomata in 72 premenopausal women provides an in-depth analysis of tumor growth in black and white women. We demonstrated that fibroids within the same woman often have different growth rates despite having a similar hormonal milieu. Indeed, each tumor appeared to have its own intrinsic growth rate, consistent with studies showing that fibroids are monoclonal in origin (15, 16) with variable molecular characteristics (17–21). The only other large study of fibroid growth was conducted in Japan, and most of the 70 participants had only a single tumor (11); thus, variation in growth of fibroids from the same woman could not be evaluated.

We observed spontaneous regression in a small percentage of fibroids, surprising in premenopausal women. Tumor shrinkage after menopause is assumed to occur; there is a dramatic reduction in clinical diagnoses after menopause (22), and postmenopausal fibroids are predominantly small lesions (23). Dewaay *et al.* (12) identified six small spontaneously resolved tumors in women approaching menopause; otherwise, however, spontaneously regressing tumors in premenopausal women have not been well documented in the literature. The women with regressing tumors in our study were having regular menses, and half were in their 30s. Many of the shrinking tumors we observed showed evidence of necrosis, suggesting that vascular events may be involved.

A fundamental question we sought to address is whether fibroid growth differs in black and white women. There is a general assumption that fibroids grow faster in black women compared with white women because black women are diagnosed at a younger age and have a higher incidence and more symptoms (5–8). Molecular markers also may differ between tumors from blacks and whites (18, 21, 24). We found significant ethnic differences in fibroid growth when age was considered. Growth rates were similar between blacks and whites in the youngest age group (<35 years) but declined in older white women so that, on average, tumors grew extremely slowly in white women in the ≥45 age group. In contrast, growth rates showed little decline with increasing age for blacks. Importantly, the greater fibroid burden observed in black women may be explained by our observation that fibroid growth rates show little decline with increasing age in black women and by the previously reported finding that black women have an earlier onset compared with white women (5, 6, 25).

The decline in tumor growth rate in older white women was an unexpected finding and could not be attributed to these women entering menopause. Participants were having regular periods, and the decline was not seen exclusively in the oldest age group. Instead, there was a gradual decline across the three age groups for whites. Even if some were perimenopausal, their fibroids would have been expected to continue growing based on the clinical literature (26, 27), which refers to perimenopausal instability of ovarian function and more frequent periods of unopposed estrogen as a possible mechanism for rapid growth (27). Dysregulation of the extracellular matrix has been suggested as an important etiologic factor in fibroid growth (28). There may be age-related changes in angiogenesis or extracellular matrix production that differ between blacks and whites. Future studies should consider the age of the woman when looking at fibroid characteristics.

The finding that fibroid growth was not influenced by tumor characteristics such as size and location was surprising and is important for research that characterizes molecular characteristics of fibroid tissue. Tumor size has been related to variation in molecular markers (17, 19–21), and it has been assumed that the molecular differences reflect differences in tumor growth rates. Our data show that large tumor size cannot be used as an indicator of a growing tumor.

Our data showed more rapid growth for solitary tumors than for multiple tumors that share a uterus. However, our sample size of women with solitary tumors was quite small, and we required participants to have either at least one large fibroid or an enlarged uterus for enrollment. It is possible that only rapidly growing tumors can attain a large size while remaining solitary, so the finding could be attributable to our sample selection. Alternatively, solitary tumors may grow faster because of less competition for uterine blood supply. To evaluate these alternatives, small solitary tumors need to be studied.

The study has other limitations. Extremely small tumors (<1.5-cm diameter) could not be measured accurately, and our focus on women with at least one already well-developed fibroid

did not allow us to examine initial tumor development. We also were unable to examine submucosal fibroids statistically because there were so few of them. However, we investigated potential biases, including biased sample selection, variation in menstrual phase at time of MRI, and other possible confounders and found little effect on our findings (*SI Materials*).

Our findings have implications for patient care and for further research directions. Current clinical practice encourages an ultrasound or pelvic examination at 6 months to evaluate growth (29). Our analysis shows that the majority of tumors grow less than 20% in 6 months, with a median growth rate of 9%. Thus, it may be possible to extend the follow-up time for clinical assessment of fibroid growth. In addition, if further research supports our findings that tumor growth rates decline in white women as they age, those approaching perimenopause might choose to delay treatment and wait for menopause when tumors are likely to shrink. Current medical therapies have focused on hormonal manipulation of well-developed tumors (30). The rapid growth of tumors in young women in both ethnic groups suggests that research is urgently needed to study tumor onset and identify preventive factors. Treatments that inhibit early tumor growth could stop development of debilitating symptoms.

Methods

Study Design. The National Institute of Environmental Health Sciences Fibroid Growth Study was a collaborative study with the University of North Carolina Medical Center that enrolled participants from 2001 to 2004 with approval from both institutional review boards. Premenopausal women with a known diagnosis of fibroids, confirmed by ultrasound, were recruited from gynecology clinics and announcements in the community (Davis *et al.*, in review). To ensure clinical relevance, enrollment was limited to women with at least one fibroid greater than 5 cm in diameter or a uterus enlarged to at least a 12-week pregnancy size (200–250 cm^3) (31). Fibroids were measured up to four times (MRI scans taken at enrollment and then at 3, 6, and 12 months). Of the 116 participants, 35 completed only one MRI scan (30 women opted for treatment, 4 women dropped out, and 1 woman had completed only one MRI scan when the field study ended). Of the 81 women with two or more MRI scans, 3 were excluded because their tumors were smaller than the size criteria for this analysis. We further limited analysis to black and white women. This left 72 women in our analysis sample (38 blacks and 34 whites). Prospective time in the study averaged approximately 9 months, primarily because of early termination when the field study ended (see details in *SI Text*).

Measurement of Tumor and Uterine Volume. Sagittal T2-weighted MRI scans without contrast were evaluated for type (submucosal, intramural, or subserosal), location, and size of fibroids (see detailed description of MRI protocol in *SI Text*). Fibroids were selected for volumetric measurement if they were seen in at least three consecutive slices and had traceable borders. When a woman had many fibroids, the technician selected tumors representing different sizes and positions in the uterus. All submucosal fibroids were measured. The final sample was limited to tumors that had volumes >5.0 cm^3 or were seen on at least five consecutive slice images ($n = 262$ fibroids, with each woman contributing 1–11 individual tumors).

Fibroid volume was determined using the volume estimation and tracking over time method developed for this study (32). All analyses used volumetric measures, but a diameter size was calculated from measured volume for descriptive purposes. Uterine volume was estimated from each participant's first and last MRI scan based on measurement of craniocaudal length (L), transverse width (W), and anterior/posterior (AP) diameter, and application of the ellipsoid formula ($L \times W \times AP \times 0.52$). Details of measurement and quality assurance are in *SI Text*.

Tumor Type and Location. The type of fibroid was defined by the position of its center in relation to the inner and outer boundaries of the uterus. Submucosal tumors were centered in the endometrial lining, intramural in the myometrium, and subserosal along the external lining or outside of the uterus. The location of a fibroid within the uterus was defined by the position of its center in relation to the fundus, corpus, or lower uterine segment (see reference diagram in *SI Text*).

Determination of Fibroid and Uterine Growth Rates. The natural logarithm of fibroid volume was used to make the distribution approximately normal. The growth rate of each tumor was based on the change in log volume between each MRI scan divided by the number of days in the interval. For each tumor, rates across intervals were averaged. For clearer clinical application, the average growth rates were converted to a 6-month percent change in volume. A 6-month interval was chosen because that is a clinically recommended follow-up period (29) and it falls within the observation period of this study. The reader is referred to *SI Text* for further details of growth rate determinations. Uterine growth rate was defined as the change in log volume divided by the number of days between the first and last MRI scans, summarized as percent change in volume per 6 months.

Statistical Analyses. We used mixed effects linear regression models to evaluate factors that may influence fibroid growth rates (PROC MIXED, version 9.1; SAS Institute, Cary, NC). This method accounted for any correlation in growth rates among tumors from the same woman. Details of the analysis and model selection are in *SI Text*. We investigated ethnicity (blacks vs. whites, based on self-reported ethnicity), age, number of fibroids in the uterus at study enrollment (1, 2, 3–8, or >8), participant BMI (kg/m^3 based on measurements taken at the first MRI scan), participant parity (nulliparous vs. parous based on self-report), initial fibroid volume, fibroid type (subserosal vs. the combined group of intramural and submucosal, combined because there were only 6 submucosal fibroids), and location of fibroid (fundus, corpus, or lower segment) as potential factors associated with tumor growth. Statistical significance of pair-wise differences was evaluated only when a factor was significant at $P = 0.05$. We also investigated the factors associated with the odds of a tumor growing rapidly (20% or more growth in a 6-month period) using random effects logistic regression analysis (SAS macro GLIMMIX; SAS Institute, Cary, NC) (see *SI Text* for details). We conducted analyses with the same primary and secondary variables as in the growth rate model and used the same 258 tumors in analysis.

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