Sarcoidosis and subsequent cancer risk: a Danish nationwide cohort study

To the Editor:

A link between sarcoidosis and malignancy was suggested by in 1972 BRINCKER [1], and subsequently supported by several studies [2–6]. However, the existing studies have different short-comings, and the causation between co-existing sarcoidosis and cancer is still being debated [7].

Initial misdiagnosis of cancer as sarcoidosis may explain a short-term increased cancer risk [6]. In addition, the clinical examinations at routine control visits increase the chance of detecting a malignant tumour (surveillance bias). Chronic inflammation or a dysregulated immune system accompanying sarcoidosis may be the biological mechanism behind an increased long-term cancer risk [4, 8]. Moreover, sarcoidosis treatment with immunosuppressive agents may increase the risk of later immune-related cancers [9].

We conducted a nationwide cohort study in Denmark (5.5 million residents) and examined the long-term risk of cancer among patients with a hospital-based diagnosis of sarcoidosis. We aimed to estimate potential influence of surveillance bias and immune suppression, thereby adding to the existing literature.

The Danish National Health Service provides free access to hospitals including outpatient clinics, and reimbursement for prescription drugs for all residents.

We used the Danish National Registry of Patients [10] to identify all patients with an inpatient or outpatient diagnosis of sarcoidosis (International Classification of Diseases (ICD) revision 8:135, and ICD-10:D86) in the period 1980 to 2011.

From the Danish National Database of Reimbursed Prescriptions, we ascertained data on use of immunosuppressive agents (glucocorticoid, methotrexate and azathioprine) since 2004 in our cohort, and since 1989 for a sub-group (one-third of the Danish population).

We linked the study cohort to the Danish Cancer Registry [11], and identified incident cancer cases. We excluded patients diagnosed with cancer before the date of sarcoidosis diagnosis.

Follow-up began at the date of first sarcoidosis diagnosis and lasted until first cancer diagnosis, death, emigration or December 2011. We estimated standardised incidence ratios (SIR), a measure of relative risk, comparing cancer incidence observed among patients with sarcoidosis with that expected based on national cancer incidence rates by age, sex and calendar year. We examined the cancer risk according to sex, age, type of sarcoidosis diagnosis (primary or secondary), and type of initial hospital contact (inpatient or outpatient). For periods with available drug data, we repeated long-term analyses for sarcoidosis patients with one or more prescriptions for immunosuppressive agents within 1 year after sarcoidosis diagnosis. We also estimated absolute risks of cancer in patients with sarcoidosis, considering death as a competing risk.

All statistical analyses were conducted using SAS (version 9.2; SAS Institute, Cary, NC, USA). The study was approved by the Danish Data Protection Agency (record number 2013-41-2522).

We identified 12 890 patients with a first-time sarcoidosis diagnosis. Median (interquartile range) age was 40 (31–54) years and 53% were male. The majority (82%) had sarcoidosis as their primary diagnosis, and 64% were diagnosed as outpatients (5496 out of 8552 patients diagnosed during 1995–2011).

Within a median (interquartile range) follow-up of 10 (4–17) years we identified 1303 incident cancers, yielding an overall cancer SIR of 1.3 (95% CI 1.3–1.4) (table 1). The majority of cancers occurred in patients aged 50–69 years, whereas age did not modify the relative risk. Stratification by primary/secondary diagnosis and inpatient/outpatient diagnosis yielded similar results. In total, 3115 patients had a prescription of immunosuppressive agents, and their median (interquartile range) follow-up was 5 (3–8) years.

The cancer risk was particularly high within the first 3 months, mainly due to an excess occurrence of lung cancer, tonsil cancer and lymphoma. The absolute 3-month cancer risk was 1.2% (lung cancer <0.2%). SIRs were also increased for gastrointestinal, urological, haematological and brain cancer during the first 3 months; whereas breast, skin and reproductive system cancers occurred as frequently as expected.

During 3 months to 3 years after sarcoidosis diagnosis, the SIR was moderately increased (mainly based on lung, tonsil, brain and haematological cancers), and the 3-year absolute cancer risk was 3.2%. In

TABLE 1 Number of observed cancers and standardised cancer incidence ratios (SIRs) in all sarcoidosis patients and those treated with an immunosuppressant

	All sarcoidosis patients[#]										Sarcoidosis patients treated with immunosuppressive agents[¶]			
	0 to <3 months		3 months to <3 years		3–10 years		>10 years		Overall		3–10 years		>10 years	
All[+]	149	9.1 (7.7–10.7)	243	1.5 (1.3–1.7)	419	1.2 (1.1–1.3)	492	1.1 (1.0–1.2)	1303	1.3 (1.3–1.4)	74	1.2 (0.9–1.5)	27	1.3 (0.9–2.0)
Tonsils	20	63.8 (39.0–98.6)	11	3.5 (1.7–6.2)	13	2.1 (1.1–3.6)	7	1.3 (0.5–2.6)	51	3.4 (2.5–4.4)	0		0	
Stomach	0		1	0.4 (0.00–2.1)	6	1.1 (0.4–2.5)	7	1.1 (0.4–2.2)	14	1.0 (0.5–1.6)	1	1.2 (0.0–6.8)	0	
Colon	6	5.8 (2.1–12.6)	11	1.1 (0.5–1.9)	37	1.7 (1.2–2.4)	28	1.0 (0.7–1.4)	83	1.4 (1.1–1.7)	6	1.6 (0.6–3.6)	2	1.6 (0.2–5.9)
Rectum	4	7.1 (1.9–18.1)	4	0.7 (0.2–1.8)	13	1.1 (0.6–1.9)	19	1.2 (0.7–1.9)	40	1.2 (0.9–1.6)	2	1.0 (0.1–3.5)	1	1.5 (0.0–8.2)
Pancreas	3	8.4 (1.7–24.6)	1	0.3 (0.0–1.6)	8	1.1 (0.5–2.2)	10	1.0 (0.5–1.9)	22	1.1 (0.7–1.6)	1	0.8 (0.0–4.4)	0	
Gall bladder/biliary tract	0		1	1.2 (0.0–6.4)	4	2.4 (0.6–6.0)	6	2.9 (1.1–6.3)	11	2.3 (1.2–4.2)	0		1	11.1 (0.3–61.7)
Lungs	32	18.7 (12.8–26.3)	25	1.5 (0.9–2.1)	31	0.9 (0.6–1.3)	26	0.6 (0.4–0.8)	114	1.1 (0.9–1.4)	11	1.8 (0.9–3.2)	2	1.0 (0.1–3.6)
Breast	3	1.4 (0.3–4.1)	19	0.9 (0.5–1.3)	42	0.9 (0.6–1.2)	54	1.0 (0.7–1.3)	118	0.9 (0.8–1.1)	6	0.8 (0.3–1.7)	2	0.8 (0.1–3.0)
Malignant melanoma	2	3.2 (0.4–11.4)	4	0.6 (0.2–1.5)	10	0.7 (0.3–1.3)	15	0.9 (0.5–1.5)	30	0.8 (0.5–1.2)	3	1.1 (0.2–3.3)	2	2.5 (0.3–8.9)
Basal cell carcinoma	5	1.9 (0.6–4.4)	53	1.9 (1.4–2.5)	86	1.4 (1.1–1.8)	107	1.2 (1.0–1.5)	251	1.4 (1.2–1.6)	15	1.2 (0.7–2.0)	5	1.2 (0.4–2.7)
Squamous cell skin cancer	1	2.6 (0.1–14.3)	12	3.0 (1.6–5.3)	20	2.4 (1.5–3.7)	42	3.2 (2.3–4.3)	75	2.9 (2.3–3.6)	5	2.6 (0.9–6.2)	1	1.5 (0.0–8.2)
Cervix uteri	1	3.3 (0.1–18.2)	4	1.3 (0.3–3.3)	6	1.0 (0.4–2.2)	5	1.1 (0.3–2.5)	16	1.1 (0.7–1.9)	1	1.3 (0.0–7.4)	0	
Uterus	1	2.6 (0.1–14.7)	5	1.3 (0.4–3.0)	7	0.9 (0.4–1.9)	11	1.2 (0.6–2.2)	24	1.1 (0.7–1.7)	1	0.9 (0.0–4.9)	1	2.7 (0.1–14.9)
Ovary	1	3.1 (0.1–17.2)	2	0.6 (0.1–2.2)	7	1.1 (0.4–2.2)	10	1.4 (0.7–2.6)	20	1.2 (0.7–1.8)	1	1.1 (0.0–6.2)	0	
Prostate	5	5.2 (1.7–12.0)	10	1.0 (0.5–1.9)	21	1.1 (0.7–1.6)	41	1.2 (0.8–1.6)	77	1.2 (0.9–1.5)	5	1.0 (0.3–2.3)	4	2.3 (0.6–6.0)
Testes	0		1	0.4 (0.0–2.1)	7	1.5 (0.6–3.1)	4	1.3 (0.3–3.3)	12	1.1 (0.6–2.0)	2	2.7 (0.3–9.7)	0	
Kidney	3	11.1 (2.3–32.4)	4	1.5 (0.4–3.8)	6	1.1 (0.4–2.3)	9	1.2 (0.5–2.3)	22	1.4 (0.8–2.1)	1	1.0 (0.0–5.4)	1	3.0 (0.1–16.5)
Bladder	2	5.9 (0.7–21.4)	3	0.9 (0.2–2.6)	7	1.1 (0.4–2.2)	4	0.5 (0.1–1.1)	16	0.8 (0.5–1.4)	2	1.7 (0.2–6.2)	1	2.7 (0.1–14.9)
Brain	6	13.1 (4.8–28.5)	16	3.4 (1.9–5.5)	12	1.3 (0.7–2.2)	6	0.6 (0.2–1.2)	40	1.6 (1.1–2.1)	2	1.2 (0.1–4.4)	0	
Hodgkin lymphoma	9	107 (49.0–203)	6	7.2 (2.6–15.7)	4	2.7 (0.7–6.9)	0		19	5.3 (3.2–8.2)	2	8.8 (1.1–31.8)	0	
Non-Hodgkin lymphoma	23	57.1 (36.2–85.7)	21	5.1 (3.2–7.8)	18	2.1 (1.2–3.3)	18	1.6 (1.0–2.6)	80	3.3 (2.6–4.1)	2	1.3 (0.2–4.7)	1	2.0 (0.1–11.3)
Myeloid leukaemia	3	21.5 (4.4–62.8)	5	3.6 (1.2–8.3)	4	1.4 (0.4–3.7)	2	0.6 (0.1–2.3)	14	1.9 (1.0–3.1)	0		0	
Multiple myeloma	5	37.4 (12.1–87.1)	4	3.0 (0.8–7.6)	6	2.2 (0.8–4.7)	5	1.4 (0.4–3.2)	20	2.5 (1.5–3.9)	1	2.1 (0.1–11.7)	0	

Data are presented as observed number or SIR (95% CI). [#]: n = 12 890; [¶]: n = 3115; [+]: the site specific numbers do not add up to the total number because not all cancer sites are presented.

addition, basal cell carcinoma and squamous cell skin cancer occurred more frequently than expected, while we found no increased risk of gastrointestinal, urological or reproductive system cancers.

Patients with sarcoidosis had 20% and 10% increased cancer risk in the periods of 3–10 years and >10 years after sarcoidosis diagnosis, respectively. The 10-year absolute cancer risk was 7.7%. The increased cancer risk beyond 3 years of follow-up was mainly due to a higher than expected occurrence of non-Hodgkin lymphoma and tonsil, colon, gall bladder/biliary tract and non-melanoma skin cancer. The increased risk of gall bladder/biliary tract cancer, basal cell carcinoma and squamous cell skin cancer persisted even beyond 10 years of follow-up. In contrast, there was no association with lung cancer during 3–10 years of follow-up, and beyond 10 years it was diagnosed less frequently than expected. Restriction to patients with prescriptions of immunosuppressive agents did not further increase the risk, but these estimates had low precision.

In this nationwide study, we confirmed an increased cancer risk shortly after the sarcoidosis diagnosis, but more importantly found a persistent increased risk of several cancers beyond 10 years.

Strengths include the large size, inclusion of outpatient diagnoses and high validity of diagnoses used [10, 11]. Nevertheless, we lacked information on diagnostic work-up, sarcoidosis severity and other clinical characteristics, and potential misclassification may have affected our results.

Our finding of an increased overall risk of cancer among sarcoidosis patients is in accordance with several previous studies using the general population as a comparison [2–6], while one study found no association when comparing sarcoidosis patients with other hospitalised patients [12].

One study argued that misclassification explained the apparent association [6]. We agree that the increased short-term risk of cancer most likely reflects the presence of occult cancer, and that reverse causality, misclassification and increased early surveillance may explain the association for at least the first 3 years after diagnosis, where routine clinical examinations are regularly offered in Denmark.

We confirmed a substantially increased risk of lung cancer during the first 3 months, which was also previously reported [2], but thereafter the risk declined substantially. Regarding the long-term risk of lung cancer, we supported the finding of a decreased risk [12]. A compensatory deficit in the period after the first 3 months conforms to our expectations. However, the finding of a decreased long-term lung cancer risk corresponds poorly with the hypothesis of chronic inflammation playing a key role in the development of cancer in patients with sarcoidosis [8, 13].

In agreement with previous studies [2, 4, 5, 14], we also found an increased risk of Hodgkin lymphoma and skin cancer. Moreover, we found a persistent strong association between sarcoidosis and non-Hodgkin lymphoma, which has been less clearly described [2, 4, 5, 15].

Steroid use increases the risk of immune-related cancer [9], including cancers associated with human papillomavirus. We found a substantial increased risk of tonsil cancer, whereas cervical cancer did not occur more often than expected. The results for other human papillomavirus-associated cancers were inconclusive. Moreover, patients using immunosuppressive agents had similar risks as the entire cohort, which, despite lack of statistical precision, may argue against a critical impact of immunosuppressive medicine.

In conclusion, a short-term increased risk of cancer in patients with sarcoidosis was potentially explained by increased surveillance, or initial misinterpretation of cancer as sarcoidosis. In contrast, the increased long-term risk of tonsil cancer, colon cancer and immune-related cancers was notable, and is unlikely to reflect surveillance bias alone.

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An integrated MDR-TB management programme results in favourable outcomes in northern Taiwan

To the Editor:

Multidrug-resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid (INH) and rifampicin (RIF). MDR-TB is difficult to treat and has become an obstacle to tuberculosis control programmes worldwide [1]. The global burden of MDR-TB has been increasing and the World Health Organization (WHO) estimated there were 450 000 incident MDR-TB cases in 2012 [2]. Based on drug-resistance surveys, 3.6% of patients newly diagnosed and 20.2% of patients previously treated for tuberculosis had MDR-TB [2]. MDR-TB demands treatment with second-line drugs that have a limited sterilising capacity, and are less effective and more toxic than first-line drugs. Among the estimated 20% of the worldwide MDR-TB cases that were enrolled in treatment in 2010, only 48% were successfully treated [2]. High mortality rates and loss to follow-up are threatening to destabilise global tuberculosis control.

In Taiwan, MDR-TB occurred in 1% of new tuberculosis cases and in 6% of re-treated tuberculosis cases [3]. In addition, laboratory-based analyses revealed that 10% of MDR-TB cases in Taiwan were extensively drug-resistant (XDR-TB) [4]. Faced with the challenge of the low treatment success rate of MDR-TB, a designated, government-organised and hospital-initiated programme led by experienced pulmonary specialists with diligent case managers, and cooperative and integrated medical groups, providing comprehensive and high-quality medical care for MDR-TB cases, was implemented by the Centers for