Growth of uterine leiomyomata among premenopausal black and white women

Shyamal D. Peddadaa, Shannon K. Laughlinb, Kelly Minerc, Jean-Philippe Guyond, Karen Hanekea,2, Heather L. Vahdatc,d, Richard C. Semelkae,d, Ania Kowalike,4, Diane Armao, Barbara Davisi,3, and Donna Day Bairdb,6

aBiostatistics Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709; bEpidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709; cIntegraed Laboratory Systems, Durham, NC 27713; dDepartment of Radiology, University of North Carolina, Chapel Hill, NC 27599; eDepartment of Obstetrics/Gynecology, University of North Carolina, Chapel Hill, NC 27599; and fLaboratory of Women's Health, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709

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Uterine leiomyomata (fibroids) are the leading cause of 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 $4,600 excess health care cost during the year following each US woman's diagnosis of fibroids. National medical costs associated with fibroids exceed 2 billion dollars annually (4). African Americans have a higher fibroid incidence (5, 6), experience more severe symptoms (7), and have a threefold higher risk of hysterectomy (8) compared with whites. Symptoms increase with the size of fibroids (7), and have a threefold higher risk of hysterectomy (8) compared with those without a rapidly growing tumor ($P = 0.027$). Uterine growth rate averaged $14\%$ higher for women with a measured rapidly growing tumor compared with women without.

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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1Present address: Novartis, Cambridge, MA 02139.
2Present address: PBM 347, 4093 Diamond Ruby, Suite 7, Christiansted, Virgin Islands 00820.
3Present address: Family Health International, Durham, NC 27713.
4Present address: Reproductive Science Center, Lexington, MA 02421.
5Present address: Millennium: The Takeda Oncology Company, Cambridge, MA 02139.
6To whom correspondence should be addressed. E-mail: baird@niehs.nih.gov.

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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

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

<table>
<thead>
<tr>
<th>Participant characteristic</th>
<th>Total n = 72 women, 262 fibroids</th>
<th>Black n = 38 women, 155 fibroids</th>
<th>White n = 34 women, 107 fibroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>23 31.9</td>
<td>14 36.8</td>
<td>9 26.5</td>
</tr>
<tr>
<td>35–44</td>
<td>28 38.9</td>
<td>17 44.7</td>
<td>11 32.3</td>
</tr>
<tr>
<td>≥45</td>
<td>21 29.2</td>
<td>7 18.5</td>
<td>14 41.2</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>43 59.7</td>
<td>21 55.3</td>
<td>22 64.7</td>
</tr>
<tr>
<td>≥1</td>
<td>29 40.3</td>
<td>17 44.7</td>
<td>12 35.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>30 41.6</td>
<td>12 31.6</td>
<td>18 53.0</td>
</tr>
<tr>
<td>25–29.9</td>
<td>21 29.2</td>
<td>13 34.2</td>
<td>8 23.5</td>
</tr>
<tr>
<td>≥30</td>
<td>21 29.2</td>
<td>13 34.2</td>
<td>8 23.5</td>
</tr>
<tr>
<td>Time since initial diagnosis of fibroids (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>25 34.7</td>
<td>10 26.3</td>
<td>15 44.1</td>
</tr>
<tr>
<td>1–2</td>
<td>17 23.6</td>
<td>10 26.3</td>
<td>7 20.6</td>
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<tr>
<td>3–5</td>
<td>8 11.1</td>
<td>6 15.8</td>
<td>2 5.9</td>
</tr>
<tr>
<td>5–9</td>
<td>12 16.7</td>
<td>7 18.4</td>
<td>5 14.7</td>
</tr>
<tr>
<td>≥10</td>
<td>8 11.1</td>
<td>5 13.2</td>
<td>3 8.8</td>
</tr>
<tr>
<td>missing</td>
<td>2 2.8</td>
<td>0 0.0</td>
<td>2 5.9</td>
</tr>
<tr>
<td>Uterine volume, cm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;250</td>
<td>14 19.4</td>
<td>7 18.4</td>
<td>7 20.6</td>
</tr>
<tr>
<td>250–499</td>
<td>19 26.4</td>
<td>10 26.3</td>
<td>9 26.5</td>
</tr>
<tr>
<td>500–999</td>
<td>26 36.1</td>
<td>14 36.8</td>
<td>12 35.3</td>
</tr>
<tr>
<td>≥1,000</td>
<td>13 18.1</td>
<td>7 18.4</td>
<td>6 17.6</td>
</tr>
<tr>
<td>Number of fibroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 6.9</td>
<td>1 2.6</td>
<td>4 11.8</td>
</tr>
<tr>
<td>2</td>
<td>11 15.3</td>
<td>5 13.2</td>
<td>6 17.6</td>
</tr>
<tr>
<td>3–8</td>
<td>27 37.5</td>
<td>15 39.5</td>
<td>12 35.3</td>
</tr>
<tr>
<td>&gt;8</td>
<td>29 40.3</td>
<td>17 44.7</td>
<td>12 35.3</td>
</tr>
<tr>
<td>Treatment*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>57 79.1</td>
<td>28 73.7</td>
<td>29 85.3</td>
</tr>
<tr>
<td>Embolization</td>
<td>2 2.8</td>
<td>1 2.6</td>
<td>1 2.9</td>
</tr>
<tr>
<td>Myomectomy</td>
<td>7 9.7</td>
<td>6 15.8</td>
<td>1 2.9</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>6 8.3</td>
<td>3 7.9</td>
<td>3 8.8</td>
</tr>
<tr>
<td>Hormonal use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>52 72.2</td>
<td>27 71.1</td>
<td>25 73.5</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>16 22.2</td>
<td>8 21.0</td>
<td>8 23.5</td>
</tr>
<tr>
<td>Other</td>
<td>4 5.6</td>
<td>3 7.9</td>
<td>1 3.0</td>
</tr>
<tr>
<td>Fibroid characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial fibroid volume (diameter)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;14.0 cm³ (&lt;3.0 cm)</td>
<td>121 46.1</td>
<td>75 48.5</td>
<td>46 43.0</td>
</tr>
<tr>
<td>14.0–64.9 cm³ (3.0–4.9 cm)</td>
<td>82 31.3</td>
<td>52 33.6</td>
<td>30 28.0</td>
</tr>
<tr>
<td>≥65.0 cm³ (≥5.0 cm)</td>
<td>59 22.5</td>
<td>28 18.1</td>
<td>31 29.0</td>
</tr>
<tr>
<td>Fibroid type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submucosal</td>
<td>6 2.3</td>
<td>6 3.9</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Intramural</td>
<td>166 63.4</td>
<td>99 63.9</td>
<td>67 62.2</td>
</tr>
<tr>
<td>Subserosal</td>
<td>90 34.4</td>
<td>50 32.3</td>
<td>40 37.4</td>
</tr>
<tr>
<td>Fibroid location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus</td>
<td>147 56.1</td>
<td>85 54.8</td>
<td>62 57.9</td>
</tr>
<tr>
<td>Fundus</td>
<td>56 21.4</td>
<td>32 20.6</td>
<td>24 22.4</td>
</tr>
<tr>
<td>Lower segment</td>
<td>59 22.5</td>
<td>38 24.5</td>
<td>21 19.6</td>
</tr>
</tbody>
</table>

*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.
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
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 char-
acteristics 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
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 post-menopausal fibroids are predominantly small lesions (23). Dewey 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 stability 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 cm³) (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 cm³ 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 transcranial width (L), transverse width (W), and anterior/posterior (AP) diameter, and application of the ellipsoid formula (L x W x AP x 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 autocorrelation 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/m² 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 other 3 types), location of fibroid (fundus, corpus, or subserosal), 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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