CHEST

Sarcoidosis and Cancer Risk

Systematic Review and Meta-analysis of Observational Studies

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BACKGROUND: An increased cancer risk in patients with sarcoidosis has been suggested, although results are conflicting in a number of case-control and cohort studies. We conducted a systematic review of all available data and performed a meta-analysis to better define and quantify the association between sarcoidosis and cancer.

METHODS: We searched Medline and Embase for all original articles on cancer and sarcoidosis published up to January 2013. Two independent authors reviewed all titles/abstracts to identify studies according to predefined selection criteria. We derived summary estimates using a random-effects model and reported them as relative risk (RR). Publication bias was evaluated using a funnel plot and was quantified by the Egger test.

RESULTS: Sixteen original studies, involving > 25,000 patients, were included in the present review. The summary RR to develop all invasive cancers was 1.19 (95% CI, 1.07-1.32). The results for selected cancer sites indicated a significantly increased risk of skin (RR, 2.00; 95% CI, 1.69-2.36), hematopoietic (RR, 1.92; 95% CI, 1.41-2.62), upper digestive tract (RR, 1.73; 95% CI, 1.07-2.79), kidney (RR, 1.55; 95% CI, 1.21-1.99), liver (RR, 1.79; 95% CI, 1.03-3.11), and colorectal cancers (RR, 1.33; 95% CI, 1.07-1.67). There was no evidence of publication bias for all cancers ($P = .9$), nor for any specific cancer site.

CONCLUSIONS: The present meta-analysis suggests a significant, though moderate, association between sarcoidosis and malignancy. CHEST 2015; 147(3):778-791

Manuscript received June 18, 2014; revision accepted September 29, 2014; originally published Online First October 23, 2014.

ABBREVIATIONS: RR = relative risk

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FUNDING/SUPPORT: This work has been partly supported by the "Fondazione di Medicina Molecolare e Terapia Cellulare" (Università Politecnica delle Marche, Ancona), the Italian Association for Cancer Research [Grant 10068 to Istituto di Ricerche Farmacologiche Mario Negri-IRCCS], and by the NIHR Respiratory Disease Biomedical Research Unit at Royal Brompton & Harefield NHS Foundation Trust and Imperial College London.

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DOI: 10.1378/chest.14-1475

Sarcoidosis is a multisystem chronic condition of unknown etiology, characterized by persistent granulomatous inflammation, which mainly affects the intrathoracic lymph nodes and the lungs, although any organ can be involved.[1] The incidence of sarcoidosis varies according to race and to latitude, suggesting a role for both environmental and genetic susceptibility, including human leukocyte antigen class 2 and cytokine polymorphisms.[2] The interplay between genetic and environmental factors is likely to define not only the risk for the disease, but also the spectrum of clinical phenotypes and prognosis.[3]

An increased incidence of cancer in patients with sarcoidosis compared with the general population has been suggested by several case reports and series.[4] However, case-control and cohort studies, conducted to properly address this issue, have reported conflicting results.[5] An overall excess risk has been reported in a number of studies, although estimates varied considerably,[5,6] and data on selected cancer sites were often inconsistent. On the other hand, other studies have not detected any increased risk.

Therefore, we conducted a systematic review of all available data and performed a meta-analysis to better explore and quantify the association between sarcoidosis and cancer.

Materials and Methods

We followed the guidelines developed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.[7] We searched Medline and Embase for all original articles of observational studies on cancer and sarcoidosis published up to January 2013, using a combination of free text and medical subject heading (MESH)/Emtree terms related to sarcoidosis, cancer, and observational studies. The electronic search was supplemented by hand searching the bibliography of relevant articles.

The following criteria were established for inclusion: (1) cohort study of patients with sarcoidosis reporting relative risk (RRs) and the corresponding CIs or sufficient information to calculate them; (2) case-control study of cancer estimating the ORs relative to a history of sarcoidosis. Exclusion criteria were: (1) diagnosis of cancer preceding the diagnosis of sarcoidosis; (2) non-English full text.

Two independent authors (M. B. and F. B.) first reviewed all titles/abstracts to identify potentially relevant articles. They then performed the study selection, based on a full-text review, according to inclusion/exclusion criteria. Disagreements were resolved by discussion. When manuscript full texts were unretrievable, the corresponding authors were contacted directly.

The two reviewers independently extracted information on study design, country, sex, number of subjects (cases, controls, or cohort size), duration of follow-up, cancer sites considered, years between diagnosis of sarcoidosis and cancer (when available), variables adjusted for in the analysis, RR estimates, and the corresponding 95% CIs.

Forest plots were generated by using random-effects models to derive all meta-analytic estimates.[8] Heterogeneity among studies was assessed by using the χ^2 test,[8] defining a significant heterogeneity as a P value $< .10$, whereas inconsistency was quantified using the I^2 statistic.[9] A sensitivity analysis was performed to verify the influence of studies including coincident cancer cases (diagnosed within the first year from diagnosis of sarcoidosis) on the summary estimates. Publication bias was evaluated using the funnel plot[10] and was quantified by the Egger test.[11]

Results

After removing duplicates between the two data sources, the search identified 1,469 references (Fig 1). The initial screening, based on titles/abstracts, led to the exclusion of 1,375 papers because they were not relevant (eg, laboratory studies, case reports, review articles), and the remaining 94 articles were retrieved for detailed full-text evaluation. Thirty-two were case reports/series, 16 were review articles, and 30 were observational studies not fulfilling the inclusion criteria, such as studies on mortality, prevalence, or those addressing the risk of sarcoidosis in patients with cancer.

Thus, 16 original studies were included in the present review. Their main characteristics are given in Table 1.[5,6,12-24] Ten were cohort studies, and six were case-control studies. Only eight studies reported "overall" cancer risk, whereas specific cancer site rates are reported in all the selected studies (Table 1). In the majority of studies, the variables adjusted for in statistical analyses were age, sex, and calendar period.

Figure 2 provides the study-specific and summary RRs for "overall" invasive cancers, overall and according to sex and time since diagnosis. This was based on eight

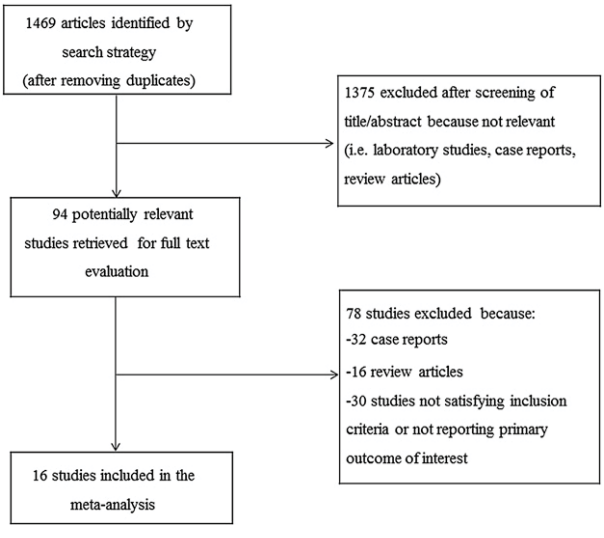

Figure 1 – *Flowchart of study selection.*