

Epidemiology of Sarcoidosis in a Prospective Cohort Study of U.S. Women

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Abstract

Rationale: Sarcoidosis is a systemic granulomatous and inflammatory disorder that most often involves the lungs but also affects many other organs. Data on sarcoidosis from large epidemiological studies remain scarce.

Objectives: To evaluate the baseline prevalence and 22-year incidence of sarcoidosis and their associations with demographic and geographic characteristics in a large cohort of U.S. women.

Methods: The Nurses' Health Study II is a prospective cohort study of U.S. female nurses enrolled in 1989 (aged 25–44 yr, n = 116,430). Data on major illnesses were collected through biennial questionnaires (1989–2011). Cases were identified by the nurses' self-report of physician-diagnosed sarcoidosis. Associations of demographic and geographic characteristics with sarcoidosis were evaluated by logistic regression and Cox models.

Measurements and Main Results: A total of 377 sarcoidosis cases were identified. The baseline prevalence was 100/100,000 women. The average annual incidence rate was 11/100,000 during 2,275,028 person-years of follow up. Incidence rate increased with age ($P = 0.003$), from 9 to 15/100,000 in women aged less than 35 to 55 or more years, respectively. Black women had a higher prevalence (odds ratio, 5.24; 95% confidence interval, 2.87–9.55) and incidence (hazard ratio, 3.80; 95% confidence interval, 2.31–6.24) than white women. Across U.S. regions, more than twofold differences were observed in sarcoidosis prevalence and incidence, with consistently higher rates in the Northeast.

Conclusions: We provide recent national data on the epidemiology of sarcoidosis among U.S. women. Important differences in prevalence and incidence were observed across U.S. regions. Large epidemiological studies are needed to better understand the causes of the observed demographic and geographic differences in sarcoidosis.

Keywords: epidemiology; prevalence; incidence; lung diseases

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Sarcoidosis is a systemic granulomatous and inflammatory disorder that typically affects the lungs but can cause a variety of manifestations in many other organs (1–4). Skin, eye, cardiac, or nervous system involvements are common (2–4). The clinical course ranges from asymptomatic forms with spontaneous remission to

chronic disease leading to significant organ impairment and death in 5% of patients (2, 5). The disease can occur at any age but is believed to be more common in young to middle-aged adults (1, 2, 4, 6). A slight female predominance has been described (3, 6–8). A higher risk of sarcoidosis in African-American men and women has

been well documented (4, 6). Worldwide variations have also been observed in sarcoidosis occurrence, with higher incidence rates found in northern Europe and lower rates in Asian populations (1, 7, 9, 10). Although genetic, lifestyle, occupational, and environmental risk factors have been suggested (11–15), the

exact etiology of sarcoidosis remains unknown (2).

Data on the prevalence and incidence of sarcoidosis from large epidemiological studies remain scarce. In the United States, currently available data on sarcoidosis are mostly based on studies restricted to small geographic areas (6, 16) or to specific, predominantly male occupational groups (17, 18). These studies do not cover recent time periods, with most data collected before 2000. More recently, the prevalence and incidence of sarcoidosis was investigated in the Black Women's Health Study (4), providing nationwide data on sarcoidosis among black women, who are a higher-risk population.

The Nurses' Health Study II (NHSII) is a large, ongoing, prospective study of U.S. female nurses. The aim of the current study was to evaluate the baseline prevalence and 22-year incidence of sarcoidosis and their associations with demographic and geographic characteristics in NHSII.

Methods

The NHSII began in 1989 when 116,430 female registered nurses from 14 U.S. states, aged 25 to 44 years, completed a mailed questionnaire on their medical history and lifestyle characteristics. Every 2 years, follow-up questionnaires have been sent to update information on potential risk factors and to identify newly diagnosed diseases (19, 20). The active follow-up rate (number of person-years in the cohort when participants are censored after their last questionnaire response) from 1989 to 2011 was 87% of the potential person-years. The NHSII and the current sarcoidosis study were approved by the Institutional Review Board at the Brigham and Women's Hospital (Boston, MA).

At the baseline questionnaire (1989), participants were asked if they ever had any of a list of physician-diagnosed conditions. In all biennial questionnaires (1991–2011), participants were asked to report physician-diagnosed condition(s) they had since the last questionnaire cycle. Although no specific question on sarcoidosis was included, participants were asked to report "other major illness" in a final free-text field. We used this information to identify self-reported cases of physician-diagnosed sarcoidosis from 1989 onward.

Participants provided demographic data at baseline. Race was categorized in three groups (white, black, other) and ethnicity in two groups (Hispanic versus non-Hispanic). U.S. region at baseline, with updating every 2 years thereafter, was categorized into four groups (West, Midwest, South, Northeast). Although the NHSII participants initially resided in 14 states, as of the mid-1990s they resided in all 50 states and the District of Columbia (21).

Statistical analyses evaluated the prevalence of sarcoidosis at baseline (1989) and the average annual incidence during follow up (1991–2011). Associations between demographics (race, ethnicity, and U.S. region) at baseline and sarcoidosis prevalence at baseline (diagnosis before 1989) were evaluated by multinomial logistic regressions. Associations between demographics and sarcoidosis incidence during follow up were evaluated by Cox proportional hazard models. We evaluated associations with U.S. region both at baseline and at the questionnaire cycle before time of diagnosis (referred to hereafter as "region at the time of diagnosis"), handling region as a time-varying covariate in the Cox proportional hazard model. All Cox models were stratified by age in months and calendar year. Results from age-adjusted and multivariable adjusted models are presented. A two-sided *P* less than 0.05 was considered statistically significant.

Results

Among the 116,430 participants in the NHSII, 116 reported sarcoidosis at baseline (1989), for a prevalence of 100/100,000 women or 0.1%. During 2,275,028 person-years of follow up from 1989 to 2011, 261 incident cases were reported, for an average annual incidence rate of 11/100,000.

At baseline, women with sarcoidosis were slightly older (mean age [SD], 36.7 [4.1] yr) than women without sarcoidosis (34.4 [4.7] yr, *P* < 0.001). The median age at diagnosis among incident cases was 48 years (range, 28–63 yr). Age-specific incidence rates are presented in Figure 1. Incidence rate increased with age (*P* = 0.003) and ranged from 9/100,000 in women younger than 35 years to 15/100,000 in women 55 years and older. Similar results were observed when restricting analyses to white women only

(96% of the study population); the number of nonwhite women was too low to study age-specific incident rates in this group specifically.

As expected, both prevalence (Table 1) and incidence (Table 2) of sarcoidosis were significantly higher in black women than in white women. Lower incidence rates were observed among women of other races (6/100,000) and among Hispanic women (5/100,000), although formal statistical testing of the difference could not be performed due to the low number of cases in these groups.

Variation in sarcoidosis prevalence and incidence were observed across U.S. regions, with consistently higher prevalence and incidence rates for women living in the Northeast than those in other regions, especially the West. Significantly higher incidence rates were also observed for women living in the Midwest (either at baseline or at the time of diagnosis) and in the South (at baseline only) than in the West. Although race distribution varied by region (proportion of white women: 90% in the West, 95% in the South, 97% in the Midwest and Northeast), geographical variations in sarcoidosis prevalence and incidence remained similar after adjustment for race (Tables 1 and 2, mutually adjusted odds ratios and incidence rate ratios).

Discussion

In a large prospective cohort study of predominantly white women in the United States, we observed an annual incidence rate of sarcoidosis of 11/100,000 over 22 years of follow up. The incidence rate increased with age and varied across U.S. regions, with more than twofold differences observed. Moreover, the risk of developing sarcoidosis was almost four times higher in black women than in white women.

Identification of sarcoidosis cases was based on self-report of a physician diagnosis of the disease on biennial questionnaires. Although cases have not been validated by medical records, the validity of these registered nurses' reports for many other health outcomes is generally high (>90%) (19–23) and provides reassurance about the accuracy of these reports. Moreover, in the Black Women's Health Study, investigators observed a very high agreement (96%) between self-report of sarcoidosis diagnosis and physician's report (4); an even higher

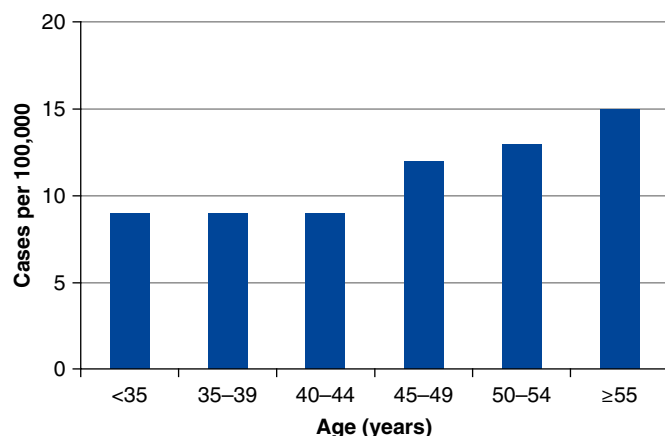


Figure 1. Age-specific incidence rate of sarcoidosis in women, Nurses’ Health Study II (n = 261 incident cases; 2,275,028 person-years). Similar results were observed in sensitivity analyses where (1) cases were restricted to participants who specifically indicated that the diagnosis of sarcoidosis occurred within 2 years before the questionnaire cycle where they first reported sarcoidosis (n = 163 incident cases; 2,274,204 person-years), (2) women with less frequent medical examination (as measured by the number of times participants reported having had physical examination during follow up) were excluded (analysis conducted with n = 223 incident cases and 1,828,972 person-years), and (3) women who returned fewer than eight biennial follow-up questionnaires (out of 11) were excluded (analysis conducted with n = 236 incident cases and 2,076,332 person-years).

agreement might be expected in NHSII, which is a study of registered nurses. Case misclassification may occur in our study but is likely to have a limited impact on the results. Nevertheless, sarcoidosis is generally underdiagnosed, especially among patients with no or minimal symptoms (24). Thus, we acknowledge that the prevalence and incidence rates in the current study may be underestimates.

Despite this limitation, our findings are very similar to previous estimates in white U.S. women: 12/100,000 reported by Rybicki and colleagues (6) and 10 to 16/100,000 reported by Henke and colleagues (16), among similar age groups. We also found, as expected, an increased risk of sarcoidosis in black women compared with white women, with very similar estimates to those previously reported (6).

Sarcoidosis has often been described as a disease occurring most commonly in younger adults, although there is some recent evidence of an increasing age at diagnosis in various populations (25, 26) as well as differences in age at onset by race (27). In a U.S. population, the peak in annual incidence in white women was observed at age 40 to 49 years and a decade earlier in black women (6). In the U.S. Black Women’s Health Study, the highest incidence rate was observed at age 40 to 49 years among black women (4). In the current study of predominantly white women, sarcoidosis incidence increased with age, and the highest incidence rates were observed in the oldest age group (50–55 yr).

Several reasons may explain this different pattern. First, the diagnosis of sarcoidosis is often delayed (24), possibly even more so among patients over the age of 50 years (28). African Americans are known to be at higher risk of sarcoidosis, and a further delayed diagnosis is possible among white patients. However, race was not associated with time to diagnosis in a study of U.S. patients with sarcoidosis (24). Alternatively, the different age patterns may be explained by race-related differences in clinical presentation (3, 5) and possibly etiology of sarcoidosis.

Studies in northern Europe (8, 9) and in Japan (7) have described a bimodal

Table 1. Prevalent sarcoidosis (before 1989) in women according to demographic and geographic characteristics at baseline, Nurses’ Health Study II

	Total	No. of Cases	Prevalence*	Age-adjusted OR		Mutually Adjusted OR	
				OR	CI	OR	CI
Race							
White	111,230	102	92	1	—	1	—
Black	2,308	12	519	5.24	2.87–9.55	5.34	2.92–9.77
Other	2,892	2	69	—	—	—	—
Ethnicity							
Non-Hispanic	114,270	116	102	—	—	—	—
Hispanic	2,160	0	—	—	—	—	—
U.S. geographic region†							
West	17,126	13	75	1	—	1	—
Midwest	38,478	30	78	1.16	0.60–2.22	1.18	0.61–2.31
South	20,404	19	93	1.38	0.68–2.81	1.32	0.64–2.73
Northeast	40,225	54	134	1.90	1.04–3.48	1.92	1.02–3.59

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

Results in bold are statistically significant.

*Cases per 100,000.

†At baseline, Nurses’ Health Study II participants resided in 14 states (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas).

Table 2. Incident sarcoidosis (1991–2011) in women according to demographic and geographic characteristics, Nurses' Health Study II

	Person-Years	No. of Cases	Incidence Rate*	Age-adjusted IRR		Mutually Adjusted IRR [†]		Mutually Adjusted IRR [‡]	
				HR	CI	HR	CI	HR	CI
Race									
White	2,182,697	241	11	1	—	1	—	1	—
Black	39,543	17	43	3.80	2.31–6.24	3.96	2.40–6.52	4.06	2.46–6.68
Other	52,787	3	6	—	—	—	—	—	—
Ethnicity									
Non-Hispanic	2,234,513	259	12	—	—	—	—	—	—
Hispanic	40,514	2	5	—	—	—	—	—	—
U.S. geographic region at baseline [§]									
West	334,591	20	6	1	—	1	—	—	—
Midwest	762,654	106	14	2.52	1.56–4.06	2.49	1.54–4.04	—	—
South	388,490	41	11	1.90	1.11–3.24	1.81	1.05–3.09	—	—
Northeast	785,558	94	12	2.14	1.31–3.47	2.13	1.32–3.47	—	—
U.S. geographic region at the time of diagnosis									
West	357,490	27	8	1	—	—	—	1	—
Midwest	720,983	101	14	2.00	1.31–3.07	—	—	1.97	1.28–3.01
South	476,070	42	9	1.25	0.77–2.03	—	—	1.18	0.72–1.91
Northeast	716,189	90	13	1.78	1.15–2.74	—	—	1.76	1.14–2.71

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; IRR = incidence rate ratio; NHSII = Nurses' Health Study II.

Results in bold are statistically significant.

*Cases per 100,000 person-years.

[†]Race and geographic region at baseline.

[‡]Race and geographic region at the time of diagnosis.

[§]At baseline, NHSII participants resided in 14 states (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas).

^{||}At the questionnaire cycle before time of diagnosis; during follow up, NHSII participants had resided in all 50 states and the District of Columbia (participants residing overseas were excluded from the analyses).

pattern in the age-specific incidence rate among women, with a first peak in young adulthood (20–35 yr) and a second peak over the age of 50 years. A recent study in Japan found that in women, only the second peak was still observed in the last decade (25). In the current study, women were already aged 25 to 44 years at baseline, and incidence in young adulthood could not be assessed; however, our results are consistent with an increase in sarcoidosis incidence after the age of 50 years for women. Interestingly, in the previous studies the bimodal distribution was observed in women only, suggesting a potential role of endogenous hormones. In the Black Women's Health Study, a later age at menopause was associated with a reduced risk of sarcoidosis incidence (29). Further studies are needed to better understand these sex and race differences in age-specific incidence pattern in sarcoidosis and the potential role of hormonal factors.

Geographical differences in the occurrence of sarcoidosis have been

described worldwide (1, 7, 9, 10, 30–32). Higher rates have been observed in northern countries than in the rest of Europe (9, 10, 32), and lower rates have been observed in Asia (7). However, few studies have investigated regional differences at a local level (10, 33). In the United States, regional distribution of sarcoidosis has not been described recently (34). In the current study, we observed up to twofold differences in prevalence and incidence of sarcoidosis across U.S. regions. Prevalence and incidence were consistently higher in the Northeast and lower in the West. Increased incidence rates were also observed in the Midwest and the South compared with the West.

Etiological agents in sarcoidosis remain unknown, and many reasons might explain the observed geographic differences. Although an increased risk of sarcoidosis in rural areas (10) and associations with rural exposures (14, 34) have been described, they are unlikely to be the sole explanation for regional disparities; in particular, it would not

explain our current observation of a higher risk in the Northeast than in the West, because the Northeast is highly urbanized. Other hypotheses, such as the role of residing in a colder environment and viral infections during the immune-forming period, have been formulated (32) but remain speculative. In the current study, one association (residence in the South) was restricted to the region of residence at baseline but was not observed for the region at the time of diagnosis, suggesting a potential role of exposures occurring earlier in life. However, this result should be interpreted with caution, because at baseline nurses resided in only 14 states, whereas all 50 states were represented during follow up. Overall, the factors explaining geographic disparities in sarcoidosis remain largely unknown and provide an important clue for future research into the etiology of this poorly understood disease.

In summary, the current study provides recent national data on the

epidemiology of sarcoidosis among U.S. women. Our finding of a continuously increasing incidence rate in 45- to 65-year-old women adds evidence to the emerging recognition that sarcoidosis often presents in older women (3, 35). This result is of clinical importance, as recent data suggest differences in older patients with sarcoidosis that may

require specific management (5). We also describe, for the first time since the 1970s, regional difference across the United States in sarcoidosis occurrence and in particular a higher risk in the Northeast. Our findings call for more large epidemiological studies on sarcoidosis, with better phenotypic characterization, to better understand the causes behind

the observed demographic and geographic differences in disease occurrence. ■

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