Risk of malignant neoplasms in patients with pulmonary sarcoidosis

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Abstract

Background – For over 20 years the association between sarcoidosis and malignancy, particularly lymphoma and lung cancer, has been disputed with misclassification being the major concern. The aim of the present study was to analyse the incidence of malignancies in a cohort of patients with sarcoidosis by linkage to a nationwide population based cancer register.

Methods – The cohort comprised 254 patients followed for a median of 25 years until death, emigration, or 31 December 1992, whichever came first. The expected number of cancer cases was calculated using the annual age and sex specific cancer rates from the Danish Cancer Registry.

Results – Thirty six cancers were registered, three of which were misclassified as sarcoidosis, leaving 33 cancers compared with 23 expected (standardised incidence ratio (SIR) = 1.4; 95% CI 0.99 to 2.0). Five lung cancers were observed compared with 2.5 expected, yielding an SIR of 2.0 (95% CI 0.7 to 4.7). There was no incidence of lymphoma and only one case of leukaemia. There was a significant excess number of pharyngeal cancers based on two cases (SIR = 15.4; 95% CI 1.7 to 56).

Conclusions – This study does not support the theory of an association between sarcoidosis and malignancy, and the main reason other studies have shown such an association is most likely to have been due to selection bias and misclassification.

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The association between sarcoidosis and malignancy, particularly lung cancer and lymphomas, has been disputed for the last two decades since the first paper by Brincker appeared in 1974.[1] It has even been suggested that a sarcoidosis-lymphoma syndrome exists.[2] The major issue in the dispute has been whether the cases of lung cancer and lymphomas observed in patients with sarcoidosis were due to misclassification as sarcoidosis can mimic cancer and vice versa.[3–7] Rømer reviewed the cases of lung cancer and lymphoma described by Brincker in detail and found that some of the cases were due to misclassification but, after excluding these cases, there was still an excess risk of cancer.[8] In a recent paper by Reich *et al*[9] 16 malignancies were observed in 243 patients with sarcoidosis, but five (31%)

of the malignancies – including one case of lung cancer and one case of lymphoma – were misclassified sarcoidosis lesions.

Numerous case reports concerning patients with concomitant sarcoidosis and cancer have been published,[10–14] but case reports are only useful for generating hypotheses rather than for testing them.

The objective of the present study was to investigate the risk of cancer in a cohort of patients with sarcoidosis followed for more than 20 years. The cancer risk was estimated through linkage to the Danish nationwide population-based cancer register.

Methods

The study group included 254 patients with sarcoidosis (127 of each sex) admitted to the Department of Pulmonary Medicine, Bispebjerg Hospital between 1952 and early 1970. All cases were admitted with a primary diagnosis of sarcoidosis. The diagnosis was confirmed by biopsy in 194 cases, while in 60 cases the diagnosis was based on chest radiographic findings and, to some extent, on symptoms (arthralgia, cough, dyspnoea, erythema nodosum, and influenza-like symptoms). The 60 patients without histological confirmation of the diagnosis had the same sex ratio, radiographic stage, forced expiratory volume in one second (FEV_1), vital capacity (VC), total lung capacity (TLC), and symptoms as those with a histologically verified diagnosis. They differed by having entered the study on average two years earlier (p<0.001, *t* test) and they were, on average, 4.7 years younger (p = 0.01, *t* test).[15]

CANCER INCIDENCE AND ANALYSIS

The sarcoidosis patient file was linked to the files of the Danish Cancer Registry by use of the Personal Identification Number unique to all Danish citizens alive on 1 April 1968. Patients who died before 1 April 1968 were linked by their name and date of birth. To avoid misclassification in cases with simultaneous sarcoidosis and cancer the period of follow up for cancer occurrence started one year after the date the diagnosis of sarcoidosis was established. The period ended at the date of death, the date of emigration or 31 December 1992, whichever came first.

Whenever a cancer was found in the Cancer Registry the patient's file was scrutinized in order to verify the cancer diagnosis. If the patient had died and necropsy was performed, the findings were compared with the diagnosis

Table 1 Demographic data of the study population (n=254)

M:F	127:127
Median age at entry (range)	28.4 (13–72)
Follow up time (years)	
0–4	15 (6%)
5–9	11 (4%)
10–19	38 (15%)
20–29	118 (47%)
≥30	72 (28%)
Treated with steroids	43 (17%)
Radiographic stage at diagnosis	
I	52 (21%)
II	134 (53%)
III	68 (27%)
Smoking history at end of follow up period	
Ever smoker	138 (54%)
Never smoker	63 (25%)
Unknown smoking history	53 (21%)
Vital status at end of follow up period	
Dead	84 (33%)
Alive	169 (67%)
Emigrated	1 (0.4%)

in the Cancer Registry and if any discrepancy was found the necropsy diagnosis was used.

Cancers of the patients with sarcoidosis, including benign tumours of the brain and papillomas of the urinary tract, were classified according to the modified Danish version of the International Classification for Diseases, Seventh Revision (ICD-7). National sets of incidences by sex and five year age groups and calendar year periods for these tumour categories were applied to the person-years under observation for the cohort to obtain the number of cancers expected had the cohort members experienced the same rate of cancer as that observed in the general population.

The statistical methods were based on the assumption that the observed number of cancer cases followed a Poisson distribution. Tests of significance and confidence intervals for the standardised incidence ratio, taken as the ratio of observed to expected numbers of cancers, were calculated using the exact confidence limits.

Results

During the follow up period 84 patients died and one emigrated. The median age at entry to the study was 28 years (range 13–72) and the median age at the end of the follow up period was 54 years (range 20–88) (table 1). The median follow up time was 25 years (range one month to 40 years) and a total of 6130 person-years were accrued.

Overall, 36 malignancies were registered. One mediastinal tumour was diagnosed before the diagnosis of sarcoidosis was made but, after careful examination of the histology of the tumour, it was misclassified sarcoidosis. Furthermore, careful examination revealed that two cases coded as lung cancer in the Cancer Registry were diagnosed as sarcoidosis at necropsy and were thus misclassified in the Cancer Registry.

This leaves 33 observed cancers compared with 23 expected, yielding a standardised incidence ratio (SIR) of 1.4 (95% confidence intervals (CI) 0.99 to 2.0) (table 2). No lymphomas occurred (0.7 expected). Five patients had lung cancer compared with 2.5 expected (SIR=2.0; 95% CI 0.7 to 4.7) and all five were in the group of patients with histologically verified sarcoidosis. The radiographic stage for these five patients at the time of diagnosis of sarcoidosis was stage II for three patients and stage III for two. Four of the patients with lung cancer were smokers and the smoking history of the fifth case was unknown. Histological examination of the lung cancer cases revealed adenocarcinoma in two cases, squamous cell carcinoma in two cases, and the information was not available for one case. The time interval between the diagnosis of sarcoidosis and the occurrence of lung cancer ranged between 13 and 17 years. The only site with a significantly increased number of cancers was the pharynx where two cancers of the tonsil were observed compared with 0.13 expected.

Discussion

These findings do not support the theory of a sarcoidosis-lymphoma syndrome, but the results are suggestive of an association between sarcoidosis and lung cancer. The first linkage to the files of the Danish Cancer Registry revealed seven cases of lung cancer, but after careful examination of the files and the necropsy results two turned out to be misclassified cases of sarcoidosis. This result, together with previous reports, shows that misclassification is a major problem in the interpretation of the potential risk of cancer.

The strength of the present study is the high proportion of biopsy-proven cases of sarcoidosis, the long follow up period, and the use of a nationwide cancer registry that enables us to assess the cancer risk compared with the rest of the population which is very homogenous in Denmark. The latter is very important because it prevents selection bias. This type of bias was a major problem in the paper by Brincker where the sarcoidosis-lymphoma syndrome was suggested.[2] Over a long period 17 cases were collected and from this case series it was concluded that the occurrence of both sarcoidosis and lymphoma was not a chance association.

Table 2 Observed and expected number of malignancies with standardised incidence ratios (SIR) and 95% confidence intervals (CI) at selected sites

Cancer site	Observed	Expected	SIR	95% CI
All malignant neoplasms	33	23.0	1.4	0.99 to 2.0
Lip	1	0.2	6.9	0.2 to 38
Pharynx	2	0.1	15.4	1.7 to 56
Stomach	2	0.7	2.9	0.3 to 11
Colon	1	1.5	0.7	0.02 to 3.7
Gallbladder	1	0.2	5.2	0.13 to 29
Pancreas	1	0.6	1.8	0.05 to 10
Lung	5	2.5	2.0	0.7 to 4.7
Breast	1	3.5	0.3	0.01 to 1.6
Cervix uteri	3	1.2	2.6	0.5 to 7.5
Ovary	2	0.8	2.6	0.3 to 9.2
Testis	1	0.4	2.9	0.07 to 16
Kidney	1	0.6	1.7	0.04 to 9.2
Bladder	1	1.0	1.0	0.02 to 5.4
Melanoma of skin	1	0.7	1.4	0.03 to 7.7
Other skin	4	2.7	1.5	0.4 to 3.9
Brain and nervous system	2	0.8	2.5	0.3 to 9.0
Non-Hodgkin's lymphoma	0	0.5	0	0 to 7.8
Hodgkin's disease	0	0.2	0	0 to 19
Multiple myeloma	1	0.2	5.1	0.1 to 28
Leukaemia	1	0.5	2.0	0.05 to 11

The limitation of the present study is the rather small number of patients with sarcoidosis which reduces the power of the study. Although the number of patients was small they were followed for a very long time, yielding more than 6000 person-years. The power is reflected in the confidence intervals and in the overall estimate of cancer risk. The upper confidence interval was 2.0, meaning that the true relative risk may be this high. If we had observed a significantly increased risk for lymphomas (Hodgkin's and non-Hodgkin's) with an expected number of 0.7, four tumours should have been observed.

Although the finding of twice the number of lung cancers as expected was not significant, we cannot disprove an association between sarcoidosis and lung cancer. However, if there is an excess risk of lung cancer in these patients it may be because they were living in Copenhagen where there is a higher incidence of lung cancer, probably due to smoking.[16] The risk of other smoking related cancers (bladder, oesophagus, buccal cavity) should therefore also be increased. No cases of oesophageal cancer occurred and one bladder cancer was reported with one expected, but an excess risk of lip and pharyngeal cancers was found. With these findings it is impossible to conclude whether the excess risk of lung cancer is attributable to smoking or whether it is a feature of sarcoidosis, but as four of the patients were smokers the latter is more likely. Unfortunately, it is not possible to use rates for Copenhagen only in calculating the expected number of malignancies.

Yamaguchi has studied the causes of death among patients with sarcoidosis and found an increased risk of death from lung cancer and lung infections,[17] but it is unclear how the diagnosis of sarcoidosis was established and it is impossible to judge whether misclassification was present. The increased risk of lung cancer in patients with sarcoidosis could be explained by a risk of malignancy occurring in scar tissue as has been suggested in patients with tuberculosis. However, this suggestion is based on case reports and no systematic epidemiological studies are available to support these observations.[18]

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