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Ethnic and racial differences in the presence of idiopathic pulmonary fibrosis at death

Jeffrey J. Swigris*, Amy L. Olson, Tristan J. Huie, Evans R. Fernandez-Perez, Joshua Solomon, David Sprunger, Kevin K. Brown

Autoimmune Lung Center and Interstitial Lung Disease Program, National Jewish Health, Denver, CO, USA

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Summary

Background: In studies of idiopathic pulmonary fibrosis (IPF), whites makeup the vast majority of subjects. Whether ethnic/racial differences in idiopathic pulmonary fibrosis occur in the general population is unknown.

Methods: To compare the presence of IPF between ethnic/racial groups of U.S. decedents from 1989 to 2007 by using the National Center for Health Statistics database.

Results: There were 251,058 U.S. decedents with IPF; 87.2% were non-Hispanic whites (White), 5.1% were non-Hispanic African American (Black), 5.4% were Hispanic, and 2.2% were from other ethnic/racial groups (Other). Whites coded with IPF died older than those in the other groups (77.9 years vs. 72.1 years for Blacks, 75.3 years for Hispanics, and 75.6 years for Others; $p < 0.0001$ for all pairwise comparisons). When controlling for age and for sex, compared with Whites, both Hispanics and Others were more likely to be coded with IPF (OR = 1.47, 95% CI 1.44–1.49, $p < 0.0001$ and OR = 1.29, 95% CI 1.26–1.36, $p < 0.0001$ respectively), while Blacks were significantly less likely to be coded with IPF (OR = 0.48, 95% CI 0.47–0.49, $p < 0.0001$). Among decedents with IPF, Hispanics were more likely, and Blacks were less likely, than Whites to die from IPF (OR = 1.24, 95% CI 1.20–1.29, $p < 0.0001$ and OR = 0.91, 95% CI 0.87–0.94, $p < 0.0001$).

Conclusion: From 1989 to 2007, Black decedents were less—and Hispanics were more—likely than Whites to die of/with IPF. Research is needed to determine if genetic differences between ethnic/racial groups explain these findings.

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* Corresponding author. Autoimmune Lung Center and, Interstitial Lung Disease Program, National Jewish Health, Southside Building, Office #G011, 1400 Jackson Street, Denver, CO 80206, USA. Tel.: +1 303 398 1621; fax: +1 303 398 1040.

E-mail address: swigrisj@njc.org (J.J. Swigris).

Introduction

Idiopathic pulmonary fibrosis (IPF), a progressive fibrosing lung disease of unknown cause, occurs throughout the world and is believed to equally affect every ethnic/racial group.¹ Epidemiological studies have identified certain risk factors for the development of IPF, including cigarette smoking and exposure to various dusts.² Because IPF is extremely rare in people less than 40 years old,¹ and disease rates increase with age,³ the aging process is also believed to be key in the pathogenesis of IPF.⁴

Historically recognized as a rare disease, formal clinical trials investigating potential therapies for IPF began in earnest only within the last 15 years. For trials that have recruited subjects from the United States (US), the racial/ethnic makeup of the study samples has consisted overwhelmingly of non-Hispanic whites (Whites). Whether this difference in the ethnic/racial makeup of US trial populations is due to differences in the background risk for the development of IPF, unequal access to medical care and resultant lower likelihood for members of ethnic/racial minority groups to be diagnosed with IPF,⁵ or differences in willingness to participate in treatment trials^{6,7} is unknown.

In a small percentage of cases, pulmonary fibrosis (PF) occurs in two or more first-degree relatives, or clusters in families over several generations.⁸ This is considered familial interstitial pneumonia (FIP). In some cases of familial clustering, specific genetic abnormalities and polymorphisms have been identified and offered as a potential mechanistic explanation.^{9–13} Certain of these genetic abnormalities have also been found in patients with sporadic IPF.^{11,14} Although not yet proved, it is likely that the incidence of these genetic abnormalities and polymorphisms differs between ethnic/racial groups. In an attempt to better understand the epidemiology of IPF, we investigated the hypotheses that all ethnic/racial groups in the US are equally likely to have IPF present at the time of death—and among those who do, equally likely to die of IPF itself.

Methods

We used analytic methodology described in detail elsewhere.^{3,15} Please see the Online Supplement for a full description of methods. Briefly, we used multiple cause of death (MCOD) files, compiled and manipulated annually by the National Center for Health Statistics (NCHS), that were derived from all US death certificates from 1989 to 2007. After a death certificate is filled out, the NCHS acquires it and applies computer algorithms to it to yield

a standardized “record axis” for the certificate. The record axis includes up to 20 associated causes of death, including the ultimate underlying cause of death (UCD). We first identified decedents with “pulmonary fibrosis” in the record axis and then excluded those younger than 50 years old or with accompanying codes for conditions with known associations with PF, including any connective tissue disease, radiation fibrosis, sarcoidosis, pneumoconiosis, or hypersensitivity pneumonitis. This allowed us to formulate a strict definition of IPF. For full details on how we isolated decedents with IPF, please see the Online Supplement. For each death certificate, ethnicity/race information was reported by the funeral director who acquired the information from an informant—often the surviving next-of-kin.¹⁶ When an informant was not available, ethnicity/race was assigned by the funeral director on the basis of observation. However, which of these methods was used for each decedent is not recorded in the database. Individuals of Hispanic ethnicity—whether black (e.g., Dominicans) or white—were categorized as Hispanic.

We used Chi-square tests to compare proportions between groups and logistic regression to determine the risk for IPF between different ethnic/racial groups while controlling for potentially confounding effects of age and sex. To investigate whether the changing definition of IPF over time might have influenced results, we conducted an analysis after dividing the data into two time periods: 1989–1999 and (from the time the first American Thoracic Society Consensus Statement on IPF(1) was published) 2000–2007. All data were analyzed using SAS[®] version 9.2 (SAS Institute; Cary, NC). Institutional Review Board approval for this study was not required, because all data contained in the database files have been de-identified and are of public record.

Results

We analyzed 38,883,187 US death records from 1989 to 2007 and identified 251,058 decedents with IPF whose ethnicity/race was known. In a total of 525,782 decedents ethnicity/race was missing on the death certificate; 2302 had IPF. Among decedents with IPF, 87.2% were White, 5.1% were non-Hispanic African American (Black), 5.4% were Hispanic, and 2.2% were from other ethnic/racial groups (Other). Fifty-three percent of IPF decedents were male, and 47% were female. Their mean age was 77.4 ± 9.9 years. Compared with White decedents, Blacks were significantly less likely, while Hispanics and Others were significantly more likely, to have IPF coded on their death certificates (Table 1).

Table 1 1989–2007 U.S. decedents with IPF according to ethnicity/race and unadjusted ethno/racial-specific risk for IPF compared with non-Hispanic whites.

	IPF present	IPF absent	% with IPF	OR (95% CI)
White	219,020 (87.2)	31,989,804 (84.4)	0.68	Reference
Black	12,861 (5.1)	3,949,958 (10.4)	0.32	0.47 (0.46–0.48)
Hispanics	13,599 (5.4)	1,366,383 (3.6)	0.99	1.45 (1.43–1.48)
Other	5578 (2.2)	632,291 (1.7)	0.87	1.29 (1.25–1.32)

Values are counts (percentages of column total); OR = odds ratio, CI = confidence interval; White = non-Hispanic white; Black = non-Hispanic African American; Other = non-Hispanic of other racial category.

White decedents with IPF were significantly older than Blacks (77.9 years vs. 72.1 years), Hispanics (75.3 years), and Others (75.6 years, $p < 0.0001$ for each comparison). White IPF decedents were more likely to be male than female, but Hispanic IPF decedents were more likely to be female than male. There was no difference in the proportion of male and female IPF decedents among Blacks or Others (Table 2). While controlling for age and gender, the effect of race was a significant predictor of dying of/with IPF in the sample as a whole. Within subgroups defined by age, while controlling for gender, race remained a significant, independent predictor of dying of/with IPF (Table 3). Compared with Whites, while controlling for gender and age, the risks for IPF among the other three ethnic/racial groups were the same for both time periods (1989–1999 vs. 2000–2007 for Blacks: OR = 0.51 vs. 0.45; for Hispanics: OR = 1.48 vs. 1.40; for Others: OR = 1.32 vs. 1.22).

Table 4 displays the underlying cause of death for IPF decedents. Compared with Whites, Blacks coded with IPF were significantly less likely to die of (as opposed to with) IPF (OR = 0.91, 95% CI 0.88–0.94, $p < 0.0001$), while Hispanics were significantly more likely than Whites to die of IPF (OR = 1.24, 95% CI 1.20–1.29, $p < 0.0001$). Blacks coded with IPF were significantly more likely than Whites coded with IPF to die of pulmonary hypertension (OR = 2.45, 95% CI 1.90–3.17, $p < 0.0001$), while Hispanics and Others were no more likely than Whites to die of pulmonary hypertension ($p = 0.1$ and 0.9 respectively). Hispanics and Others coded with IPF were significantly less likely, and Blacks were significantly more likely, than Whites coded with IPF to die of lung cancer (for Hispanics: OR = 0.59, 95% CI 0.52–0.68, $p < 0.0001$; for Others: OR = 0.76, 95% CI 0.64–0.91, $p < 0.0001$; for Blacks: OR = 1.11, 95% CI 1.01–1.23, $p < 0.0001$ respectively).

Discussion

Between 1989 and 2007, we examined death records of over 38 million decedents and identified 251,058 coded with IPF. Compared with White decedents, Blacks were

significantly less likely to be coded with IPF. Although the overwhelming majority of decedents with IPF were White, decedents in the Hispanic or Other (e.g., Native American, Asian, or Pacific Islander) categories were significantly more likely than White decedents (45% and 29% greater odds respectively) to be coded with IPF. We believe this is the first such systematic, nationwide assessment of the ethnic/racial distribution of IPF and the first time the risk for having IPF at the time of death has been compared between ethnic/racial groups.

For decedents coded with IPF, we uncovered other differences between ethnic/racial groups: although they were less likely than Whites to be coded with IPF, Blacks coded with IPF died younger (six years on average). Furthermore, although the proportion of decedents dying from pulmonary hypertension (PH) was small in each group, and the absolute differences between racial groups were not that great (thus calling into question the clinical relevance of these findings), Blacks coded with IPF had odds of dying from PH that were over two-fold greater than Whites coded with IPF. Hispanic decedents were more likely than Whites to be coded with IPF. Hispanics coded with IPF were also more likely than Whites coded with IPF to be female, to die younger (on average, 2.5 years younger than Whites coded with IPF), and to die of IPF itself. However, Hispanics coded with IPF were less likely than Whites coded with IPF to die of lung cancer.

The prevailing theory holds that IPF develops in individuals because of some combination of age, genetic predisposition, and external (perhaps environmental) factors.⁴ Because of the work done on people with FIP, some of the genetic factors linked to IPF (sporadic disease) are known; these include mutations in genes that code for certain surfactant proteins, coding regions of telomerase genes (resulting in shortened telomeres),^{9–13} and most recently, a polymorphism in the promoter region of the gene encoding mucin 5B.¹⁴ What is not known is whether these (or other, yet-to-be-discovered) mutations or polymorphisms associated with lung fibrosis occur with equal frequency in all peoples, regardless of ethnicity/race—or even whether these genetic abnormalities have different gender predilections within a given ethnic/racial group.

Table 2 1989–2007 U.S. decedents with IPF according to ethnicity/race and gender.

	IPF present	IPF absent	Odds ratio for female sex (95% CI) p value
White			
Females	102,214 (46.7)	16,933,453 (52.5)	0.79 (0.78–0.80)
Males	116,806 (53.3)	15,252,405 (47.5)	<0.0001
Black			
Females	6526 (50.7)	2,030,264 (51.4)	0.97 (0.94–1.0)
Males	6335 (49.3)	1,919,694 (48.6)	0.14
Hispanics			
Females	6822 (50.2)	659,346 (48.2)	1.08 (1.04–1.12)
Males	6777 (49.8)	707,037 (51.8)	<0.0001
Other			
Females	2599 (46.6)	299,541 (47.4)	0.97 (0.92–1.02)
Males	2979 (53.4)	332,750 (52.6)	0.25

Values = counts (percentage); IPF = idiopathic pulmonary fibrosis; White = non-Hispanic white; Black = non-Hispanic African American; Other = non-Hispanic of other racial category; CI = confidence interval.

Table 3 Logistic regression models for IPF with race, age, and sex as covariates. Individual models are for the sample as a whole and for each subgroup stratified on deciles of age.

Covariates	Model for sample as whole <i>n</i> = 38,357, 405 with IPF = 251,058	Model for decedents 50 y ≤ age < 60 y <i>n</i> = 3,607, 782 with IPF = 13,917	Model for decedents 60 y ≤ age < 70 y <i>n</i> = 6,281, 453 with IPF = 38,181	Model for decedents 70y ≤ age < 80 y <i>n</i> = 10,686,749 with IPF = 85,616	Model for decedents ≥ 80 y <i>n</i> = 17,781,421 with IPF = 113,344
Ethnicity/Race					
White	Reference	Reference	Reference	Reference	Reference
Black	0.48 (0.47–0.49)	0.80 (0.77–0.84)	0.58 (0.56–0.61)	0.45 (0.43–0.46)	0.41 (0.40–0.43)
Hispanic	1.47 (1.44–1.49)	1.53 (1.44–1.63)	1.52 (1.46–1.58)	1.45 (1.41–1.50)	1.54 (1.50–1.58)
Other	1.29 (1.26–1.33)	1.18 (1.14–1.22)	1.31 (1.23–1.39)	1.33 (1.27–1.39)	1.31 (1.26–1.37)
Age	1.003 (1.003–1.004)	—	—	—	—
Female sex	0.80 (0.79–0.81)	1.18 (1.14–1.22)	0.91 (0.89–0.93)	0.82 (0.81–0.84)	0.79 (0.78–0.80)

Values are counts; OR = odds ratio, CI = confidence interval; IPF = idiopathic pulmonary fibrosis; White = non-Hispanic white; Black = non-Hispanic African American; Other = non-Hispanic of other racial category.

Such discoveries are eagerly awaited and will likely be made in the not-to-distant future.

Our data raise suspicion that genetics may account for some of the between ethnic/racial group differences we observed. The data suggest Blacks are less likely than Whites to develop IPF, but Blacks who do, could be characterized by a different phenotype, dying younger and with PH. An alternative explanation for the lower likelihood of IPF (a disease linked to aging) among Black decedents is that they die at a younger age (of competing comorbidities like atherosclerotic heart disease and diabetes)—before IPF occurs, or before it becomes severe enough to be clinically recognized.

Like any epidemiological study, ours has limitations. By relying on death certifiers to generate the primary data, we can not be certain—nor could we test the fidelity—of diagnoses. We believe by carefully excluding decedents with any code for connective tissue disease, sarcoidosis, pneumoconiosis, radiation fibrosis, or hypersensitivity pneumonitis, or decedents in age groups within which IPF rarely occurs, we isolated a group who are most likely to have a diagnosis of IPF. The database we used does not include potentially important variables related to health care access and utilization. For example, health insurance status and whether a decedent had a regular primary care provider—factors that increase the likelihood of being diagnosed with, and treated for, a chronic disease—are data not available in this set. It could be that Blacks are simply not diagnosed with IPF, because they are less likely than Whites to have health insurance and thus access to appropriate primary (and secondary) health care. However, this does not explain why, in this study, Hispanics, another under-served minority group, were more likely than Whites to be coded with IPF. Indeed, from 1994 to 2004, among working-aged US adults, 49% of Mexican Americans and 33% of other Hispanic Americans (and 25% of Blacks), but only 16% of Whites, were uninsured.¹⁷

Likewise, history of cigarette smoking—a known risk factor for IPF—is a variable not included in this dataset. There are fewer Black than White cigarette smokers in the US¹⁸; however, Blacks are more likely than Whites to develop lung cancer.¹⁹ It would be interesting to know whether the risk for IPF conferred by cigarette smoking differs depending on ethnicity/race. Unfortunately, such a study could not be accomplished by using this dataset.

The designations of ethnicity/race here—as is the case for all US death certificates—were made by someone other than the decedent. Although self-reported ethnicity/racial categorization—the method used for the US census—may be more valid than designation by another person, there appears to be strong agreement between death certificate- and census-derived ethnicity/race categorization: there is greater than 99% agreement for whites, greater than 98% agreement for blacks, and greater than 89% agreement for Hispanics.^{16,20–22} Most pointedly, we would not expect misclassification of ethnicity/race to hinge on the presence or absence of IPF. Regardless, such non-differential misclassification should bias estimates toward the null, suggesting the associations between ethnicity/race and IPF might be even stronger than we report.

Our group has asked a number of questions of the database used in this study, but the focus of the current study is unique. In a different study using this database, we

Table 4 Percentages of decedents with IPF in each ethno/racial group according to underlying cause of death (UCD).

	PNA	Stroke	IPF	Sepsis	PH	Lung CA	COPD	Cardiac	Other
White	1.93	1.23	62.31	0.45	0.21	2.99	6.07	11.40	13.09
Black	1.69	1.26	59.98	0.81	0.52	3.30	6.05	11.16	14.77
Hispanics	2.51	0.77	67.35	0.61	0.22	1.79	5.29	8.49	12.77
Other	2.92	1.40	63.05	0.86	0.30	2.29	5.06	8.61	15.33

White = non-Hispanic white; Black = non-Hispanic African American; Other = non-Hispanic of other racial category; PNA = infectious pneumonia; IPF = idiopathic pulmonary fibrosis; PH = pulmonary hypertension; CA = cancer; COPD = chronic obstructive pulmonary disease; Cardiac = myocardial infarction/ischemia, congestive heart failure, cardiomyopathy, cardiac dysrhythmia/sudden cardiac death.

calculated mortality rates for IPF over time among different ethnic/racial groups.³ Although that and the current study focus on the same disease, they address very different issues. In the current study, we deal only with decedents and not mortality rates, which by definition depend on and vary with the living population (denominator for mortality rate calculation).

Conclusions

In contrast to current beliefs, our data suggest that not all ethnic/racial groups are equally predisposed to the development of IPF and that when IPF is present, the natural history may depend to some extent on the ethnicity/race of the patient. Blacks appear significantly less likely than Whites to develop the disease, but when IPF is present, they die at a younger age. Hispanics are more likely than Whites to have IPF present at the time of death. When IPF is present, differences in the underlying cause of death between ethnic/racial groups were also seen. Whether genetic differences account for these differences requires further research.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.rmed.2012.01.002](https://doi.org/10.1016/j.rmed.2012.01.002).

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Author contributions

Conception and design: JS, AO, TH, EFP, JS, DS, KB
 Analysis and interpretation: JS, AO, TH, EFP, JS, DS, KB
 Drafting the manuscript for important intellectual content: JS, AO, TH, EFP, JS, DS, KB

Conflict of interest statement

None of the authors has any real or potential conflicts of interest with the contents of this manuscript.

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