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Smoking, obesity and risk of sarcoidosis: A population-based nested case-control study

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ABSTRACT

Background: Smoking and obesity might alter the risk of sarcoidosis. However, the data remained inconclusive.
Methods: A cohort of Olmsted County, Minnesota residents diagnosed with sarcoidosis between January 1, 1976 and December 31, 2013 was identified based on individual medical record review. For each sarcoidosis subject, one sex and aged-matched control without sarcoidosis was randomly selected from the same underlying population. Medical records of cases and controls were reviewed for smoking status at index date and body mass index (BMI) within 1 year before to 3 months after index date.
Results: 345 incident cases of sarcoidosis and 345 controls were identified. The odds ratio of sarcoidosis comparing current smokers with never smokers adjusted for age and sex was 0.34 (95% confidence interval (CI), 0.23–0.50). The odds ratio of sarcoidosis comparing current smokers with never smokers and former smokers adjusted for age and sex was 0.38 (95% CI, 0.26–0.56).
The odds ratio of sarcoidosis comparing overweight subjects (BMI $\geq$ 25 kg/m^2 but < 30 kg/m^2) with subjects with normal/low BMI was 1.12 (95% CI, 0.72–1.75). The odds ratio of sarcoidosis comparing obese subjects (BMI $\geq$ 30 kg/m^2) with subjects with normal/low BMI was 2.54 (95% CI, 1.58–4.06). The odds ratio of sarcoidosis comparing obese subjects with non-obese subjects was 2.38 (95% CI, 1.60–3.56).
Conclusion: In this population, current smokers have a lower risk of developing sarcoidosis while subjects with obesity have a higher risk of developing sarcoidosis.

1. Introduction

Sarcoidosis is a systemic disorder characterized by the presence of chronic granulomatous inflammation. The etiology of sarcoidosis is not known. It has been hypothesized that the interaction between genetic predisposition and environmental factors plays an essential role in the pathogenesis. A recent study of New York City's fire-fighters who were exposed to the World Trade Center disaster in 2001 found a substantially higher incidence of sarcoidosis compared with the historical incidence in the same population [1]. However, no single etiologic agent has ever been demonstrated to be clearly causative in the pathogenesis of sarcoidosis [2,3].

Smoking is a strong risk factor for several pulmonary diseases such as chronic obstructive pulmonary disease and lung cancer. However, interestingly, previous studies have demonstrated that smoking was associated with a lower risk of sarcoidosis [3–5] although those studies were conducted using referral-based cohorts that might not represent the true spectrum of the disease.

Obesity is associated with increased risk of some autoimmune disorders such as psoriasis and rheumatoid arthritis [6,7]. A recent study using the Black Women's Health Study cohort has demonstrated a higher risk of sarcoidosis among African-American women who had body mass index (BMI) of more than 30 kg/m^2 [8]. Nonetheless, data on the association between obesity and risk of sarcoidosis in other populations are still limited.

This study used a previously identified population-based cohort of patients with sarcoidosis [9] to conduct a case-control study investigating the relationship between smoking, obesity and sarcoidosis.

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2. Materials and methods

Approval for this study was obtained from the Mayo Clinic and Olmsted Medical Center institutional review boards and the need for informed consent was waived (Mayo Clinic IRB 14–008651, Olmsted Medical Center IRB 012-OMC-15). Through the resources of the Rochester Epidemiology Project (REP), a cohort of Olmsted County, Minnesota (MN) residents diagnosed with sarcoidosis between January 1, 1976 and December 31, 2013 was identified. The data linkage-system allows virtually complete identification of all clinically recognized cases of sarcoidosis because of the ability to obtain complete access to medical records from all local healthcare providers, including the Mayo Clinic, the Olmsted medical Center and its affiliated hospitals, local nursing homes and few private practitioners, of all residents for over six decades. The potential use of REP database for epidemiologic studies has been previously described [10].

For the current study, potential cases of sarcoidosis were identified from diagnostic codes related to sarcoidosis and non-caseating granuloma. Diagnosis of sarcoidosis was then confirmed by individual medical record review which required physician diagnosis supported by the presence of non-caseating granuloma, radiographic evidence of intrathoracic sarcoidosis and compatible clinical presentations. Patients with evidence of other granulomatous diseases such as tuberculosis were excluded. The only exception for the histopathological confirmation was stage I pulmonary sarcoidosis that required only the presence symmetric bilateral hilar adenopathy on thoracic imaging. Cases with a diagnosis of sarcoidosis prior to residency in Olmsted County were excluded.

For each patient with sarcoidosis, one control subject without sarcoidosis at the time of the patient's sarcoidosis diagnosis was randomly selected from the same underlying population and assigned an index date that corresponded to the sarcoidosis incidence date. Matching criteria were similar age (±3 years) and same sex.

The medical records of cases and controls were reviewed for smoking status at date of diagnosis/index date. At Mayo Clinic, smoking history is routinely obtained in the medical history questionnaire completed by patients prior to appointments. Smoking status was divided into three categories of current smoker, former smoker and never smoker. Subjects in both cohorts were also reviewed for body weight and height to calculate BMI. The body weight and height closest to date of diagnosis/index date within 1 year before to 3 months after date of diagnosis/index date were used. This restriction was applied to minimize the effect of glucocorticoids, a commonly used medication in sarcoidosis, on body weight. Overweight was defined as BMI $\geq$25 kg/m^2 but <30 kg/m^2. Obesity was defined as BMI $\geq$30 kg/m^2.

2.1. Statistical analysis

Descriptive statistics (means, proportions etc.) were used to summarize the data for cases and controls. Logistic regression models adjusted for age, sex and ethnicity were used to calculate odds ratios. Conditional logistic regression models were not used due to missing data for smoking status and BMI, which would lead to elimination of the case-control pair in matched analyses. For the smoking analysis, odds ratios were calculated for the 3 group comparison of the risk of sarcoidosis between current, former and never smokers, with never smokers as the reference group, and for the 2 group comparison between current smokers and non-current smokers (i.e., former smokers plus never smokers). For the obesity analysis, 3 group comparison was conducted between obese, overweight and low/normal BMI patients and a 2 group comparison was performed between obese and non-obese subjects (i.e., subjects with BMI < 30 kg/m^2). A p-value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

For the years 1976–2013, 345 incident cases of sarcoidosis and 345 controls were identified. Baseline characteristics of cases and controls are described in Table 1. The demographics were similar between the 2 cohorts except for more non-White subjects among cases.

3.1. Smoking

Among cases, smoking status at date of diagnosis was available in 332 subjects (96%). Of these, 198 (60%) were never smokers, 71 (21%) were former smokers and 63 (19%) were current smokers. Among controls, smoking status at index date was available in 317 subjects (92%). Of these, 132 (42%) were never smokers, 70 (22%) were former smokers and 115 (36%) were current smokers. The odds ratio of sarcoidosis comparing current smokers with never smokers adjusted for age and sex was 0.34 (95% confidence interval (CI), 0.23–0.50). The odds of sarcoidosis was not significantly different between former smokers and never smokers (OR 0.68; 95% CI, 0.45–1.01). The odds ratio of sarcoidosis comparing current smokers with combined never smokers and former smokers adjusted for age and sex was 0.38 (95% CI, 0.26–0.56). Further adjustment for obesity and ethnicity did not impact the results (OR 0.36; 95% CI, 0.22–0.57).

3.2. Obesity

BMI within 1 year before to 3 months after date of diagnosis/index date was available in 313 cases (91%) and 200 controls (58%). Among these 313 cases, 129 (41%) were obese, 103 (33%) were overweight and 81 (26%) had normal/low BMI. Among these 200 controls, 47 (24%) were obese, 82 (41%) were overweight and 71 (36%) had normal/low BMI. The odds ratio of sarcoidosis comparing overweight subjects with subjects with normal/low BMI was 1.12 (95% CI, 0.72–1.75). The odds ratio of sarcoidosis comparing obese subjects with subjects with normal/low BMI was 2.54 (95% CI, 1.58–4.06). The odds ratio of sarcoidosis comparing obese subjects with non-obese subjects was 2.38 (95% CI, 1.60–3.56). Further adjustment for smoking and ethnicity did not impact the results (OR 2.48; 95% CI, 1.62–3.80).

Excluding 4 cases of sarcoidosis who had body weight measured after the initiation of glucocorticoids, in order to minimize any possible confounding effects from this therapy, had no impact on the results.

4. Discussion

The current study is the first to utilize a population-based cohort to investigate the relationship between smoking, obesity and sarcoidosis. A negative association between current smoking and risk of sarcoidosis was found. The results are consistent with previous referral-based studies from Western countries [3–5].

It is unclear as to why current smokers have a lower risk of sarcoidosis. It is possible that this association is not causal but is a result of confounding. However, it is known that smoking is associated with suppression of T-lymphocyte function and phagocytic activity of macrophages. Therefore, it is also possible that smoking might interfere with the macrophage-lymphocyte activation process that results in granuloma formation [5,11]. Indeed, a negative