Published in final edited form as:

Lung. 2009 ; 187(1): 1–7. doi:10.1007/s00408-008-9111-9.

Racial Differences in Sarcoidosis Granuloma Density

Robert R. Burke,

Division of Pulmonary, Critical Care and Sleep Medicine, Henry Ford Hospital, Detroit, MI 48202, USA

Chad H. Stone,

Department of Pathology and Laboratory Medicine, Henry Ford Hospital, Detroit, MI 48202, USA

Suzanne Havstad, and

Department of Biostatistics and Research Epidemiology, Henry Ford Hospital, One Ford Place 3E, Detroit, MI 48202, USA

Benjamin A. Rybicki

Department of Biostatistics and Research Epidemiology, Henry Ford Hospital, One Ford Place 3E, Detroit, MI 48202, USA

Robert R. Burke: RBURKE1@hfhs.org; Chad H. Stone: CSTONE3@hfhs.org; Suzanne Havstad: SHAVSTA1@hfhs.org; Benjamin A. Rybicki: brybick1@hfhs.org

Abstract

Study Objectives—While sarcoidosis generally inflicts a greater morbidity on African-American compared with Caucasian patients, no studies have examined whether racial differences exist in the intensity of the histologic hallmark of sarcoidosis, noncaseating granulomas.

Design and Setting—The study was conducted as a retrospective case series in a tertiary referral center.

Patients—The study included 187 patients with histopathologic confirmation of sarcoidosis by trans- and/or endobronchial biopsy between July 1991 and December 2001.

Measurements and Results—Granuloma density was the average number of granulomas per biopsy piece on the slide with the most intense granulomatous inflammation at fourfold magnification. Overall, African-American patients had a twofold greater median granuloma density than Caucasians ($p = 0.005$). In a negative binomial multivariate model, radiographic pattern had the strongest association with granuloma density, with Scadding stage II and III patients having adjusted granuloma densities of 60% ($p = 0.005$) and 105% ($p = 0.0001$) higher than stage I patients. In the specific-tissue types, radiographic stage-adjusted granuloma densities in African-American patients were 49% greater in bronchial tissue ($p = 0.03$), but only a 27% greater in alveolar tissue ($p = 0.51$).

Conclusions—A greater granuloma density in bronchiolar lung tissue of African-American sarcoidosis patients may explain racial differences in diagnostic yield by lung biopsy and disease

severity at diagnosis. This association persists even after controlling for Scadding radiographic stage, a measure of disease severity strongly associated with granuloma density.

Keywords

Granuloma; Histopathology; Bronchoscopy; Chest radiography; Sarcoidosis; Pulmonary alveoli; Bronchi; Binomial model; African-Americans

Introduction

Annual age-adjusted incidence of new sarcoidosis cases is approximately 10–40 per 100,000 and the disease is at least three times more common in African-Americans than in Caucasians [1]. Disease pathogenesis is related to hyper-Th1 cellular activation by a presumed unknown antigen. The disease can involve every organ system, but lung disease predominates. Diagnosis of sarcoidosis is most certain when based on histologic confirmation of noncaseating granulomas in affected tissue.

Sarcoidosis severity at diagnosis and the disease course are significantly different by race. African-Americans have more advanced disease at diagnosis when considering forced vital capacity, chest radiographic stage, and extra-thoracic involvement compared with Caucasians [1–4]. African-Americans are also more likely to have a chronic disease course with a lower frequency of disease remission, and more new organ development [2, 4].

Bronchoscopic lung biopsies are the most commonly utilized method for the histopathologic confirmation of noncaseating granulomatous inflammation [5], but the racial distribution and biopsy yield of patients undergoing diagnostic bronchoscopy is infrequently described. In a retrospective analysis, Torrington et al. [6] reported a significantly higher yield of endobronchial and transbronchial biopsies in African-Americans compared with Caucasians (85 vs. 38%; $p = 0.0008$), but these same authors, in a prospective study, found race was not a significant factor with regard to biopsy yield. Neither of these studies was designed to specifically test whether race is associated with granuloma density and consequently is a factor in biopsy yield. Furthermore, no studies have produced any histopathologic evidence that would suggest race is related to the extent of granuloma burden in sarcoidosis.

To determine whether lung granuloma density is greater in African-Americans compared with Caucasians, we retrospectively measured granuloma density in bronchoscopic lung biopsy specimens at diagnosis. We tested for the association of race with granuloma density after adjusting for other factors that could influence granuloma density such as chest radiograph stage, biopsy type, presence of necrosis, and biopsy number.

Methods

Study subjects were identified retrospectively among patients presenting with clinical indications for sarcoidosis who subsequently had histopathologic confirmation of pulmonary sarcoidosis from flexible bronchoscopic lung biopsies taken between July 1991 and December 2001. All pathologic specimens were negative for special stains and cultures for mycobacterium and fungal infections. The specimens also had limited or no necrosis (the

presence of necrosis is more commonly associated with infection but may be present in a limited number of sarcoidosis granulomas). Chest radiograph involvement was characterized according to the Scadding classification scale [7]. Subjects with normal (stage 0) and stage IV chest radiographs were excluded a priori due to small numbers.

Biopsies were reviewed for granuloma counts by a single pulmonary pathologist (CHS). Biopsy type was classified by three levels: (1) endobronchial biopsy (EBBX), (2) transbronchial biopsy (TBBX), and (3) both endobronchial and transbronchial biopsies. Transbronchial needle aspirates of lymph nodes were excluded. All biopsies were formalin fixed and embedded in paraffin. For each biopsy specimen a minimum of three slides were prepared from stepwise tissue section levels, with each slide affixed with at least three 4- μ m-thick adjacent tissue sections, per standard technique (Fig. 1). All slides were initially scanned at low magnification (4 $\times$ objective) to determine which sample tissue section had the greatest number of granulomas per standard pathologic procedure. The selected sample tissue section was then examined, at intermediate magnification (10 $\times$ objective) for the following parameters: total number of tissue pieces, the type of tissue obtained per piece (bronchial predominant vs. alveolar predominant), the total number of granulomas present, the distribution of granulomas (bronchial vs. alveolar), and the presence/absence of necrosis. To prevent a biased assessment of granuloma count, the pathologist was blinded to patient demographic and clinical data.

Data were analyzed with SAS statistical software (SAS Institute, Cary, NC). Univariate data analyses included Student *t* tests for normally distributed continuous variables, Wilcoxon rank sum tests for non-normally distributed continuous variables, χ^2 tests for categorical variables, and Fisher's exact tests for dichotomous variables with low cell counts. Granuloma density was defined as the mean number of granulomas per biopsy piece. Due to data overdispersion, we decided on an analytic strategy of using a negative binomial regression model, which is a generalization of the Poisson regression model for discrete data that accounts for overdispersion by including a disturbance or error term [8]. The advantage of the negative binomial distribution over the Poisson is that the latter requires the mean and variance to be equal while the former does not. A negative binomial regression model of granuloma density was fit using PROC GENMOD in SAS [9] with granuloma count as the outcome variable. Crude and adjusted associations with granuloma density were examined for race (African-American vs. Caucasian), sex, chest radiograph stage (I, II, III), and biopsy type (TBBX, EBBX, or both). Second- and third-order interactions were also tested in a saturated model.

Results

Study Population and Biopsy Characteristics

The study sample was drawn from a larger sample of sarcoidosis patients ($n = 235$) who initially underwent bronchoscopic biopsy for diagnostic purposes. Among these patients, the 139 of 169 (82%) African-American patients and the 48 of 66 (72%) Caucasian patients who had lung tissue containing granulomas consistent with sarcoidosis ($n = 187$) on initial biopsy comprised the analytic sample for the current study. The remaining 48 patients without histopathologic evidence for sarcoidosis on initial evaluation were later confirmed

to have disease either based on a second biopsy with histopathologic evidence of noncaseating granulomas or by clinical observation. Among African-American patients, 149 of 169 (88%) were eventually histopathologically confirmed (repeat bronchoscopy, transbronchial needle aspiration, surgical lung biopsy, or skin biopsy) to have sarcoidosis. A similar percentage of the Caucasian patients, 89% (59/66), eventually had histopathologic confirmation of disease.

In our analytic sample of 187 sarcoidosis patients, granuloma density had a distribution that was highly skewed to the right irrespective of race (Fig. 2). The study sample was predominantly African-American (74%) and female (66%) with a mean age at diagnosis for African-American patients of 39.5 ± 12.0 years and 42.2 ± 12.0 years for Caucasians (Table 1). While African-American patients were more likely than Caucasians to have an advanced radiograph stage at the time of diagnosis (African-American patients had more stage II and III radiographic patterns, whereas for Caucasian patients stage I was the most frequent), the racial difference in radiographic stage was not statistically significant ($p = 0.2$). Most patients were diagnosed by transbronchial biopsy (64.2%), and type of biopsy chosen by the operator was not associated with race ($p = 0.6$). A total of 1086 biopsy pieces were used for counting granulomas. The mean and median number of pieces per person was 5.8 ± 2.4 and 5, respectively, with no racial differences observed in the number of biopsy pieces ($p = 0.84$). In total, 3022 granulomas were recorded with 75% of the granulomas found in the bronchial tissue that comprised 71% of the pieces examined. In the 103 patient tissue samples that consisted of both bronchial and alveolar tissue, granuloma density was higher in the bronchial compared with alveolar tissue (2.67 ± 2.75 vs. 2.35 ± 5.00), but this difference was not statistically significant. There was a modest statistically significant correlation in granuloma density between the two tissue types ($r = 0.22$; $p = 0.02$). Granuloma density varied by race, with the median granuloma density in African-Americans twofold greater than in Caucasians (Table 1, Fig. 2).

Granuloma Density Analysis

Since granuloma density was variable between the two tissue types, we first analyzed each separately (Table 2). African-American patients had an 86% greater bronchial granuloma density compared with Caucasian patients ($p = 0.0007$). After adjustment for radiographic stage and other confounders, the bronchial granuloma density for African-American relative to Caucasian patients decreased to 48%, but was still statistically significant ($p = 0.03$). Scadding stage was also a strong independent predictor of bronchial granuloma density, with adjusted 72% ($p = 0.003$) and 112% ($p = 0.0003$) increases in radiographic stage II and stage III granuloma density compared with stage I patients.

In the analysis of granuloma density in alveolar tissue, we found two observations with granuloma density estimates that were extreme outliers and therefore we removed them from the analysis. In the remaining 118 observations, African-American patients had a 68% greater alveolar granuloma density compared with Caucasian patients that increased to 76% in the adjusted model but did not achieve statistical significance ($p = 0.09$). Radiographic stage also had a positive association with alveolar granuloma density similar to that observed in bronchial tissue, but the beta estimates for both stage II and stage III disease

were slightly lower and failed to achieve statistical significance in either crude or adjusted models.

In Table 3 we show the parameter estimates for all variables of interest in the models that were run in Table 2: race, radiographic stage, sex, age, necrosis, and biopsy type. We also added covariates for tissue source (bronchial, alveolar, or both). Both African-American race and radiographic stage remain significant in the combined analysis of the two tissue types, with a trend for greater granuloma density moving from radiographic stage I to III. Interestingly, a greater granuloma density was associated with patient samples in which granulomas were found exclusively in either bronchial or alveolar tissue compared with patient samples that had granulomas in both tissue types.

In stratified analyses of race and sex associations with granuloma density, we found that radiographic pattern was not associated with granuloma density in African-American females and Caucasian males but was strongly associated with granuloma density in the other two race/sex groups (Fig. 3). The adjusted difference of granuloma density for stage III lung tissue compared with stage I lung tissue ranged from sixfold in Caucasian females and African-American males, but was only 20 and 44% in African-American females and Caucasian males, respectively. Second-order interaction coefficients for race $\times$ stage, sex $\times$ stage, or race $\times$ sex did not reach statistical significance, i.e., $p = 0.34$, $p = 0.38$, and $p = 0.93$ respectively, but a third-order interaction coefficient for race $\times$ sex $\times$ stage was statistically significant ($p = 0.008$).

Discussion

We report the first histopathologic comparison of granuloma density in sarcoidosis by race, and have observed that African-American sarcoidosis patients have 86% greater bronchial granuloma density compared with Caucasian patients. Furthermore, we found that bronchiolar granuloma density was increased in African-American patients even after controlling for radiographic stage of disease. Radiographic stage of disease had a strong positive association with granuloma density in two of the four demographic subgroups in our study, Caucasian females and African-American males. While radiographic stage was not associated with granuloma density in either Caucasian male or African-American female patients, in the latter an approximately twofold higher granuloma density was observed irrespective of radiographic stage. In fact, when combining granuloma density data across radiographic stage, African-American females had about a 30% greater granuloma density compared with either African-American males or Caucasian females.

Previous studies of bronchoscopic lung biopsy yields have given discrepant results regarding the influence of race on yield. Torrington et al. [6], in a retrospective series, evaluated the effect of race and radiographic stage on bronchoscopic lung biopsies at diagnosis. The endobronchial biopsy yield was 85% in African-Americans compared with 38% in Caucasians ($p < 0.001$). Transbronchial biopsy yields were also significantly higher in African Americans versus Caucasians with yields of 74 vs. 50%, respectively ($p < 0.01$). The results presented by Torrington et al. did not control for the effect of radiographic pattern, a likely strong confounder that might influence both the decision of a clinician to

biopsy and his ability to sample granuloma-laden tissue. Shorr et al. [10], in a follow-up prospective study, reported that African-American race was not significantly associated with improved endobronchial biopsy yield; however, their data showed that African-American patients had a 2.1-fold greater odds of positive biopsy. Assuming that biopsy yield is influenced by both granuloma density and volume of lung with disease involvement, then our results provide a partial explanation for the greater endobronchial biopsy yield observed in African-Americans.

African-Americans have more extensive disease burden and a more recalcitrant disease course as thoroughly reviewed by Westney and Judson [11]. African-Americans were also found to have more severe disease as assessed by the newly developed Sarcoidosis Severity scoring tool [12]. One possible explanation for the greater granuloma density we observed in African-Americans is that African-American patients undergo a more severe uncontrolled immune reaction to the disease-inciting agent. Alternatively, African-American patients may have biopsies performed later in their disease course. Judson et al. [4] evaluated the impact of race, income, and insurance status as predictors of time from symptom onset or physician presentation to diagnosis. A higher Scadding stage was associated with a prolonged diagnosis from symptoms and physician presentation (< 6 months vs. >6 months), but race was not a significant factor.

African-American females had a much higher granuloma density in radiographic stage I disease compared with the other race/sex groups, suggesting an earlier heightened immune response in the lungs of African-American female patients that is sustained with radiographic progression of disease. Few studies have specifically investigated sarcoidosis phenotypes of African-American females, but recently Westney et al. [13] showed that African-American females have more comorbid disease than their male counterparts and Evans et al. [14] showed that in sarcoidosis patients presenting with uveitis, African-American females had significantly more adnexal granulomas diagnosed clinically in patients with eyelid and conjunctival nodules. As in African-American females, we also found no association between radiographic stage and granuloma density in Caucasian males. However, the mean granuloma density in Caucasian males was much lower, and the race/sex/stage stratum of stage III Caucasian males had the lowest number of observations ($n = 3$), which limits the inference that can be made about radiographic stage and granuloma density in this race/sex group.

In bronchial tissue, we describe more granuloma density (24%) in patients with stage III lung disease compared with stage II and in patients with stage II compared with stage I. It is currently unknown if the radiographic stage II lung is qualitatively different in terms of granulomatous inflammation compared with a stage III lung, but spontaneous remission rates are significantly less in stage III compared with those in stage II [15]. The increased granuloma density we observed in stages II and III could be partially explained by improved sampling, where the operator is directed at “involved” lung tissue in patients with stage II or III and random lung tissue in patients with stage I. The cross-sectional nature of our data does not allow us to make any inferences with regard to radiographic progression and increased granulomatous inflammation, but one could postulate that loss of adenopathy in stage III disease may represent a loss of the control of the inflammatory response.

Total lung granuloma burden is a combination of volume of lung involvement and granuloma density within that volume. Our study focused on “granuloma density” and was not able to assess the volume of lung involvement. Israel et al. [16] used the modified International Labor Organization/University of Cincinnati (ILO/UC) classification score for pneumoconiosis to show that African-Americans did not have more extensive parenchymal lung involvement in sarcoidosis. Since our investigation is limited to the area of the lung sampled for biopsy, we cannot conclude that African-Americans have more total (i.e., volume $\times$ density) lung granuloma inflammation even though African-Americans had a 30% higher granuloma density in all lung tissues after adjusting for chest radiograph stage.

Few have published on methods for assessing granuloma density and no validated method to measure density of granulomas exists, with past studies using granulomas per 10 $\times$ field or subjective categories such as few, moderate, and extensive [17, 18]. The method we used to measure granuloma density involved a single pathologist blind to patient characteristics determining the tissue sample set with the greatest granuloma density and then systematically counting the granulomas present in that tissue sample set. This selection of the most “afflicted” sample set is standard methodology within pathology practice, with any error inherent in the process likely random and therefore biasing estimates of effect toward the null. In the total sarcoidosis patient cohort that underwent bronchoscopy, the diagnostic yield was 82% for African-American and 72% for Caucasian patients. Assuming that further sampling of lung tissue of histologic-negative subjects in our cohort would eventually yield evidence of granulomas, but at a lower density than that observed in the initially positive patients, introducing these subjects into the analysis would likely further increase the race difference we observed in granuloma density. By excluding radiographic stage 0 and IV patients, we limit our study inference to patients with radiographic stages I–III, but newly diagnosed sarcoidosis patients at the tail ends of the radiographic spectrum typically make up only 10–15% of all patients diagnosed [1, 2].

In summary, in a retrospective analysis of a racially heterogeneous population of sarcoidosis patients at time of diagnosis, we found African-American race to be significantly associated with greater granuloma density, even after controlling for radiographic stage. These findings may provide partial histopathologic evidence for the racial differences in severity of disease at diagnosis related to lung involvement, such as reduced forced vital capacity, worse symptomatology requiring treatment, and differences in endobronchial biopsy yields.

References

1. Rybicki BA, Major M, Popovich JJ, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol.* 1997; 145:234–241. [PubMed: 9012596]
2. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, McLennan G, Moller DR, Newman LS, Rabin DL, Rose C, Rybicki B, Weinberger SE, Terrin ML, Knatterud GL, Cherniak R. Case Control Etiologic Study of Sarcoidosis (ACCESS) research group. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med.* 2001; 164:1885–1889. [PubMed: 11734441]
3. Edmondstone WM, Wilson AG. Sarcoidosis in Caucasians, Blacks and Asians in London. *Br J Dis Chest.* 1985; 79:27–36.10.1016/0007-0971(85)90004-X [PubMed: 3986110]

4. Judson MA, Thompson BW, Rabin DL, Steimel J, Knattreud GL, Lackland DT, Rose C, Rand CS, Baughman RP, Teirstein AS. ACCESS Research Group. The diagnostic pathway to sarcoidosis. *Chest*. 2003; 123:406–412.10.1378/chest.123.2.406 [PubMed: 12576358]
5. Teirstein AS, Judson MA, Baughman RP, Rossman MD, Yeager H Jr, Moller DR. The spectrum of biopsy sites for the diagnosis of sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2005; 22:139–146. [PubMed: 16053030]
6. Torrington KG, Shorr AF, Parker JW. Endobronchial disease and racial differences in pulmonary sarcoidosis. *Chest*. 1997; 111:619–622.10.1378/chest.111.3.619 [PubMed: 9118697]
7. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. *BMJ*. 1961; 5261:1165–1172. [PubMed: 14497750]
8. Agresti, A. Categorical data analysis. New York: John Wiley & Sons, Inc; 1990.
9. SAS Institute Inc. SAS/STAT Users' Guide, ver. 9. Vol. 3. SAS Institute Inc; Cary, NC: 2002.
10. Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial biopsy for sarcoidosis: a prospective study. *Chest*. 2001; 120:109–114.10.1378/chest.120.1.109 [PubMed: 11451824]
11. Westney GE, Judson MA. Racial and ethnic disparities in sarcoidosis: from genetics to socioeconomics. *Clin Chest Med*. 2006; 27:453–462.10.1016/j.ccm.2006.04.002 [PubMed: 16880055]
12. Wasfi YS, Rose CS, Murphy JR, Silveira LJ, Grutters JC, Inoue Y, Judson MA, Maier LA. A new tool to assess sarcoidosis severity. *Chest*. 2006; 129:1234–1245.10.1378/chest.129.5.1234 [PubMed: 16685014]
13. Westney GE, Habib S, Quarshie A. Comorbid illnesses and chest radiographic severity in African-American sarcoidosis patients. *Lung*. 2007; 185:131–137.10.1007/s00408-007-9008-z [PubMed: 17384899]
14. Evans M, Sharma O, LaBree L, Smith RE, Rao NA. Differences in clinical findings between Caucasians and African Americans with biopsy-proven sarcoidosis. *Ophthalmology*. 2007; 114:325–333.10.1016/j.ophtha.2006.05.074 [PubMed: 17123620]
15. ATS/ERS/WASOG. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med*. 1999; 160:736–755. [PubMed: 10430755]
16. Israel HL, Karlin P, Menduke H, DeLisser OG. Factors affecting outcome of sarcoidosis. Influence of race, extrathoracic involvement, and initial radiologic lung lesions. *Ann N Y Acad Sci*. 1986; 465:609–618.10.1111/j.1749-6632.1986.tb18537.x [PubMed: 3460398]
17. Hsu RM, Connors AF Jr, Tomashefski JF Jr. Histologic, microbiologic, and clinical correlates of the diagnosis of sarcoidosis by transbronchial biopsy. *Arch Pathol Lab Med*. 1996; 120:364–368. [PubMed: 8619748]
18. Gupta D, Jorapur V, Bambery P, Joshi K, Jindal SK. Pulmonary sarcoidosis: spirometric correlation with transbronchial biopsy. *Sarcoidosis Vasc Diffuse Lung Dis*. 1997; 14:77–80. [PubMed: 9186993]

Fig. 1.

Method of granuloma counting. **(a)** Paraffin block with embedded lung biopsy tissue is **(b)** partitioned into three sections from which **(c)** three 4-μm-thick sections are cut and **(d)** mounted on three slides. At 4× magnification, the pathologist then identifies the slide with the greatest granuloma density (black box), **(e)** which is then examined under 10× magnification and the number of tissue pieces and granulomas counted

Fig. 2.
Distribution of granuloma density in lung tissue of Caucasian ($n = 48$) and African-American ($n = 139$) sarcoidosis patients

Fig. 3. Negative binomial regression model predicted least-squares mean estimates of granuloma density by race, sex, and chest radiograph stage

Table 1Baseline characteristics of study population by race ($n = 187$)

	African-American ($n = 139$)	Caucasian ($n = 48$)	<i>p</i> value
Mean age (SD)	39.5 (9.1)	42.2 (12.0)	0.17 [*]
Gender, <i>n</i> (%)			0.002 ^{**}
Female	101 (72.7%)	23 (47.9%)	
Male	38 (27.3%)	25 (52.1%)	
Chest X-ray stage			0.21 ^{**}
I	39 (28.1%)	20 (41.7%)	
II	64 (46.0%)	17 (35.4%)	
III	36 (25.9%)	11 (22.9%)	
Biopsy type			0.57 ^{**}
Endobronchial only	9 (6.5%)	2 (4.2%)	
Transbronchial only	91 (65.5%)	29 (60.4%)	
Endo- and transbronchial	39 (28.1%)	17 (35.4%)	
Median number of pieces (IQR)	5 (3)	6 (3)	0.84 ^{***}
Median granuloma density (IQR)	2.17 (3.97)	1.00 (2.04)	0.005 ^{***}
Necrosis, <i>n</i> (%)			0.37 ^{****}
Absent	125 (89.9%)	46 (95.8%)	
Present	14 (10.1%)	2 (4.2%)	

* Student's *t* test;** χ^2 test;

*** Wilcoxon rank sum test;

**** Fisher's exact test

Association of race and radiographic stage with granuloma density in specific tissue histologies based on a negative binomial model

Table 2

Parameter	Tissue source	No. patients	Crude estimates		Adjusted estimates ^a	
			$\beta \pm SE$	p value	$\beta \pm SE$	p value
African-American race	Bronchial	170	0.62 $\pm$ 0.18	0.0007	0.40 $\pm$ 0.19	0.03
	Alveolar	118	0.52 $\pm$ 0.32	0.11	0.57 $\pm$ 0.33	0.09
Radiographic stage ^b						
II	Bronchial	170	0.60 $\pm$ 0.19	0.001	0.54 $\pm$ 0.18	0.003
	Alveolar	118	0.31 $\pm$ 0.33	0.34	0.46 $\pm$ 0.34	0.18
III	Bronchial	170	0.84 $\pm$ 0.21	< 0.0001	0.75 $\pm$ 0.21	0.0003
	Alveolar	118	0.58 $\pm$ 0.36	0.11	0.68 $\pm$ 0.36	0.06

^aMultivariate model includes radiographic stage, gender, age, necrosis, and biopsy type. Biopsy number controlled as offset variable

^bReferent group is stage I

Table 3

Full model of granuloma density in sarcoidosis patients in combined alveolar and bronchiolar tissue histologies ($n = 185$)

Parameters	$\beta \pm \text{SE}$	p value
African-American race	0.40 ± 0.17	0.02
Female sex	0.18 ± 0.16	0.27
Age	-0.006 ± 0.007	0.39
Radiographic stage ^a		
II	0.47 ± 0.17	0.005
III	0.72 ± 0.19	0.0001
Necrosis	-0.62 ± 0.25	0.01
Tissue source ^b		
Bronchial only	0.42 ± 0.16	0.007
Alveolar only	0.57 ± 0.25	0.02
Biopsy type ^c		
Endobronchial only	0.38 ± 0.32	0.22
Transbronchial only	0.03 ± 0.32	0.93

^aReferent group is stage I

^bReferent group is bronchial and alveolar tissue

^cReferent group is endobronchial and transbronchial biopsy