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Uterine Leiomyomata in Relation to Insulin-Like Growth Factor-I, Insulin, and Diabetes

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Abstract

Background—Insulin-like growth factor-I (IGF-I) and insulin stimulate cell proliferation in uterine leiomyoma (fibroid) tissue. We hypothesized that circulating levels of these proteins would be associated with increased prevalence and size of uterine fibroids.

Methods—Participants were 35–49-year-old, randomly selected members of an urban health plan who were enrolled in 1996–1999. Premenopausal participants were screened for fibroids with ultrasound. Fasting blood samples were collected. Associations between fibroids and diabetes, plasma IGF-I, IGF binding protein 3 (BP3), and insulin were evaluated for blacks (n = 585) and whites (n = 403) by using multiple logistic regression.

Results—IGF-I showed no association with fibroids in blacks, but in whites the adjusted odds ratios (aORs) for both mid and upper tertiles compared with the lowest tertile were 0.6 (95% confidence intervals [CI] = 0.3–1.0 and 0.4–1.1, respectively). Insulin and diabetes both tended to be inversely associated with fibroids in blacks. The insulin association was with large fibroids; aOR for the upper insulin tertile relative to the lowest was 0.4 (0.2–0.9). The aOR for diabetes was 0.5 (0.2–1.0). Associations of insulin and diabetes with fibroids were weak for whites. BP3 showed no association with fibroids.

Conclusions—Contrary to our hypothesis, high circulating IGF-I and insulin were not related to increased fibroid prevalence. Instead, there was suggestion of the opposite. The inverse association with diabetes, although based on small numbers, is consistent with previously reported findings. Future studies might investigate vascular dysfunction as a mediator between hyperinsulinemia or diabetes and possible reduced risk of fibroids.

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Uterine leiomyomata, commonly called fibroids, are the leading indication for hysterectomy in the United States.¹ The condition is especially common for blacks, a group with estimated cumulative hysterectomy rates for fibroids of 20% by age 45.² Fibroids are benign smooth muscle tumors of clonal origin.³ Incidence increases with age from menarche to perimenopausal ages.⁴ Both estrogen and progesterone may stimulate their development. Although the mechanisms by which these hormones influence tumor onset and progression is not well understood (reviewed in Schwartz and Marshall⁵), their actions are mediated at least in part by growth factors.

Insulin-like growth factor-I (IGF-I) may be one of the growth factors that plays an important role in the pathogenesis of fibroids.⁶ IGF-I production can be stimulated by growth hormone, and its actions include cell proliferation and inhibition of apoptosis.⁷ In 1990 Boehm et al⁸ reported elevated IGF-I expression in fibroid compared with normal myometrium, and upregulation of gene expression and protein has been seen in several subsequent studies.⁹⁻¹⁷ Upregulation of IGF-I is also seen in fibroid tissue from the Eker rat, an animal model for fibroids.¹⁸ IGF-I stimulates fibroid cell mitosis in vitro.^{19,20} Based on human fibroid cell culture, Swartz et al⁶ demonstrated estrogen-dependent IGF-I upregulation and its linkage to transcription factors that increase the rate of cell cycle transition, thus providing a detailed description of IGF-I proliferative and anti-apoptotic effects in fibroids.

The extent to which circulating IGF-I may contribute to tumorigenesis is unknown. Most of the circulating IGF-I is produced in the liver. Higher levels have been associated with increased risk of breast cancer, another hormonally mediated tumor (reviewed by Renehan et al,²¹ but see also Baglietto et al²²). Two studies have examined circulating levels of IGF-I in which women with and without uterine fibroids were compared. Neither showed differential levels, although sample sizes were small (cases and controls combined were 81 in 1 and 40 in the other).^{23,24}

There are at least 6 high-affinity IGF binding proteins in the circulation that regulate the activity of IGF-I, the primary being binding protein 3 (BP3).²⁵ BP3 may reduce IGF-I activity by preventing its binding to the receptor, but by binding IGF-I, it prolongs the half-life for IGF-I from minutes to hours. BP3 can also act independently of IGF-I, with antiproliferative effects.²⁵ Both BP3 mRNA and protein are found in normal and fibroid smooth muscle cells.²⁶ To our knowledge no prior study has examined the association between circulating levels of BP3 and fibroid status.

Insulin has also been hypothesized to play a role in fibroid pathogenesis.²⁷ Insulin and IGF-I have similar growth-promoting activity, and both have weak binding affinity to the other's receptor.²⁸ Experimental treatment of fibroid tissue with insulin can increase cell proliferation in vitro.²⁹ In addition, hyperinsulinemia may stimulate increased ovarian hormone production, which might indirectly increase the development of fibroids.³⁰

We hypothesized that increased circulating IGF-I and hyperinsulinemia would be associated with increased development of uterine fibroids. To test this hypothesis we measured IGF-I, BP3, and insulin in fasting blood samples taken from women in the National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study, a study that recruited randomly selected 35–49-year-old members of an urban health plan and screened them for fibroids with ultrasound, thus identifying both clinically diagnosed and subclinical cases.

Methods

Participants

The NIEHS Uterine Fibroid Study was designed to estimate prevalence and age-specific cumulative incidence of uterine fibroids and to investigate risk factors. Detailed methods have been described.³¹ Briefly, the computerized membership records of a prepaid health plan in Washington, DC were used to select randomly 35–49-year-old women. Those selected were screened for eligibility by telephone. Eligibility criteria were 1) the computerized listing had correctly identified 35–49-year-old woman with current membership at the study site, and 2) a telephone interview could be conducted in English. A total of 1323 black and white women agreed to participate (Fig. 1) (83% of those identified as eligible). The research was approved by the NIEHS and George Washington University Human Subject's Review Boards, and participants gave informed consent. The analysis is limited to premenopausal participants who made a study clinic visit at which time a fasting blood sample was drawn (Fig.1).

Determination of Fibroid Status

Fibroid status was determined for most participants by a transabdominal and transvaginal ultrasound screening examination. Participants who had recently undergone an ultrasound examination at the clinic for clinical purposes (21%) were not asked to repeat an examination for the study. We used ultrasounds from the prior 2 years if they showed “no fibroids”, and ultrasounds from the prior 5 years if they showed fibroids. For these women fibroid data were abstracted from the clinic radiology reports. The study ultrasound examinations were performed by sonographers who were certified by the American Registry of Diagnostic Medical Sonographers and were trained for the study to collect and record consistent data on fibroids (minimum diameter of 0.5 cm). They were under the direct supervision of 1 radiologist with fellowship training in ultrasound, and each study was checked at its completion by this radiologist. The examinations were performed on ultrasound units ATL HDI 9, Acuson 128 XP, and Diasonics DRF 400 by using transabdominal (3.5–5.0 mHz) and transvaginal (5.0–7.0 mHz) ultrasound probes. Sonographers completed a data collection form designed for this study that included data on uterine size (length, width, anterior to posterior diameter), heterogeneity of the echo pattern (none, diffuse, or focal), and size of the largest fibroid. Any questionable sonograms were reviewed by a single radiologist. Those uteri with diffuse heterogeneity but no focal fibroids (39 whites and 76 blacks) were categorized as having fibroids, but statistical analyses were also repeated without these women, and results did not change. For 18 participants who did not complete their ultrasound screening examinations and 1 whose ultrasound examination was indeterminate, we accepted self-report of a prior diagnosis. We did not rely on self-report of “no fibroids” because undiagnosed fibroids are common; about half of the undiagnosed women in our study were found to have fibroids at ultrasound screening.³¹

Assays

The NIEHS clinical chemistry laboratory measured IGF-I and BP3 in plasma that had been stored at -80°C. IGF-I was measured by extraction using radioimmunoassay kits (Nichols Institute Diagnostics San Juan Capistrano, CA). BP3 was measured by immunoradiometric assay kits (Diagnostic Systems Laboratories, Webster, TX). Insulin was measured in plasma at the Duke University Clinical and Research Laboratory. All intra- and interassay coefficients of variation were less than 10%.

Other Variables

Weight was measured at the clinic visit, and other data were collected during a telephone interview conducted by trained interviewers or from responses to a self-administered questionnaire. Diabetics were those responding “yes” to the question on the self-administered questionnaire “Has a doctor or health professional ever told you that you had diabetes, high blood sugar or “sugar,” not pregnancy induced?” Gestational diabetes was ascertained with the reproductive history questions in the telephone interview. For each delivery the participant was asked “Did you have any special medical problems during the pregnancy including (a list of 8 complications, 1 of which was) gestational diabetes (diabetes beginning during pregnancy)?”

Statistical Analyses

We evaluated the relation of IGF-I, BP3, insulin, and diabetes with uterine fibroids first using logistic regression, and then using a Bayesian multistate analysis.³² Plasma protein levels were divided into tertiles based on the combined sample of blacks and whites, and the lowest tertile was used as the reference group. Black women have a higher risk of fibroids and substantially different distributions of many covariates, so all analyses were performed separately for the 2 ethnic groups. Prior analyses of data from this study indicated that age, age of menarche, body mass index (BMI), physical activity, and number of deliveries after age 24 years were related to fibroid development.^{31,33} These potential confounders were included a priori.

Using logistic regression, we estimated the age-adjusted odds of fibroids and then the fully-adjusted odds of fibroids for tertiles of IGF-I, BP3, and insulin. The relation between diabetes and fibroids was also examined with age-adjusted and fully-adjusted logistic models. Sensitivity analyses were conducted to assess the impact of minor variations in our diagnostic definition of fibroids. For IGF-I, BP3, and insulin we also conducted logistic analyses based on size of the largest fibroid as the outcome (this analysis could not be done for diabetes because of the small numbers of diabetic women). The fibroid diameter, as a continuous variable, was not normally distributed, and various transformations did not produce normality. Therefore, we categorized the largest tumor diameter (small; <2cm; medium; >2 to <4 cm; or large; ≥4 cm), and compared each category as a separate outcome with women without fibroids (LOGISTIC procedure in SAS, SAS Institute, Cary, NC). Because fibroids are common, prevalence differences for the important associations from the logistic analyses were estimated with binomial regression³⁴ to provide more meaningful estimates of effect.

The Bayesian analysis provided a method for evaluating effects on tumor onset compared with tumor progression, thus allowing us to begin to estimate associations with incidence in this cross-sectional study. We used a multistate modeling approach³² with a flexible stochastic model that incorporates data on age at any prior diagnosis, age at study ultrasound, and size of largest fibroid (if any were found) to characterize onset and subsequent progression of fibroids. Fibroid onset is defined as the time at which the tumors first grow large enough to be detectable by a sonogram. Even though a large percentage of participants with fibroids had never had a clinical diagnosis of fibroids, the true onset time is unknown. During a preclinical phase and even after clinical diagnosis, fibroids may continue to grow. Our Bayesian approach utilizes survival analysis techniques to integrate data on first diagnosis of fibroids (for those who had been diagnosed before study enrollment) and size of the largest fibroid. The analysis is implemented using a Markov chain Monte Carlo algorithm, after choosing noninformative prior distributions. Hypothesis tests of ordered trends in tumor onset and progression across categories of the variables of interest are based

on estimated posterior probabilities. Posterior probabilities 0.95 or more are considered important.

Results

Characteristics of the study participants are shown in Table 1. Of the 585 blacks 427 had fibroids; of the 403 whites, 203 had fibroids. Insulin was log-normally distributed, and both the IGF-I and BP3 distributions were approximately normal. Blacks had higher levels of insulin and lower levels of BP3 than whites. As expected, insulin was highly correlated with BMI, IGF-I was inversely correlated with both age and BMI, and BP3 was correlated with IGF-I (see distributions and correlations in eAppendix, available with the online version of this article).

The associations of IGF-I, BP3, and insulin with uterine fibroids based on logistic regression are shown in Figure 2. Age-adjusted and fully-adjusted models differ primarily because of adjustment for BMI in models of insulin and IGF-I, and adjustment for IGF-I in models of BP3. For IGF-I, there appeared to be an inverse association with fibroids in whites. When the association was examined by estimating prevalence differences, the estimates for the mid and upper tertiles of IGF-I compared with lower tertile were -11% (CI = -23% to 1%) and -9% (-23% to 4%), respectively. In fibroid size-specific models the reduction in fibroid development with IGF-I was seen for small and medium fibroids, but there was no evidence of reduced prevalence of large fibroids (Fig. 2). IGF-I was not associated with fibroids in blacks, and in an analysis of blacks and whites combined, the *P*-value for interaction by race was 0.07.

For BP3, there was no evidence of an association with fibroids in any of the analyses. The molar ratio of IGF-I to BP3 was also examined, but it was highly correlated with IGF-I ($r = 0.84$ and 0.85 for blacks and whites, respectively) and showed similar, although slightly weaker, associations to those seen for IGF-I.

For insulin, neither age-adjusted nor fully-adjusted analyses showed convincing evidence for an association with presence of fibroids. When size of the largest fibroid was examined, there appeared a tendency for elevated insulin to be protective for large fibroids in both ethnic groups, and the association was stronger in blacks (Fig. 2). The estimated reductions in prevalence of large fibroids for blacks in mid and upper tertiles of insulin compared with the lower tertile were -12% (-22% to -1%) and -16% (-27% to -5%), respectively. When we excluded women who had been diagnosed with diabetes (43 blacks and 9 whites), there was little change in the relative odds of fibroids associated with insulin, IGF-I, and BP3.

There was an inverse association between diabetes and fibroids, especially for blacks (Table 2), where the estimated reduction in prevalence was -14% (0% to -29%). Black women who reported gestational diabetes but no other diagnosis of diabetes also tended to be less likely to have fibroids, but the confidence interval was broad (Table 2). All diabetes was adult onset with the exception of two black women who reported diagnoses at ages 13 and 16. Of those diagnosed with diabetes, 81% reported taking medication. Among blacks (the ethnic group with more diabetics) the inverse association between diabetes and fibroids was very similar for the 13 women who had been diagnosed at least 5 years prior to study enrollment compared with the 32 women who had more recent diagnoses (adjusted ORs = 0.47 and 0.52, respectively).

Bayesian analyses to examine the relation of IGF-I, insulin, and diabetes with tumor onset versus tumor progression controlled for the same factors included in multivariable logistic analyses. IGF-I in whites was inversely associated with tumor onset (posterior probability, $pp = 0.97$), not tumor progression ($pp = 0.45$). Insulin in blacks was inversely associated

with tumor progression ($pp = 0.98$), not tumor onset ($pp = 0.50$). Diabetes was marginally protective of tumor onset in blacks ($pp = 0.90$), but the association with progression was weaker ($pp = 0.62$).

To evaluate the robustness of our results, we repeated the logistic analyses with minor changes in our definition of fibroids. First, we reassigned women who had no fibroids at ultrasound and no prior surgery for fibroids but had been previously told by a doctor that they had fibroids (32 blacks and 17 whites). They were moved from the “no fibroid” to the “fibroid” group. Second, we excluded women who had no focal fibroids but whose sonogram showed diffuse heterogeneity (75 blacks and 39 whites). These reanalyses showed results that were similar to those based on the original categorization of fibroid diagnosis. We also examined potential effect modification by BMI and exercise on the associations between insulin and IGF-I with presence of any sized fibroid. In none of these analyses was the interaction term important ($p > 0.10$).

Discussion

IGF-I and insulin have both been shown to increase cellular proliferation of fibroid tissue in culture.^{19,20,29} IGF-I expression or protein level is up-regulated in fibroids compared with normal myometrium,⁹⁻¹⁷ and IGF-I mediates proliferative actions of estrogen in fibroid tissue.⁶ Given these findings as well as the data linking IGF-I with breast cancer, we hypothesized that increased circulating levels of IGF-I and insulin would be associated with increased fibroid development. However, we found either no association or inverse effects for fibroids in both age-adjusted and fully-adjusted models of circulating IGF-I and insulin. Reduced prevalence of fibroids was seen for white women with mid or upper tertile values of IGF-I, whereas there was no association for black women. Blacks with mid or upper tertile values of insulin had a reduced prevalence of large fibroids, and consistent with the insulin association, blacks with diabetes also had a reduced prevalence of fibroids. Circulating BP3 was not associated with fibroid development.

To our knowledge, no previous large epidemiologic study has examined the association between circulating IGF-I or insulin levels and fibroid development, although 2 studies have reported on associations with diabetes. Based on very small numbers Faerstein et al¹⁶ found no association with diagnosed diabetes ($OR = 0.9$; $CI = 0.4-2.2$), but an increased relative odds of 2.0; (0.4–12.6) for the women taking medication for diabetes. Consistent with our findings, Wise et al³⁵ found a reduced risk of fibroids among diabetics in the Black Women's Health Study (0.77; 0.60–0.98).

Circulating IGF-I comes primarily from the liver. It may be that factors such as fat metabolism that affect liver IGF-I transcription and secretion (thus determining circulating levels) have little influence on tissue levels in the uterus where transcription can occur in situ under the influence of estrogen.⁶ In situ expression may be a major difference between breast tissue and fibroid tissue. Few breast cancer cell lines express IGF-I.³⁶ If IGF-I is a risk factor for breast cancer as some but not all studies suggest,²² the endocrine effects of circulating levels may be more important for breast cancer than for fibroids. The inverse association between circulating IGF-I levels and fibroid development in whites was surprising, but the reported associations between IGF-I and endometrial cancer are also generally inverse (reviewed in Lacey et al³⁷). Circulating IGF-I has been positively correlated with vitamin D levels,³⁸ which could possibly be a confounder, given its reported antiproliferative effects.

We had hypothesized that hyperinsulinemia would increase fibroid risk because of its proliferative effects on uterine smooth muscle in culture. However, there are also biologic

pathways whereby hyperinsulinemia and diabetes might plausibly decrease fibroid development. Vascular dysfunction is part of the pathogenesis of diabetes and could inhibit tumor development. Insulin resistance and diabetes can be associated with cytotoxic effects both from accompanying hyperglycemia and from other circulating cytotoxic factors,³⁹ and these factors could have direct antitumorigenic effects.

Our assessments of IGF-I, BP3, and insulin were based on measurements from a single blood sample. However, these factors track over time for individuals,^{40,41} and single measures have been predictive of disease incidence after several years of followup. The primary limitation of this study is the cross-sectional nature of data collection. IGF-I and insulin levels were measured in blood samples taken at the same clinic visit as the ultrasound screening for fibroids. A large percentage of fibroid cases were newly detected at screening (42% of black cases and 68% of white cases). Still, some fibroids were already large, and time of initial development is unknown because fibroids can remain asymptomatic for years. However, it seems unlikely that fibroids determine circulating IGF-I levels or prevent diabetes, so reverse causation is probably not an issue. Although numbers were limiting, we examined time-since-diabetes diagnosis within our black sample and found that the diabetes-related inverse association did not appear to vary by time-since-diagnosis, again suggesting that reverse causation is unlikely.

This analysis was also limited to premenopausal women with an intact uterus. This excluded a subset of women who had previously had hysterectomies for fibroids, and more blacks were excluded than whites. If IGF-I and insulin were related to more severe, early-onset disease, we could miss such an association by limiting to the premenopausal sample. However, when we examined tumor size, there was no suggestion that the exposures of interest increased the risk of large tumors, so this selection may have had little effect on results.

In summary, we found no evidence for increased risk of fibroids with high circulating IGF-I or insulin levels. In fact, both factors showed tendencies for protective associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Sample

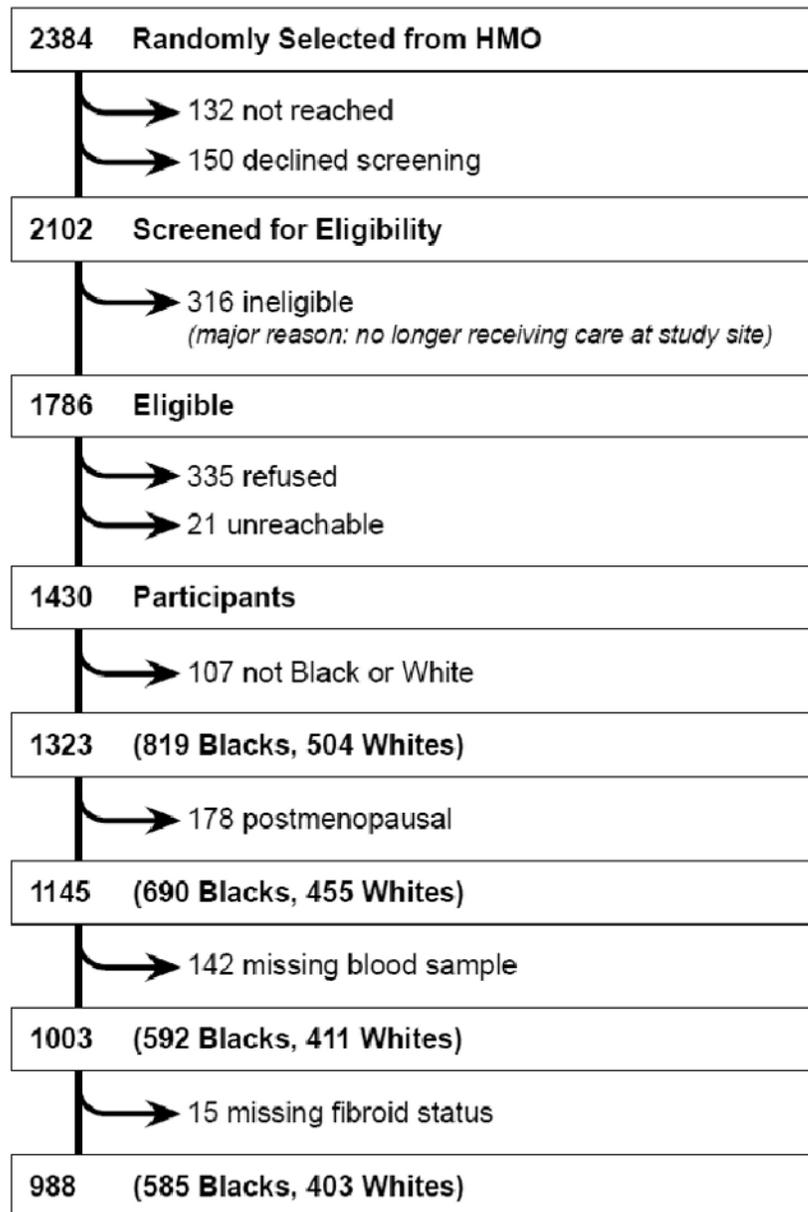


Figure 1. Flowchart showing the number of premenopausal black and white women in the NIEHS Uterine Fibroid Study from whom we collected blood and have data on fibroid status.

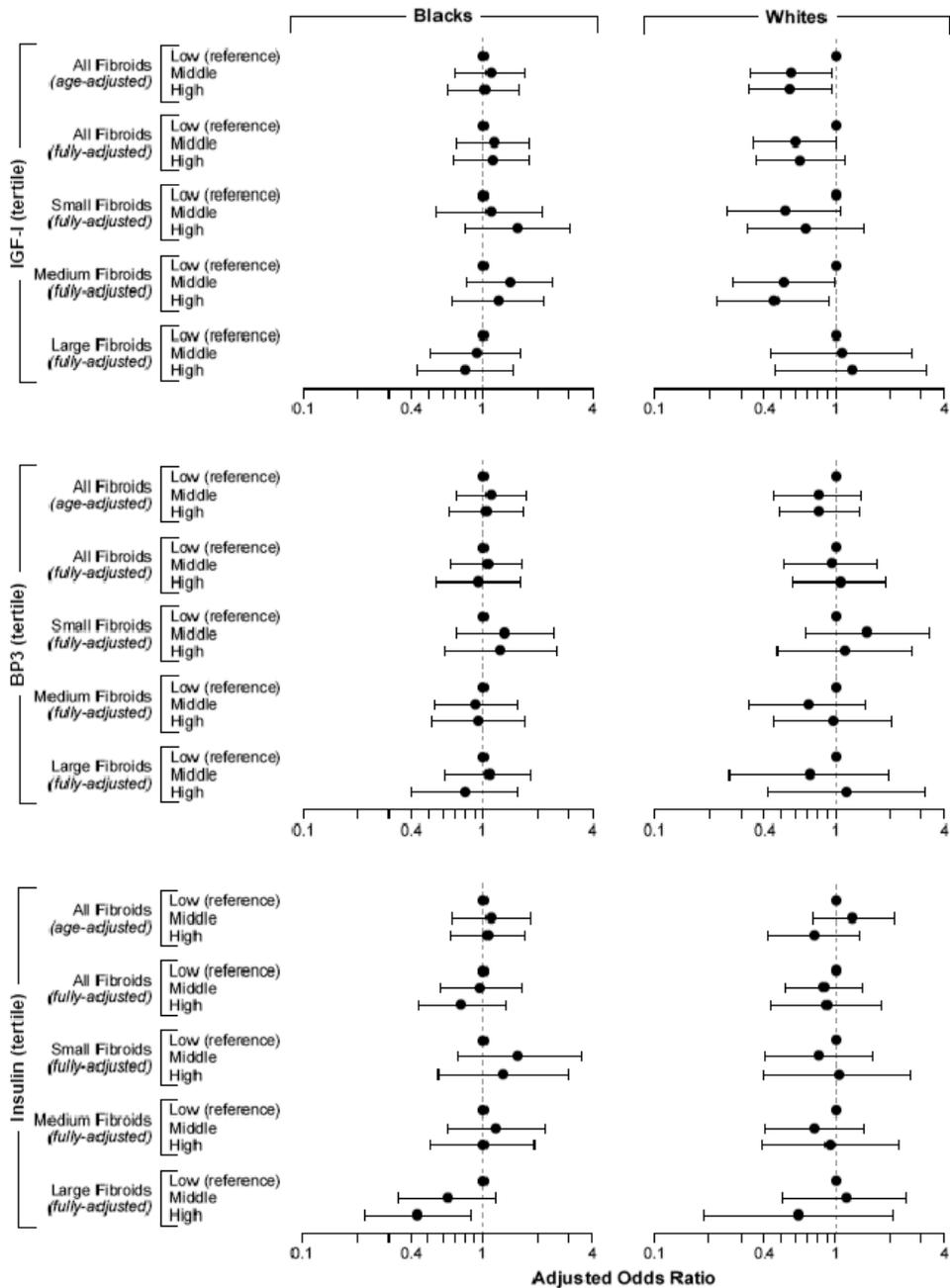


Figure 2. Relative odds of having fibroids (any sized fibroid, small: <2 cm diameter; medium: ≥2 to <4 cm diameter; and large fibroids: ≥4 cm diameter) associated with tertile of IGF-I, BP3, and insulin. The fully-adjusted ORs are adjusted for age, age of menarche, number of full-term pregnancies after age 24, BMI, and physical activity. There is also adjustment for BP3 in the fully-adjusted IGF-I models and for IGF-I in the fully-adjusted BP3 models. The horizontal lines show 95% confidence intervals.

TABLE 1

Characteristics of Premenopausal Participants in the NIEHS Uterine Fibroid Study with Blood Specimens and Fibroid Data.

Characteristic	Blacks n = 585 No. (%)	Whites n = 403 No. (%)
Fibroid status ^a		
None	158 (27)	200 (50)
Small	95 (16)	70 (17)
Medium	191 (33)	89 (22)
Large	141 (24)	44 (11)
Source of fibroid status data		
Ultrasound	564 (96)	396 (98)
Surgical report	11 (2)	2 (1)
Self-report	10 (2)	5 (1)
Age (y)		
35–39	216 (37)	136 (34)
40–44	209 (36)	136 (34)
45–49	160 (27)	131 (33)
Education		
High school or less	124 (21)	12 (3)
Some beyond high school	269 (46)	33 (8)
College degree	71 (12)	67 (17)
Postbaccalaureate	116 (20)	281 (72)
Missing	5	10
BMI at enrollment		
<25	149 (25)	234 (58)
25–29.99	180 (31)	96 (24)
30–34.99	115 (20)	37 (9)
35+	141 (24)	36 (9)
Age of menarche (y)		
<11	63 (11)	17 (4)
11	92 (16)	61 (15)
12	160 (27)	111 (28)
13	140 (24)	135 (34)
14	57 (10)	43 (11)
>14	70 (12)	34 (8)
Missing	3	2
Parous		
No	121 (21)	236 (59)
Yes	464 (79)	167 (41)
No. of full-term pregnancies delivered after age 24		
0	294 (50)	255 (63)

Characteristic	Blacks n = 585 No. (%)	Whites n = 403 No. (%)
1	181 (31)	56 (14)
2	87 (15)	81 (20)
3+	22 (4)	11 (3)
Smoking status		
Never	279 (48)	234 (58)
Past	136 (23)	137 (34)
Current, < 10/d	102 (18)	14 (3)
Current, 10-19/d	55 (9)	12 (3)
Current, 20+/d	9 (2)	6 (1)
Alcohol (drinks/wk)		
<0.5	301 (55)	60 (16)
0.5-2	122 (22)	113 (30)
>2-7	65 (12)	102 (27)
7+	60 (11)	96 (26)
Missing	37	32

^aFibroid status was categorized based on the diameter of largest fibroid (<2 cm, small; ≥2-4 cm, medium; ≥4 cm, large).

TABLE 2

Age-adjusted and Fully-adjusted Relative Odds of Fibroids for Women with Diabetes Compared with Those without Among Premenopausal Blacks and Whites in the NIEHS Uterine Fibroid Study Enrolled 1996–1999

Diagnosis	Blacks			Whites		
	No. ^a	OR ^b	OR ^c (95% CI)	No. ^a	OR ^b	OR ^c (95% CI)
None	385:125	1.00	Reference	180:179	1.00	Reference
Gestational	21:10	0.74	(0.34–1.62)	4:3	0.72	(0.16–3.29)
Diabetes	30:15	0.67	(0.35–1.29)	5:4	0.96	(0.24–3.76)

^aNumber with fibroids:number without fibroids.

^bAdjusted for age.

^cAdjusted for age, age of menarche, parity after age 24, BMI, and physical activity.