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Risk of Cancer Among Sarcoidosis Patients With Biopsy-verified Nonnecrotizing Granulomatous Inflammation: Population-based Cohort Study

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ABSTRACT. ***Objective.*** To assess the long-term risk of hematologic cancers, invasive solid tumors, and nonmelanoma skin cancer (NMSC) among sarcoidosis patients with biopsy-verified nonnecrotizing granulomatous inflammation.

Methods. We used Danish administrative registers with nationwide coverage to construct a cohort of 3892 patients with sarcoidosis and an age- and sex-matched comparison cohort of 38,920 population controls. For all patients, a biopsy demonstrating nonnecrotizing granulomatous inflammation had been obtained from the lower respiratory tract at the time of diagnosis. Study outcome was time to diagnosis of cancer. Follow-up began at time of sarcoidosis diagnosis and continued for up to 10 years. We calculated hazard ratios (HRs) as estimates of the cancer risk among the patients with sarcoidosis relative to that among the population controls and used cumulative incidence functions to calculate absolute 10-year risk estimates.

Results. We observed an increased long-term risk of hematologic cancers (HR during the first 2 years of follow-up: 2.71 [95% CI 1.18–6.25]; HR after > 2 years of follow-up: 2.12 [95% CI 1.29–3.47]) and NMSC (HR after > 2 years of follow-up: 1.82 [95% CI 1.43–2.32]) among the patients with sarcoidosis. An increased risk of invasive solid tumors was only observed during the first 2 years (HR 1.55, 95% CI 1.18–2.04). Compared with the population controls, the patients with sarcoidosis had an increased absolute 10-year risk of hematologic cancers (risk difference 0.56%, 95% CI 0.11–1.01%) and NMSC (risk difference 1.58%, 95% CI 0.70–2.47%).

Conclusion. Sarcoidosis patients with biopsy-verified nonnecrotizing granulomatous inflammation have an increased long-term risk of hematologic cancers and NMSC compared with the general population.

Key Indexing Terms: cancer, risk, sarcoidosis

Sarcoidosis is a disease of unknown etiology characterized by nonnecrotizing granulomatous inflammation. The lower respiratory tract is affected in > 90% of patients with sarcoidosis, but the disease can involve any organ system of the body.[1,2,3]

A range of cohort studies have indicated that patients with sarcoidosis have an increased risk of malignant diseases compared with the general population, but available data are conflicting. An increased risk of hematologic cancers has been observed in some cohort studies,[4,5,6,7,8] whereas other studies showed no increase in risk of hematologic cancers among patients with sarcoidosis.[9,10,11,12] Moreover, some studies have demonstrated an increased risk of invasive solid tumors[4,6,7,8,10,11] and/or nonmelanoma skin cancer (NMSC)[4,5,6,7] among patients with sarcoidosis, whereas the risk of invasive solid tumors[5,9,12] or NMSC[11,12] did not differ between patients with sarcoidosis and population controls in other analyses.

Based on investigations demonstrating excess risk of cancer among patients with sarcoidosis, it has been speculated that a causal association might exist between sarcoidosis and cancer.[4,7,8,10] Putative risk factors for carcinogenesis in sarcoidosis encompass chronic inflammation[6,7,10,13,14] and impaired tumor immune surveillance due to immunologic dysfunction.[8,9,14] However, noncausal explanations for the observed association between sarcoidosis and neoplasms have also been considered, including diagnostic misclassification of cancers as sarcoidosis[5,6,7,11] and surveillance bias.[4,5,6,7,10]

Sarcoidosis is a diagnosis of exclusion, and the differential diagnoses comprise a variety of malignant and nonmalignant diseases.[2] Ideally, a tissue biopsy showing nonnecrotizing granulomatous inflammation should be obtained to reduce the risk of diagnostic misclassification, but a tentative diagnosis of sarcoidosis is sometimes made without histologic demonstration of the inflammatory disease processes.[1,2,3]

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In many of the previously published epidemiological studies on risk of cancer in sarcoidosis, hospital discharge codes were used to identify the patients with sarcoidosis, and the proportion of patients diagnosed without characteristic biopsy findings was not described.[4,5,6,7,10] Studies based exclusively on sarcoidosis patients with biopsy-verified nonnecrotizing granulomatous inflammation are therefore warranted to evaluate the potential link between sarcoidosis and cancer with greater accuracy.

The aim of the present study was to assess the long-term risk of hematologic cancers, invasive solid tumors, and NMSC among patients for whom the clinical diagnosis of sarcoidosis is supported by histopathology. By means of administrative registers with nationwide coverage, we identified a large cohort of patients diagnosed with sarcoidosis in the hospital system of Denmark. For all patients, a biopsy showing nonnecrotizing granulomatous inflammation had been obtained from the lower respiratory tract at time of the clinical diagnosis. We subsequently compared the cancer risk in the cohort with that among age- and sex-matched population controls.

METHODS

The study was performed as a matched, nationwide, population-based cohort study.

Data sources. The Danish National Hospital Register has collected data on all inpatient hospital contacts in Denmark since 1977. From 1995 onward, data on outpatient visits and visits to emergency departments have also been collected. For each hospital contact, a record is established in the register. The record contains dates of admission and discharge/start and end dates for outpatient visits, a primary diagnosis, and supplementary diagnoses (if appropriate). Diagnoses were coded according to a Danish version of the International Classification of Diseases (ICD), 8th revision, until the end of 1993, and according to the ICD-10 from 1994 onward.[15]

The Danish National Pathology Register has been provided with information on pathology specimens analyzed in Denmark with partial coverage since the 1970s and complete coverage since 1997. A record in the register contains a multitude of data concerning a given biopsy specimen, including information regarding the anatomical site of the biopsy and the histological findings, coded in accordance with a Danish version of the Systematized Nomenclature of Medicine (SNOMED).[16]

The Danish Civil Registration System was established in 1968 and contains continuously updated information on deaths and migrations among all citizens of Denmark.[17]

The Danish Cancer Register contains information on cancers diagnosed in Denmark from 1943 onward. In the register, diagnoses are coded according to the ICD-7 until 1978 and thereafter, according to the ICD-10 and the ICD for Oncology, 3rd revision. The coverage is estimated to be close to 100%.[18]

Sarcoidosis cohort. The sarcoidosis cohort encompassed all Danish citizens with (1) a first-time hospital contact under a clinical diagnosis of sarcoidosis during 1999–2018 (ICD-8: 135.99; ICD-10: D86); (2) a biopsy specimen from the lower respiratory tract, obtained within 3 months of the first sarcoidosis-related hospital contact, demonstrating nonnecrotizing granulomatous inflammation (SNOMED codes: M44200 [nonnecrotizing granulomatous inflammation], M44202 [nonnecrotizing epithelioid cell granuloma], M44210 [Boeck sarcoid]); (3) no prior registration in the Danish National Pathology Register with similar biopsy findings; and (4) no cancer diagnosis except NMSC before date of study inclusion. For the patients, date of study inclusion was defined as date of first sarcoidosis-related hospital contact or as date of biopsy, whichever came last.

Comparison cohort. Data from the Danish National Hospital Register, the Danish Civil Registration System, and the Danish Cancer Register was used to construct a comparison cohort. For each patient, 10 age- and sex-matched population controls were randomly selected from the Danish general population. The population controls were required to be alive, not diagnosed with sarcoidosis, not diagnosed with any cancer except NMSC, and living in Denmark at the date of study inclusion of the patients to whom they were matched. The population controls were assigned the same date of study inclusion as their corresponding patient.

Cancers. Cancer diagnoses were identified by linkage with the Danish Cancer Register. Patients and population controls were tracked from date of study inclusion for cancers in the following categories: hematologic cancers (ICD-10: C81–95), any solid tumor except NMSC (ICD-10: C00–C80, except C44), upper gastrointestinal (GI) tract (ICD-10: C00–C17.0), lower GI tract (ICD-10: C17.1–C21), respiratory tract (ICD-10: C30–34, C38.4), breast (ICD-10: C50), male genital organs (ICD-10: C60–C63), urinary tract (ICD-10: C64–C68), invasive solid tumors, other categories (ICD-10: C22–25, C38.0–C38.3, C40–C41, C43, C45–C49, C51–C58, C69–C80), NMSC (ICD-10: C44).

Deaths, loss to follow-up, and emigrations. Information concerning the vital status of patients and population controls was collected from the Danish Civil Registration System.

Statistical analysis. The study outcome was time to diagnosis of cancer. Follow-up began at date of study inclusion and continued until date of the cancer diagnosis of interest, death, emigration, loss to follow-up, 10 years of follow-up, or December 31, 2018, whichever came first.

If a study subject was diagnosed with several cancers belonging to > 1 category of cancer during follow-up, the various cancers were counted once in each of the relevant categories. If a study subject was diagnosed with several cancers belonging to the same category during follow-up, only the first cancer within the category was counted. If a study subject had been diagnosed with NMSC before date of study inclusion, the person was only followed for cancers in other categories. Thus, the analyses concerning hematologic cancers and invasive solid tumors included all patients with sarcoidosis and all population controls. In contrast, the analyses concerning NMSC included only patients with sarcoidosis who had not been diagnosed with NMSC prior to the date of study inclusion, each matched with up to 10 population controls without preexisting NMSC from the comparison cohort.

Cox regression analyses were used to calculate hazard ratios (HRs), adjusted for age as a continuous variable and sex, as estimates of the cancer risk among patients relative to that among population controls. In the main analyses, separate HRs were calculated for early and late observational periods to account for the possibility of nonproportional hazard during follow-up. In all analyses, the proportional hazard assumption was tested using Schoenfeld residuals. Absolute 10-year risk estimates for cancers were calculated by means of the cumulative incidence function. In these analyses, death was considered a competing risk. Differences in absolute risk estimates were calculated as previously described.[19] The chi-square test was used to compare proportions. We used IBM SPSS version 27 (IBM Corp.), Stata version 16 (StataCorp), and R 4.0.2 (The R Foundation) to perform the analyses.

Ethics. The study was approved by the Danish Data Protection Agency (jr. no.: P-2020-570).

RESULTS

Cohort characteristics. During 1999–2018, 13,968 patients were registered in the Danish National Hospital Register with a first-time diagnosis of sarcoidosis. Among these, 3892 patients met the inclusion criteria of the present study. Our sarcoidosis cohort therefore included 3892 patients with biopsy-verified nonnecrotizing granulomatous inflammation, whereas the

comparison cohort comprised 38,920 population controls. Baseline characteristics of patients and population controls are listed in Table 1, which also shows the number of study subjects diagnosed with cancer within each of the predefined categories during follow-up. Less than 0.05% of the individuals under study were lost to follow-up. In the sarcoidosis cohort, median time between first hospital contact for sarcoidosis and biopsy was 11 (IQR 5–27) days.

Risk of hematologic cancers. Twenty-six of the 3892 patients with sarcoidosis and 118 of the 38,920 population controls were diagnosed with hematologic cancer during follow-up. Of these 26 patients with sarcoidosis, 20 were diagnosed with lymphoid cancer and 6 were diagnosed with myeloid cancer.

The risk of hematologic cancers was increased in the sarcoidosis cohort during the first 2 years of follow-up (HR 2.71, 95% CI 1.18–6.25; Table 2) and after > 2 years of follow-up (HR 2.12, 95% CI 1.29–3.47; Table 2). During the 10-year follow-up period, an increased risk was observed for both lymphoid cancers (HR 2.10, 95% CI 1.30–3.41) and myeloid cancers (HR 2.91, 95% CI 1.17–7.20).

The absolute 10-year risk of hematologic cancers was 1.08% among the patients with sarcoidosis and 0.52% among the population controls (risk difference: 0.56%, 95% CI 0.11–1.01%; Table 3 and Figure 1).

Table 1. Characteristics of 3892 patients with sarcoidosis[a] and 38,920 population controls[b].

	Patients With Sarcoidosis	Population Controls
Persons, n	3892	38,920
Age at date of study inclusion, yrs, median (IQR)	45 (35–56)	45 (35–56)
Men, n (%)	2468 (63)	24,680 (63)
Time between first hospital contact for sarcoidosis and biopsy[a], days, median (IQR)	11 (5–27)	–
Follow-up duration, yrs, median (IQR)[c]	5.85 (2.72-10.0)	5.88 (2.69–10.0)
Follow-up, PY[c]	23,088	230,842
Persons diagnosed with cancer in various categories during follow-up, n		
Hematologic cancers	26	118
Upper GI tract	13	95
Lower GI tract	27	211
Respiratory tract	15	232
Breast	19	212
Male genital organs	32	265
Urinary tract	19	76
Invasive solid tumors, other categories[d]	45	342
NMSC[e]	94	557

[a] Patients were required to have a first-time hospital contact for sarcoidosis during 1999–2018 and a concomitant biopsy specimen from the lower respiratory tract demonstrating nonnecrotizing granulomatous inflammation. [b] Each patient was matched with 10 population controls of similar age and sex. [c] Follow-up began at time of sarcoidosis diagnosis and continued for up to 10 years. [d] Composite of other categories with 1–9 cases in the sarcoidosis cohort. [e] Among 3818 patients and 37,522 population controls. GI: gastrointestinal; NMSC: nonmelanoma skin cancer; PY: person-years.

Table 2. Age-and sex-adjusted risk of cancer among 3892 patients with sarcoidosis[a] compared with 38,920 population controls[b].

	HR (95% CI) 0–2 Years After Date of Study Inclusion[c]	HR (95% CI) > 2 Years After Date of Study Inclusion[c]
Hematologic cancers	2.71 (1.18–6.25)	2.12 (1.29–3.47)
Any solid tumor except NMSC	1.55 (1.18–2.04)	1.03 (0.84–1.27)
Upper GI tract	0.95 (0.22–4.07)	1.51 (0.80–2.85)
Lower GI tract	1.09 (0.47–2.54)	1.38 (0.87–2.17)
Respiratory tract	1.08 (0.50–2.36)	0.49 (0.24–1.00)
Breast	1.01 (0.44–2.34)	0.87 (0.49–1.53)
Male genital organs	1.75 (0.97–3.16)	1.03 (0.64–1.65)
Urinary tract	4.36 (2.07–9.16)	1.73 (0.85–3.51)
Invasive solid tumors, other categories[d]	1.66 (0.96–2.86)	1.21 (0.83–1.77)
NMSC[e]	1.21 (0.73–2.00)	1.82 (1.43–2.32)

[a] Patients were required to have a first-time hospital contact for sarcoidosis during 1999–2018 and a concomitant biopsy specimen from the lower respiratory tract demonstrating nonnecrotizing granulomatous inflammation. [b] Each patient was matched with 10 population controls of similar age and sex. [c] Follow-up began at time of sarcoidosis diagnosis and continued for up to 10 years. [d] Composite of other categories with 1–9 cases in the sarcoidosis cohort. [e] Among 3818 patients and 37,522 population controls. GI: gastrointestinal; HR: hazard ratio; NMSC: nonmelanoma skin cancer.

Risk of invasive solid tumors. One hundred sixty of the 3892 patients with sarcoidosis and 1388 of the 38,920 population controls were diagnosed with at least 1 invasive solid tumor during follow-up. An increased risk of any solid tumor except NMSC was observed among the patients with sarcoidosis during the first 2 years of follow-up (HR 1.55, 95% CI 1.18–2.04), but not after > 2 years (HR 1.03, 95% CI 0.84–1.27; Table 2). Ten patients with sarcoidosis were diagnosed with urinary tract cancer during the first 2 years (7 with kidney cancer), corresponding to an HR of 4.36 (95% CI 2.07–9.16) for urinary tract cancer within this time period. For invasive solid tumors in other categories, we did not observe substantially increased HRs during early or late follow-up (Table 2). After > 2 years, the risk of respiratory tract cancer tended to be lower in the sarcoidosis cohort than that in the comparison cohort (HR 0.49, 95% CI 0.24–1.00; Table 2).

The absolute 10-year risk of any solid tumor except NMSC was 6.60% in the sarcoidosis cohort and 5.94% in the comparison cohort (risk difference: 0.66%, 95% CI –0.44 to 1.77%; Table 3 and Figure 1).

Risk of NMSC. The proportion of study subjects diagnosed with NMSC prior to date of study inclusion did not differ between the sarcoidosis cohort and the comparison cohort (74 of 3892 patients with sarcoidosis vs 695 of 38,920 population controls; $P > 0.6$).

Among the 3818 patients with sarcoidosis without preexisting NMSC, 94 were diagnosed with NMSC after date of study inclusion. In comparison, 557 out of 37,522 matched population controls without preexisting NMSC were diagnosed

Table 3. Absolute 10-year risk estimates[a] for cancer among 3892 patients with sarcoidosis[b] and 38,920 population controls[c].

	Absolute 10-yr Risk, % (95% CI)		
	Patients With Sarcoidosis	Population Controls	Difference
Hematologic cancers	1.08 (0.71–1.59)	0.52 (0.43–0.63)	0.56 (0.11–1.01)
Any solid tumor except NMSC	6.60 (5.60–7.72)	5.94 (5.62–6.27)	0.66 (–0.44 to 1.77)
NMSC[d]	4.10 (3.31–5.02)	2.52 (2.31–2.74)	1.58 (0.70–2.47)

[a] Follow-up began at time of sarcoidosis diagnosis. [b] Patients were required to have a first-time hospital contact for sarcoidosis during 1999–2018 and a concomitant biopsy specimen from the lower respiratory tract demonstrating nonnecrotizing granulomatous inflammation. [c] Each patient was matched with 10 population controls of similar age and sex. [d] Among 3818 patients and 37,522 population controls. NMSC: nonmelanoma skin cancer.

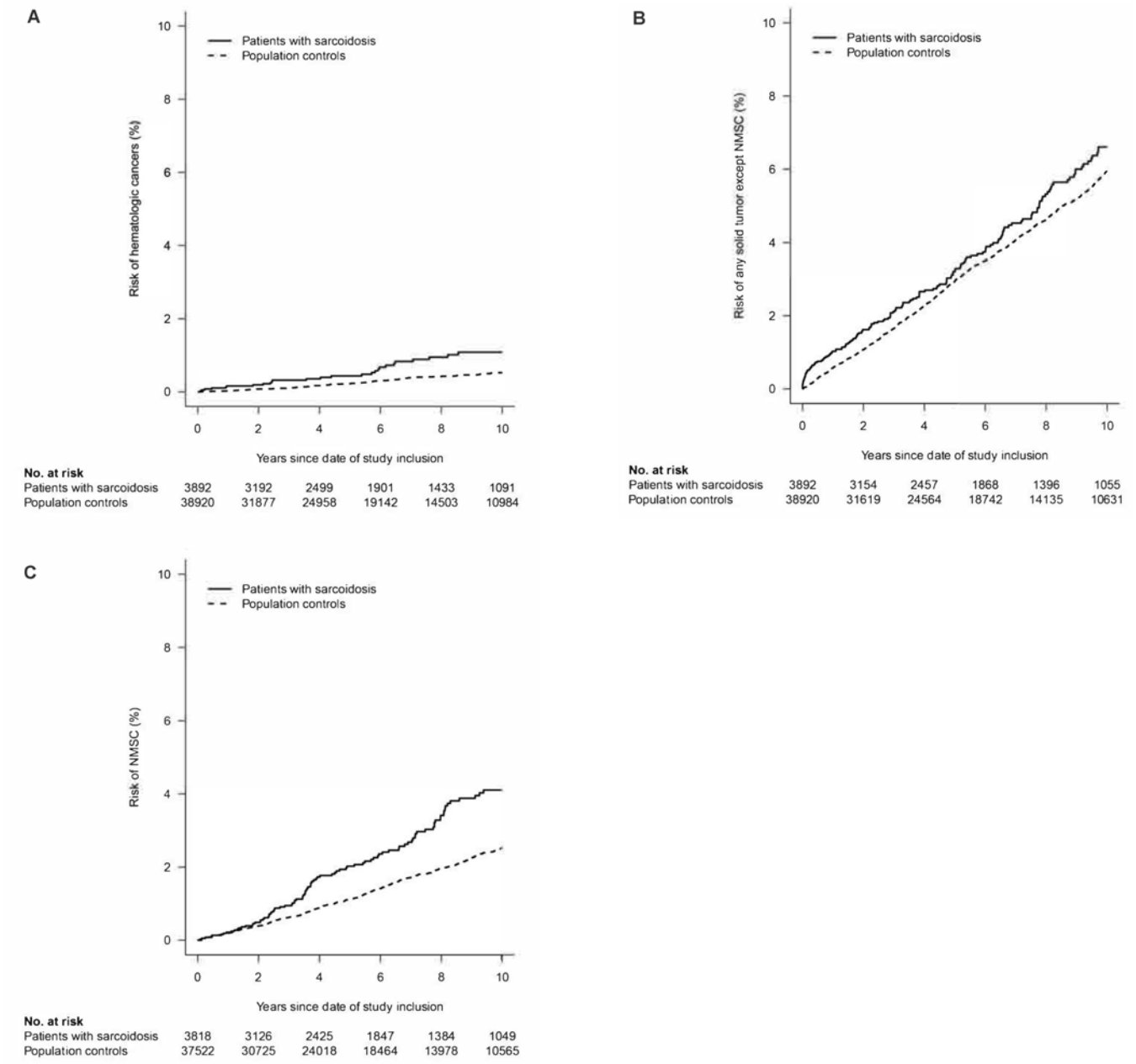

Figure 1. Cumulative incidence estimates for (A) hematologic cancers, (B) any solid tumor except NMSC, and (C) NMSC among patients with sarcoidosis and population controls. NMSC: nonmelanoma skin cancer.

with NMSC. The risk of NMSC was not increased in the sarcoidosis cohort during the first 2 years of follow-up (HR 1.21, 95% CI 0.73–2.00; Table 2). After > 2 years, the risk of NMSC was markedly higher among the patients with sarcoidosis than among the population controls (HR 1.82, 95% CI 1.43–2.32; Table 2).

The absolute 10-year risk of NMSC was 4.10% among the patients with sarcoidosis and 2.52% among the population controls (risk difference: 1.58%, 95% CI 0.70–2.47%; Table 3 and Figure 1).

DISCUSSION

In the present population-based cohort study, we observed an increased long-term risk of certain cancers among sarcoidosis patients with biopsy-verified nonnecrotizing granulomatous inflammation.

In agreement with findings in other studies,[4,5,6,7,8] we observed an increased risk of hematologic cancers in our cohort of patients with sarcoidosis, and the risk of these cancers was increased during early as well as late follow-up periods. Further, our findings support previous observations of an increased risk of both lymphoid and myeloid cancers among patients with sarcoidosis.[4,6]

The increased risk of hematologic cancers observed in the sarcoidosis cohort during the first 2 years of follow-up may, to some extent, reflect diagnostic misclassification of cancer-induced sarcoid reactions as sarcoidosis.[20] However, considering the severe clinical features of hematologic cancers, we find it implausible that the increased risk of hematologic cancers observed after > 2 years of follow-up should be a consequence of such diagnostic misclassification. Of note, we observed an absolute 10-year risk of hematologic cancers in our sarcoidosis cohort of 1.08% and a difference in absolute 10-year risk of hematologic cancers between patients and population controls of only 0.56%. Thus, even though the risk of hematologic cancers seems to be increased among patients with sarcoidosis compared with that in the general population, the excess absolute risk is low.

We did not detect strong associations between sarcoidosis and invasive solid tumors. An increased risk of urinary tract cancer was observed among the patients with sarcoidosis during the first 2 years of follow-up. This finding raises the possibility that a pathogenic link may exist between sarcoidosis and cancers of the urinary tract. However, the risk of urinary tract cancer was not increased beyond the second year of follow-up. Further, renal cell carcinomas are frequently detected coincidentally among patients undergoing diagnostic procedures due to other diseases.[21,22] It therefore seems likely that the increased risk of urinary tract cancer observed during initial observational periods was a result of surveillance bias. We did not observe an increased risk of invasive solid tumors in other categories, but insufficient statistical power may have prevented us from detecting further associations between sarcoidosis and cancer.

The relative risk of NMSC was increased in the sarcoidosis cohort after > 2 years of follow-up, and the difference in absolute risk of NMSC between patients and population controls was 1.58% after 10 years. These findings are in line with earlier reports of an increased long-term risk of NMSC in sarcoidosis.[4,6,7]

The mechanisms responsible for the increased risk of hematologic cancers and NMSC among patients with sarcoidosis are incompletely understood and cannot be determined from our data. The pathogenesis of sarcoidosis is believed to involve an exaggerated inflammatory response in addition to impaired immune reactivity.[1,3,14] It has also been proposed that these abnormalities may drive an increased risk of cancer by causing chronic proliferation of cells and/or reduced immune surveillance of neoplasms.[13,14] Moreover, an increased risk of NMSC has been demonstrated among users of corticosteroids,[23,24] and exposure to certain nonsteroidal immunosuppressive agents has been linked with an increased risk of hematologic cancers[25,26,27] and NMSC.[28,29,30] It could therefore be speculated that the cancer risk in sarcoidosis is driven by both the inflammatory disease and its treatment. However, since many patients with sarcoidosis never receive immunosuppressive therapy or receive therapy only for short periods of time,[1] immunosuppressive medications may influence the risk of hematologic cancers and NMSC to a lesser extent than disease-related factors. It is also possible that patients receiving therapy for sarcoidosis have an increased likelihood of being diagnosed with NMSC secondarily due to the close medical monitoring typically offered to persons treated with immunosuppressants.

Our study has strengths and weaknesses. Based on data from nationwide registers, we identified a large cohort of patients diagnosed with sarcoidosis. Importantly, the clinical diagnosis was supported by characteristic biopsy findings in all cases. Our methodological approach enabled us to performed long-term tracking of patients and population controls with minimal loss to follow-up and to collect reliable information regarding incident cancers.

We did not have access to information on immunosuppressive therapies prescribed during follow-up, and this precluded an evaluation of the cancer risk associated with exposure to different medications. Information concerning sarcoidosis manifestations could not be collected, and this prevented us from assessing the influence of disease severity on the risk of cancer among the patients with sarcoidosis.

As in other studies,[4,6,7] we observed a long-term risk of respiratory tract cancer, which tended to be lower in the sarcoidosis cohort than in the comparison cohort. This observation could potentially reflect that a diagnosis of pulmonary sarcoidosis is a strong incentive for smoking cessation. A negative association between ever-smoking and risk of sarcoidosis has been observed in epidemiological analyses,[31,32] and a low prevalence of ever-smokers among patients with sarcoidosis may also influence the long-term risk of respiratory tract cancer in this patient group. However, we were unable to explore the relationship between exposure to tobacco and risk of smoking-related cancers in our sarcoidosis cohort due to absence of data on lifestyle factors.

In conclusion, we observed an increased long-term risk of hematologic cancers and NMSC among sarcoidosis patients with biopsy-verified nonnecrotizing granulomatous inflammation. Our observations substantiate the hypothesis that an

association exists between sarcoidosis and cancers of the hematopoietic system.[33] Further studies are needed to elucidate the pathogenic background for this association and to identify risk factors for the development of hematologic cancers and NMSC among patients diagnosed with sarcoidosis.

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