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Sarcoidosis and cancer revisited

To the Editor:

The authors of a recent article in the *European Respiratory Journal* [1] have chosen, by identical means, to verify the hypotheses of BRINCKER and WILBECK'S [2] that: a) sarcoidosis and malignancy are associated; b) sarcoidosis predisposes to malignancy; c) this pattern is encountered predominantly in patients with chronic sarcoidosis; and d) the association is limited to lung cancer and lymphomas. This study has disposed of the third part of the hypothesis, the late age of onset of sarcoidoisis in association with malignancy is, as the authors point out, an artefact of the study design, which confines itself to a limited (as opposed to a lifetime) period of observation.

If one pools the author"s male and female data, one finds an odds ratio (OR) observed/expected (O/E) of 1.25, 95% confidence interval (CI) = 0.8, 1.9; if one conforms to the practice of previous studies and excludes nonmelanoma skin cancer, the OR is 1.16, 95% CI = 0.7, 1.8. Does this resolve this vexatious dispute? Not quite. Absence of evidence is not evidence of absence.

For a two-tailed α of 0.05, this study provides a β error of 85%, *i.e.*, an 85% likelihood of incorrectly accepting the null hypothesis if there is a 25% higher incidence of malignancy in patients with sarcoidosis; a sarcoidosis sample size of 4,500, nearly 10-fold that available to the authors, would be required to reduce the β error to 20%; if one excludes nonmelanoma skin cancers the required sample size would be correspondingly larger. The epidemiological approach is even more problematic for specific malignancies: to achieve a 90% power at the same α level, 1,500 patients with sarcoidosis, followed for 10 yrs would be required to demonstrate an association between sarcoidosis and Hodgkin′s disease if the true frequency of Hodgkin′s disease in persons with sarcoidosis was 10-times that in the general population. In brief, the demonstration of an association between sarcoidosis and malignancy by epidemiological means requires unattainable sample sizes, which is why we proposed linkage criteria [3].

By excluding patients with pre-existent or coincidental cancer, the authors limited their hypothesis testing to whether sarcoidosis engenders the development of malignancy. Several authors have suggested the opposite: that malignancy and/or therapy infrequently generate a systemic granulomatous response not easily distinguished from sarcoidosis [3–5]. Can the authors provide any information on this hypothesis from their database?

The authors point out that we observed about half as many cases of sarcoidosis associated with malignancy as they did, 4.5% *versus* 8.6% [3]. The studies are not comparable however, because we did not exclude persons with pre- or co-existent cancer and the duration of observation was considerably more brief.

I was curious to know why the authors excluded persons with bilateral hilar adenopathy known to be of <6 months duration to rule out causes other than sarcoidosis. A recently published study estimated that 99.95% of patients with asymptomatic bilateral hilar adenopathy had sarcoidosis [6]. Could this exclusion have skewed the data?

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From the authors:

We thank J.M. Reich for his commentary on our study on malignancy in sarcoidosis, and for the opportunity to reply to the letter. J.M. Reich states that "absence of evidence is not evidence of absence". Of course we cannot disagree, but we are still convinced that our conclusions are valid.

Our purpose was to examine the occurrence of malignancy in a sarcoidosis population, with the inherent weaknesses of such a study, as also discussed in our article [1]. The question of an overall association of sarcoidosis and malignancy including whether malignancy predisposes to sarcoidosis was beyond the scope of the study. Three of our patients had malignant disease diagnosed before sarcoidosis; they were excluded from the calculations. Therefore, our study could not provide any information on the occurrence of systemic granulomatous response to malignancy or cancer therapy.

We also agree that the question is difficult to solve using ordinary epidemiological methods. Therefore, REICH *et al*. [2] used a "linkage analysis" in their study on overall association of malignancy and sarcoidosis. However, this methods also has several drawbacks as pointed out in a later discussion [3]. Therefore it may also be inappropriate to compare our results with those of REICH *et al*. [2].

Although our sample size was rather small for epidemiological studies, it is noteworthy that our results are in agreement with a similar Danish study from the Copenhagen area [4], and in both studies rather long observation periods were available, proving the validity of the results. So, although malignancy may theoretically be more frequent than expected in sarcoidosis, this figure is in reality extremely small for practical reasons.

Regarding Reich′s remarks on bilateral hilar adenopathy and our demand for an observation period of at least 6 months before inclusion in the series, it should be stated that a sufficient period of observation was most important in asymptomatic patients without histological evidence. If granulomas were demonstrated the patient was included at once. Since the 1960's it has been found that isolated bilateral hilar adenopathy in asymptomatic patients in the majority of cases was caused by sarcoidosis, as later confirmed by WINTERBAUER *et al*. [5] and more recently by REICH *et al*. [6]. The requirement of 6 months of observation (with frequently repeated examinations) was used to avoid inclusion of cases with other causes of bilateral hilar adenopathy or, when bilateral hilar adenopathy was slight or doubtful, to exclude the patient if bilateral hilar adenopathy in subsequent examinations could not be confirmed. Actually we have no exact number of these patients, but in fact they were rather few and we do not think that their exclusion significantly skews the data.

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