Department of Medicine
Division of Pulmonary Medicine
Helsinki University Central Hospital
Helsinki
and
Mjölbolsta Hospital
Karjaa, Finland

SARCOIDOSIS IN FINLAND AND HOKKAIDO, JAPAN

A STUDY OF TWO GENETICALLY DIFFERENT POPULATIONS

by

Anne Pietinalho

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SUPERVISED BY

Olof Selroos
Associate Professor, Pulmonary Medicine
Department of Medicine
University of Helsinki
Lund, Sweden

Anja Tiilikainen
Professor, Department of Medical Microbiology
University of Oulu
Oulu, Finland

REVIEWED BY

Hannu Tukiainen
Professor, Pulmonary Medicine
University of Kuopio
Kuopio, Finland

Pentti Tukiainen
Professor, Pulmonary Medicine
Department of Medicine
University of Helsinki
Helsinki, Finland

OPPONENT AT THE DISSERTATION

Anders Eklund
Professor, Pulmonary Medicine
Department of Medicine
Karolinska Institute
Stockholm, Sweden

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To my family

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LIST OF ORIGINAL COMMUNICATIONS

1. Pietinalho A, Hiraga Y, Hosoda Y, Löfroos A-B, Yamaguchi M, Selroos O: The frequency of sarcoidosis in Finland and Hokkaido, Japan. A comparative epidemiological study. Sarcoidosis 1995; 12: 61-67

2. Pietinalho A, Ohmichi M, Hiraga Y, Löfroos A-B, Selroos O: The mode of presentation of sarcoidosis in Finland and Hokkaido, Japan. A comparative analysis of 571 Finnish and 686 Japanese patients. Sarcoidosis Vasc Diff Lung Dis 1996; 13: 159-166

3. Pietinalho A, Ohmichi M, Hiraga Y, Löfroos A-B, Selroos M: The prognosis of pulmonary sarcoidosis in Finland and Hokkaido, Japan. A comparative five-year study of biopsy-proven cases. Sarcoidosis Vasc Diff Lung Dis; 1999 (In Press)

4. Pietianlho A, Ohmichi M, Hirasawa M, Hiraga Y, Löfroos A-B, Selroos O: Familial sarcoidosis in Finland and Hokkaido, Japan. A comparative study. Respiratory Medicine 1999; 93: 408-412

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6. Pietinalho A, Furuya K, Yamaguchi E, Kawakami Y, Selroos O: The angiotensin-converting enzyme DD gene is associated with poor prognosis in Finnish sarcoidosis patients. Eur Respir J. 1999; 13: 723-726

LIST OF ABBREVIATIONS IN ALPHABETICAL ORDER

S-ACE:	Serum angiotensin-converting enzyme level
S-Afos:	Serum alkaline phosphatase level
BHL:	Bilateral hilar lymphadenopathy
S-Ca:	Serum calcium level
U-Ca:	Urinary calcium level
DLco:	Diffusing capacity for carbon monoxide
EN:	Erythema nodosum
ESR:	Erythrocyte sedimentation rate
FEV1:	Forced expiratory volume in one second
FVC:	Forced vital capacity
B-Hb:	Blood haemoglobin level
HLA:	Human leukocyte antigen
HLA-Cw*:	Human leukocyte antigen-Cw (DNA determined by PCR)
B-leuk:	Blood leukocyte count
S-LZM:	Serum lysozyme level
PCR:	Polymerase chain reaction

Chest radiographs:

Stage I:	Bilateral hilar lymphadenopathy
Stage II:	Parenchymal shadows and bilateral hilar lymphadenopathy in chest
Stage III:	Parenchymal shadows alone
Stage IV:	Fibrotic changes

1. INTRODUCTION

Sarcoidosis is a multi-organ granulomatous disease the cause of which is unknown, most often affecting the lungs, eyes, skin and peripheral lymph nodes. Sarcoidosis is most prevalent in young and middle-aged individuals with a slight female predominance (1). The mode of presentation, clinical picture and course of sarcoidosis vary considerably (2). Sarcoidosis is most often a benign disease from which recovering is slow. Fifty percent of patients with initial stage-I changes in their chest radiographs (bilateral hilar lymphadenopathy) have normal radiographs within two years. Patients with stage-II to stage-III changes (parenchymal infiltrates with or without bilateral hilar lymphadenopathy) need longer times before radiographs become normal. Corticosteroids have been found beneficial to control symptoms and improve the rate of clearance of radiographic changes. Whether the long-term prognosis in sarcoidosis is affected by current treatment is however a matter of debate (3, 4). International guidelines relating to management and treatment strategies with which all physicians might be satisfied have been lacking. However, a very new statement has just been made by three organisations [American Thoracic Society (ATS), European Respiratory Society (ERS) and World organisation of Sarcoidosis and Other Granulomatous Diseases (WASOG)] to quide physicians in makeing diagnosis and in treating patients with sarcoidosis (5).

Epidemiological studies may aid understanding of causes of sarcoidosis. Great variations have been observed between ethnic groups in relation to susceptibility to development of sarcoidosis, and in relation to the clinical picture of and outcome in the disease (1, 4, 6). Sarcoidosis is commonest in northern Europe and the USA. There is an impression that it is rare in Chinese, inhabitants of south-east Asia, black Africans in tropical zones, and north American Indians (7a).

It has been reported, that there are differences in prevalences, clinical pictures and outcomes relating to sarcoidosis between Finland and Hokkaido, Japan (8, 9, 10, 11, 12) despite similarities between these areas.

Finland is a northern European country, Hokkaido a northerly island of Japan. Both areas have four-season climates, with cold winters and cool summers (13). Population numbers are similar, at about 5 million. Frequencies of occurrence of tuberculosis are similar. In 1983, the incidence of tuberculosis in Finland was 39.2 per 100,000 inhabitants, in Hokkaido 34.5 per 100,000. Having regard to the reported differences and known similarities, it was felt, that comparison of sarcoidosis in the two areas would be of interest.

2. REVIEW OF LITERATURE

2.1. Incidence and prevalence of sarcoidosis

2.1.1. Worldwide incidence and prevalence of sarcoidosis

Sarcoidosis occurs throughout the world but is most prevalent in northern Europe and the USA (1,14). Sarcoidosis very often affects the intrathoracic organs. More than 90% of sarcoidosis patients exhibit intrathoracic lesions at some stage of the disease (7b, 14). Health-screening surveys intended to detect tuberculosis, are one of the most useful sources of data for epidemiological studies on sarcoidosis. Reported prevalences have varied largely depending on how frequently screening surveys have been carried out but also because of differences in diagnostic criteria in various countries. Hospital records also provide useful information about numbers of patients having the diagnosis of sarcoidosis.

In most studies a slightly higher overall incidence of sarcoidosis has been found in women than in men. Highest age-adjusted incidences in both sexes have been found in the age group 20-40 years (1, 3, 6). A slight peak in incidence has also been seen in middle-aged women (3, 6). However, in India male predominance, with the highest incidence in patients more than 40 years of age, has been found (15, 16).

In almost all studies on sarcoidosis only a few cases below age 15 years have been reported. Siltzbach and Greenberg surveyed 1,050 sarcoidosis cases and found 18 (1.7%) below age 15 years, of which only five were below age nine years (17). In the Nordic countries only 4% of sarcoidosis patients have been 19 or fewer years of age (18). Differences in incidences and prevalences of sarcoidosis between different races and areas have been reported. Afro-Americans have been found to be most susceptible to the disease (1, 19). Some studies on the incidence and prevalence of sarcoidosis throughout the world are listed in Table I.

Table I:
Examples of epidemiological studies on sarcoidosis.

Author(s)	**Ref.**	**Publication year**	**Population surveyed, number of sarcoidosis cases**	**Epidemiological features**
James	14	1992	Worldwide, 3676	≥50% of patients were ≤40 years of age
Hillerdal et al.	3	1984	Swedish, 505	A peak in prevalence in relation to women in middleage and older
Hosoda	6	1988	World wide, 4487	As above
Gupta et al.	15	1985	Indian, 90	Male predominance, patients more than 40 years of age
Gupta & Gupta	16	1990	Indian, 125	As above
Siltzbach & Greenberg	17	1968	American, 1050	Sarcoidosis rare in those younger than 19 years of age
Milman & Selroos	18	1990	Scandinavians, 7683	As above
James	14	1992	Worldwide, 3676	Highest susceptibility in Afro-Americans
Cooch	19	1961	U.S. Army personnel, 462 sarcoidosis cases	As above

2.1.2. Incidence and prevalence of sarcoidosis in Finland

In 1960 Riska and Selroos performed the first epidemiological study in Finland of hospitalized sarcoidosis patients. They analysed data from the Statistical Department of the Finnish Medical Board. Forty-eight verified and 23 suspected sarcoidosis cases were found, giving an estimated prevalence of 1.6 per 100,000 (20). In 1960-1961 Pätiälä et al. surveyed mass-radiographs and esimated the prevalence of sarcoidosis to be 4.6 per 100,000. On surveying mass-radiographs from southern Finland in 1960-1962 they found a prevalence of 5.1 per 100,000 (21). In a six-year study in southern Finland from 1959-1965 Selroos examined incidences, prevalences and the nature of sarcoidosis. He reported an annual incidence ranging from two to 16 per 100,000. The mean prevalence of sarcoidosis during the period was 8.0 per 100,000 (22). The findings reported were similar to reported for Denmark and Sweden (18). Selroos then studied sarcoidosis in 12 areas in Finland in which the epidemiological situations with regard to tuberculosis differed. He reported the average annual incidence to be 5.3 and the prevalence to be 7.5 per 100,000. No correlation with prevalence of tuberculosis was demonstrated (8). Elo conducted an epidemiological study of sarcoidosis in south-western Finland from 1965-1977. It involved 356 sarcoidosis cases detected by mass-radiographic surveys and clinical examinations, of which 286 were biopsy-proven. Reported incidences and prevalences were the highest ever seen in Finland: an average annual incidence of 17.6 and prevalence of 102 per 100,000 (9). The most recent epidemiological study in Finland was related to 1971-1980. It was based on 354, of which 95% were histologically verified cases in northern Finland giving an average annual incidence of 14.2 in men, 15.3 per 100,000 in women (10).

Finnish sarcoidosis incidences by age and sex have been found to exhibit a peak in the age group 30-39 years, especially in women, with another peak in the age group 50-59 years (20, 22). However, in a later study the highest incidence in women was in the age group 40-49 years (8). The incidence in men has consistently been highest in age group 20-39 years (8, 9, 10). The above-mentioned epidemiological Finnish studies are listed in Table II.

TableII:
Epidemiological studies on sarcoidosis in Finland up to 1984

Author(s)	Ref.	Year(s)	Study population and area	Type of study	Prevalence per 100,000	Incidence per 100,000
Riska & Selroos	20	1960	Hospital patients in Finland	Hospital survey	1.6	
Riska & Selroos	20	1960-1962	Southern and south-western Finland; 210.000 inhabitants	Mass X-ray	5.1	
Pätiälä et al.	21	1960-1961	All Finland; 1,450,000 X-rays; 4,477,000 inhabitants	Mass X-ray	4.6	
Selroos	22	1959-1965	Southern and south-western Finland; 357,180 inhabitants 15 years of age or over	Mass X-ray	8.1 (2.5-18.3)	7.6 (1.9-16.1)
Selroos	8	1962-1967	12 tuberculosis districts with different incidences and prevalences of tuberculosis; 1,530,000 X-rays	Mass X-ray (confirmed cases)	7.5	
Elo	9	1965-1977	South-western Finland; 999,900 X-rays; 378,300 inhabitants	Hospital series 1965-1977 and mass X-ray 1974-1977	102 (25-152)	17.6 (14.4-21.2)
Poukkula et al.	10	1970-1981	Northern Ostrobothnia; 300,000 inhabitants 15 years of age or over	Two hospital series; 95% with histological confirmation		15

2.1.3. Incidence and prevalence of sarcoidosis in Hokkaido

In Japan nationwide sarcoidosis surveys have been conducted every third to sixth year since 1959 (1, 23, 24). Sources for surveys have been hospitals with 150-200 or more beds. Findings have been based on mass-radiographic surveys and hospital records. Reported incidences from the outset to 1984 gradually increased beginning with an overall incidence of 0.1 but rising to 1.2 in men and 1.4 in women per 100,000 in 1984. Similar increases in prevalences have been seen. In the 1963 and 1968 surveys overall prevalences were 1.2 and 3.9 per 100,000, respectively. In the 1972 and 1984 surveys the prevalences in men were 3.0 and 3.8 per 100,000, in women 3.3 and 5.6 per 100,000, respectively.

In Japan, sarcoidosis has been commoner in northern and eastern regions than in southern and western parts. In 1974 Hosoda presented figures from three sources: Ministry of Health and Welfare surveys from 1960-1961, 1964 and 1970, The Ten-Year Study (1961-1970) of the Japanese National Railways Sarcoidosis Study Team, and The Joint Study Teams' annual mass-radiographic surveys of school cildren. Highest incidence rates were found in Hokkaido (4.8 per 100,000) and Tohoku (3.1 per 100,000). In other parts of Japan the incidenceses ranged from 0.5 to 1.6 per 100,000. (25). In 1974 Hiraga et al. reported separately on the Ten-Year Study (1961-1970), which was based on mass-radiographic surveys and clinical examinations of Japanese railway workers. Sixty-six sarcoidosis cases were found, of which only five were women. Highest incidences were in Hokkaido (10.5 per 100,000), Tohoku (6.2 per 100,000) and Kanto (6.6 per 100,000) in personnel of 29 or fewer years of age. In other regions of Japan incidences ranged fom 1.2 to 5.6 per 100,000. In personnel of 30 or more years of age incidence in Japan varied from 1.2 to zero. Incidence was 1.0 per 100,000 in Hokkaido (26). In 1977 Hiraga reported on an outbreak of sarcoidosis in Furano, Hokkaido. The prevalence of sarcoidosis was 140 per 100,000 inhabitants (27). On the basis of six nationwide Japanese sarcoidosis surveys, Yanagawa et al. reported on regional differences in prevalences. Northern Japan, Hokkaido, and Akita and Miyagi had prevalences of more than twice the average prevalence for Japan (28). In the first nationwide survey a male predominance (1.2:1) was found, with peak incidence in the age group 20-29 years (29). In subsequent nationwide surveys age-adjusted incidences were highest around age 20 for both sexes. Incidences in women peaked around ages 40 and 50 years, but there were only slight peaks in men of the same ages (28). Japanese epidemiological studies on sarcoidosis are listed in Table III.

TableIII:
Epidemiological sarcoidosis studies in Japan up to 1984 with special reference to Hokkaido. Non-age-adjusted incidences and prevalences shown.

Nation-wide study no.	Ref.	Year(s)	Study population and area	Type of study	Prevalence per 100,000	Incidence per 100,000	New cases in Hokkiado
I	24	1959	Large hospitals	Mass X-ray and hospital examinations		0.1	13
II	24	1961	Hospitals with 159 or more beds, TB sanatoria and health centres	As above			
III	24	1962-1964	As above	As above		0.4	63
IV	24	1965-1969	As above	As above		0.4	117
V	23, 24	1972	As above	As above	1.4(0.2-5.3) 3.0[a], 3.3[c]	0.9 1.2[b], 1.4[d]	
VI	24	1973-1977	As above	As above		0.9	
VII	12	1984	As above	As above	3.8[a], 5.6[c]	1.2[b], 1.4[d]	288

a= estimated prevalence for men in Japan overall, c= for women;
b= estimated incidence for men in Japan overall, d= for women.

2.2. Clinical picture of sarcoidosis

2.2.1. Worldwide clinical picture of sarcoidosis

Since Hutchinson (1869) described the skin disease, later called sarcoidosis, a vast number of papers on symptoms and findings have been published. In the 1980s more than 600 papers were published on pulmonary sarcoidosis alone. Almost every organ in the human body has shown to be a possible target. According to a worldwide review of 3676 sarcoidosis patients the commonest target organ was the lung. On average, 51% of patients had stage-I lesion, 41% had stage-II or stage-III lesions. Of extrathoracic findings, peripheral lymphadenopathy was present in 22% of cases [range 0.3 (Naples) to 37% (New York)]. Erythema nodosum (EN) was found in 17% of cases [range 4% (Tokyo) to 33% (Edinburgh)]. The third commonest extrathoracic finding was ocular sarcoidosis [15%, range 0% (Naples) to 33% (Tokyo)]. All other extrathoracic findings occurred in fewer than 10% of cases (14).

The clinical picture in sarcoidosis varies from absence of symptoms to several severe symptoms (2, 6, 7c). In numerous reports as many as half of the patients have initially been asymptomatic (3, 18). The most commonly reported symptoms have been respiratory (30). More than 90% of sarcoidosis patients exhibited lung changes at some time point (7b, 7d, 30).

Racial differences have been found to influence the clinical picture in sarcoidosis considerably. In a study relating to the Nordic countries, covering 30 years, a typical picture on presentation was acute sarcoidosis with BHL and EN, often combined with arthralgy (18). Similar findings have been reported from London (31). In Afro-Americans sarcoidosis has been found to be more serious often involving extensive pulmonary fibrosis, and extrathoracic lesions affecting the skin, heart, brain and kidney (31, 32, 33). Many patients with sarcoidosis (over 50% in some cases) are tuberculin-skin-test negative (34, 35, 36).

2.2.2. Clinical picture of sarcoidosis in Finland

Almost 50% of Finnish sarcoidosis patients were asymptomatic on presentatíon and were identified via mass-radiographic surveys (8, 9). In symptomatic patients cough is the commonest symptom, in 25-29% of cases (8, 10). Acute sarcoidosis with EN is the typical clinical picture in all

Nordic countries. In Finnish series the percentage of EN has ranged from 18 to 39 (8, 9, 10).

Almost all Finnish sarcoidosis patients exhibit pulmonary findings at some time. In 1964 Riska and Selroos reported pulmonary lesions in 69 of 71 verified sarcoidosis patients (15). In other series all of the 140 (8) and 356 patients (9) exhibited chest radiographic changes. Poukkula et al. reported that 15 of 354 sarcoidosis patients had a normal chest radiographs (10).

Radiographic stage-I, stage-II and stage-III findings have been reported in 55, 39 and 6% of cases (8), 25, 72 and 3% of cases (9) and 62, 34 and 3% of cases (10), respectively. Stage-I changes have therefore been the commonest chest-radiography finding in two of the three largest Finnish epidemiological studies on sarcoidosis.

The commonest extrathoracic findings have been changes in peripheral lymph nodes, in 3-29% of cases (8, 9, 10), eyes, in 4-28% of cases (8, 9, 10, 37), and skin, in 2-6% of cases (8, 9, 10).

More than half of Finnish sarcoidosis patients have had positive tuberculin-skin-test results. Selroos reported positive skin-test results in 52% of patients, to 1 or 10 TU (tuberculin units) PPD (purified protein derivative) and Elo in 59% of patients to 1, 10 or 100 TU PPD. Test results were more often positive in patients with BHL than in patients with parenchymal lesions (8, 9). A lower incidence of tuberculin-skin-test positivity was reported by Poukkula et al. Of 332 tuberculin-tested patients only 25% reacted positively to 1 TU PPD. The test was not continued using higher concentrations. Poukkula et al. showed, however, that test results were positive as often in patients who had undergone BCG vaccinations as in those who had not (10).

2.2.3. Clinical picture of sarcoidosis in Hokkaido

Data from six nationwide Japanese sarcoidosis surveys reveals that half of the patients were initially symptom-free. Asymptomatic patients were commoner in younger than in older age groups. Photophobia was the commonest symptom, in more than 20% of cases. Cough was the second commonest symptom (4%). BHL was twice as common as parenchymal shadows (28).

In the two nationwide surveys of sarcoidosis in 1972 and 1984, patients were divided in to two groups, annually patients in prevalence and incidence studies. In both surveys and both groups BHL was present in about 90% of

the patients. In prevalence patients the percentage of cases with parenchymal lesions increased from 38 to 43, with eye lesions from 31 to 44% from 1972 to 1986 (12). Sarcoidosis patients in Furano, Hokkaido, exhibited BHL in 95% of cases. Fifty-three per cent exhibited some type of extrathoracic lesion. One third had eye lesions (27).

In the first Japanese nationwide survey, of 94 patients, it was found that in addition to pulmonary changes patients had also exhibited extrathoracic manifestations such as lesions of peripheral lymph nodes, eyes and skin. However, no EN was seen. Sixty-eight of 84 patients (81%) were tuberculin-negative (29). On continuing the study one case of EN was found (38).

Among extrathoracic findings, eye lesions were the commonest but skin lesions were also often seen. Hosoda (1974) reported eye lesions in 36% of men and 46% of women, and skin lesions in 19% of men and 9% of women. Changes in chest radiographs were commonest in young patients. Eye and skin lesions were commonest in older age groups (28).

2.3. Outcome in sarcoidosis

2.3.1. Worldwide outcome in sarcoidosis

Many studies have been performed with the aim of identifying prognostic factors in sarcoidosis. Several factors associated with poor outcome have been reported, e.g. silent insidious onset (40) initial respiratory symptoms (41), pulmonary fibrosis, large skin infiltrations, lupus pernio, bone cysts, upper respiratory-tract changes, chronic uveitis, keratoconjunctivitis sicca, advanced age, black race (7e, 42, 43, 44), persistent lymphocytosis and high initial IgG content of BAL fluid (45). The only factors associated with good outcome have been acute onset of sarcoidosis together with BHL and EN, and preserved-tuberculin-skin-test positivity (34, 40, 42, 46).

Eighty to 94% of patients initially exhibiting EN have been shown to experience complete remission (18, 42, 47). Highest remission rates have been reported for patient groups with EN with BHL. In 1990 Milman and Selroos reviewed Nordic sarcoidosis studies and showed on basis of combined data from Danish, Finnish and Swedish studies that 88% of patients with acute onset of sarcoidosis together with EN and BHL experienced complete remission of disease within two years (40).

Over-all clear-up rates for the sarcoidosis population overall have varied. In a survey of 3676 sarcoidosis patients worldwide (14) 65% had normal

chest radiographs during follow-up, in the Nordic survey (40) 74% of cases had normal chest radiographs during follow-up. On grouping patients according to initial chest-radiographyc findings, patients with stage-I and stage-II changes were found to have more favourable outcomes than those with stage-III changes. In a 10-year Swedish follow-up study, after a 5-year observation period 82% of patients with initial stage-I changes presented a normal picture, and 68% of stage-II patients but only 33% of stage-III patients (3). For combined data for Nordic countries the corresponding clear-up percentages were 82% (stage-I), 66% (stage-II) and 30% (stage-III) (40). In contrary, Afro-Americans and Indians had less favourable outcomes even when BHL was found on presentation (16, 32, 48, 49).

Age has been found to be of importance in relation to outcome in sarcoidosis. On presentation, about one third of sarcoidosis patients were more than 40 years of age. Such sarcoidosis patients had, even on presentation, more symptoms and more severe extrathoracic changes than younger patients. Treatment with glucocorticosteroids was more often necessary and clinical course worse than in younger patients (2, 3, 50).

In a study of 194 sarcoidosis patients (including nine Afro-Americans) in the Mayo Clinic, the 10-year survival rate for sarcoidosis patients was 80%. The survival rate for the basic population was 91% (51). In a study of 184 Afro-American sarcoidosis patients the survival rate was 85%. In the basic population it was 95% (52). In the Nordic countries patients with initial stage-I changes had approximately the same mortality rate as the basic population but patients with stage-II to stage-IV changes had a mortality rate of 5.9%, three times that expected (40). In a Danish survey, extrapulmonary lesions did not increase the mortality rate in sarcoidosis patients but initial respiratory symptoms and a decreased FEV1 did (53). Epidemiological studies of the effects of initial chest-radiography findings on outcome in sarcoidosis and relating to some other topics are listed in Table IV.

Table IV:
Epidemiological studies on sarcoidosis worldwide and some aspects relating to outcome.

Author(s)	Ref.	Publication year	Population surveyed	Outcome aspects
James et al.	14	1976	3676 persons world-wide	Overall normalization rate for chest X-rays during 5-year follow-up 65%
Milman & Selroos	40	1990	5310 Scandinavians	Normalization rate 74%
Hillerdal et al.	3	1984	505 Swedes	Normalization rate on chest radiographs during 5-year follow-up: Stage I: 82%/ II: 65%/ III:33%
Milman & Selroos	40	1990	5310 Scandinavians	Normalization rates: Stage I: 82%/ II: 66%/ III: 30%
Sones & Israel	48	1961	211 Americans	Afro-Americans and Indians had less favourable outcomes, even with initial stage-I sarcoidosis
Israel & Washburne	32	1980	322 Americans	As above
Gupta	49	1988	State-of-the-art lecture	As above
Gupta & Gupta	16	1990	125 Indians	As above
Mayock et al.	2	1963	145 Americans	Patients 40 or more years of age had worse clinical courses outcomes than younger patients
Hillerdal et al.	3	1984	505 Swedes	As above
Margolis & Israel	50	1983	12 Americans	As above
Milman & Selroos	40	1990	5310 Scandinavians	Stage-II and stage-III patients had high mortality rates
Carr & Gage	51	1954	149 Americans	Survival rates were lower in sarcoidosis population than in the basic population (80% versus 91%)
Sones & Israel	52	1960	184 Afro-Americans	Survival rates were lower in sarcoidosis population than in the basic population (85% versus 95%)

2.3.2. Outcome in sarcoidosis in Finland

In Finland, outcome in sarcoidosis has been investigated in several studies (8, 9, 10, 54, 55).

Hannuksela et al. observed 135 sarcoidosis patients with acute untreated disease. They found outcome to be very good in patients with initial BHL and EN. The resolution rate during 2 years of follow-up was 93%. In patients with EN and stage-II changes it was 63%. In patients with stage-I to stage-II changes but no EN it was 73% (54).

In an earlier study Hannuksela et al. had found an association between positive tuberculin-skin-test results, acute onset of sarcoidosis with EN, and rapid resolution of the disease (46). In a study of 140 sarcoidosis patients followed up for five years outcome was good in patients with initial EN and stage-I or stage-II radiographic changes. Patients with extrathoracic lesions experienced slightly worse courses of disease. Eight patients had stage-III changes in their chest radiographs. One of these patients died. Two experienceded slight improvement in lung- function test results. The others appeared to have irreversible pulmonary lesions (8).

Four of 356 sarcoidosis patients died during the period of observation. The overall mortality rate was 1.5%, however, in the group with initial stage-III changes the mortality rate was 25% (9).

In 571 sarcoidosis patients who included 37 patients of more than 65 years of age, the improvement rate in the elderly during five years of follow-up was lower than in younger patients but the difference was not statistically significant (55).

2.3.3. Outcome in sarcoidosis in Hokkaido

Several surveys have been performed in Japan in relation to the course of and outcome in sarcoidosis (56, 57, 58, 59).

Yamamoto et al. followed up 775 sarcoidosis patients following them for at least 3 years to asses whether there was a relationship between the clinical picture on presentation and outcome. The most favourable prognostic factors were age under 29 years, absence of subjective symptoms, absence of lung, eye and skin lesions, and normal serum gamma-globulin levels. A combination of age under 29 years and absence of eye lesions was the most favourable situation, seen in 260 patients. All sarcoidosis lesions disappeared within two years in 70% of these patients (56).

Izumi reported on 61 of 153 sarcoidosis patients from Kyoto observed from 1981-1985. Fifty per cent of patients had eye symptoms, 13% respiratory

symptoms. Sixty-four percent of patients had stage-I changes in their chest radiographs, 20% stage-II and 15% stage-III. The poorest outcome was seen in patients with symptoms and stage-III lesions in their chest radiographs or extrathoracic lesions on presentation with the disease (58).

Nagai et al. examined clinical profiles on presentation in 337 patients with pulmonary sarcoidosis followed up for more than 10 years. Advanced age, symptoms on presentation, parenchymal shadows and corticosteroid treatment were associated with less favourable outcomes. (59).

2.4. Familial sarcoidosis

2.4.1. Familial sarcoidosis throughout the world

Martenstein was the first to suggest the possibility of a hereditary factor in sarcoidosis (60). Since then, some 500 cases of sarcoidosis with familial connections have been reported. The prevalence of familial sarcoidosis has varied in studies from 1.7% to 14% (61, 62). In most studies sibling-sibling and parent-offspring relationships have been most prevalent (61, 63, 64).

Jörgensen surveyed 2471 patients and found 40 close relatives with the same disease, indicating a hereditary background (62). A report on outbreak of sarcoidosis in the Isle of Man shows that inheritance may have played a role (65).

Wiman, in Sweden, surveyed 299 sarcoidosis patients, including 20 familial cases. The prevalence of familial sarcoidosis was 6.9%. He concluded that genetic drift may be of importance (66).

Sharma et al. surveyed 687 patients with sarcoidosis in Los Angeles and London. The series included Caucasians, Afro-Americans and Caribbeans. They found 16 families in which there were two or more sarcoidosis cases (33 cases in all) and noted that certain ethnic groups were more prevalent (especially Afro-Americans) but that genetic susceptibility also played a role (67).

2.4.2. Familial sarcoidosis in Finland

In Finland there have been only a few studies on heredity in sarcoidosis. Elo (9) and Poukkula et al. (10) studied sarcoidosis epidemiologically in two areas. The prevalences of familial sarcoidosis in these areas were 3.4% and 6%.

Selroos et al. reported identical twin sisters with clinically almost identical sarcoidosis (stage-II pulmonary changes and hypercalciuria) despite their having lived for many years in different areas of Finland. One had received two courses of corticosteroid treatment. Both twins recovered within similar times (68).

2.4.3. Familial sarcoidosis in Hokkaido

In Japan, Kawabe et al. reported a mother-daughter pair who suffered from sarcoidosis nine years apart. The authors suggested that inhaled agents and genetic factors could have led to the sarcoidosis (69).

Ito et al. surveyed 2700 consecutive patients with sarcoidosis, and found 16 familial cases, giving a prevalence of familial sarcoidosis of 0.6% (70).

In 1977, in Furano, Hokkaido, an outbreak of 33 sarcoidosis cases was reported, giving a very high prevalence of sarcoidosis, for Japan, of 140 per 100,000. Of the 33 cases 29 were in 14 families. Both genetic and environmental factors were suspected to lie behind the high prevalence (27).

In 1992, in a study of 80 familial sarcoidosis cases, a brother-sister relationship was commonest, followed by a parent-child (mainly mother-child) relationship (71).

2.5. Genetics of sarcoidosis

2.5.1. Genetics of sarcoidosis in general

For decades it has been suggested that genetic factors may predispose to sarcoidosis and that such factors may determine the clinical picture of the disease. Mechanisms of inheritance have been discussed. Jörgensen suggested that sarcoidosis could be inherited as a multifactorial trait (62). James et al. investigated nine sarcoidosis families in Great Britain. They felt that the familial distribution of sarcoidosis within the nine families was consistent with autosomal resessive inheritance (61).

Headings reported a series of 80 black patients with sarcoidosis, including 11 families in which there have been two or more sarcoidosis cases. They found support for the idea of a multigenic inheritance mode (64). Maliarik et al. also found support for this idea in a study involving

linkage analysis of major histocompatibility genes in familial sarcoidosis (72).

The human leukocyte antigen (HLA) system has been found important in relation to susceptibility to several other diseases. A number of studies have been made of the relationships between HLA type and sarcoidosis. Differences between ethnic groups have been found. In Germany an association between HLA-DR5 and sarcoidosis has been reported (73), in Turkey an association between HLA-A9 and -B5 and sarcoidosis (74). In black populations associations between sarcoidosis and HLA-B7 (75), between sarcoidosis and HLA-B15 (76) and between sarcoidosis and HLA-Aw30 (77) have been reported. In contrast, Whitsett et al. found no association between HLA type and sarcoidosis in Afro-American patients (78).

In 1990 Lenhart et al. found negative associations between sarcoidosis and HLA-Cw5 and -Cw7, suggesting that these HLA could protect against sarcoidosis (79).

Persson et al. showed an association between HLA-A7 and sarcoidosis patients with negative tuberculin-skin-test results and symptoms (80).

HLA type has been shown to have an association with the clinical picture of and/or outcome in sarcoidosis more often than an association with susceptibility to sarcoidosis.

An association between sarcoidosis arthritis, with or without EN, and HLA-B8/DR3 has been reported by a number of investigators (81, 82, 83, 84, 85). Both HLA-B8 and -DR3 have shown to be associated with a good outcome in sarcoidosis (81, 86). In a Swedish study of 122 Scandinavian sarcoidosis patients, those with the HLA-DR17(3) (previously known as HLA-DR3) phenotype had significantly better outcomes than the others. On the other hand, in patients with the HLA-DR14(6) and -DR15(2) phenotypes there was an association with chronic sarcoidosis (87).

In a study in which two ethnic sarcoidosis groups (British and West Indian) were compared a relatively high incidence of HLA-Cw7 in the British sarcoidosis patients, and a correlation between good outcome and HLA-B8, -Cw7 and -DR3 were found. In contrast, in West Indians a relatively high incidence of HLA-DR7 was found. However, no association between HLA type and clinical manifestations was demonstrable (88). Finco et al. found an association between poor outcome and HLA-DR5, especially in men (89). Studies on HLA and sarcoidosis are listed in Table V.

Table V:
Worldwide studies on sarcoidosis and HLA.

Author(s)	HLA type	Associations with
Akokan et al. (1977)	A1, B5	Susceptibility to sarcoidosis
Al-Arif et al. (1980)	B15	Susceptibility to sarcoidosis
Berlin et al. (1997)	DR17(3) DR14(6), DR15(2)	Good outcome Chronic sarcoidosis
Brewerton et al. (1977)	B8	Arthritis with or without EN
Finco et al. (1991)	DR5	Poor outcome (in men)
Gardner et al. (1984)	Cw7 Cw7, B8, DR3 DR7	Susceptibility to sarcoidosis Good outcome Susceptibility to sarcoidosis
Guyatt et al. (1982)	B8	Arthritis with or without EN
Hedfors & Lindström (1983)	B8	Arthritis with or without EN
Kremer (1986)	DR3	Arthritis with or without EN
Lenhart et al. (1990)	Cw5, Cw7	Protection against sarcoidosis
McIntyre et al. (1977)	B7	Susceptibility to sarcoidosis
Neville et al. (1980)	B8	Arthritis with or without EN
Newill et al. (1983)	Aw30	Susceptibility to sarcoidosis
Nowack & Goebel (1986)	DR5	Susceptibility to sarcoidosis
Persson et al. (1975)	A7	Negative tuberculin skin test
Smith et al. (1981)	B8	Arthritis with or without EN
Whitsett et al. (1983)	-	None

2.5.2. Genetics of sarcoidosis in Finland

A recent report on HLA types in the Finnish population showed that the commonest were A2, A3, B35, B7, DR1, DR2, Cw7 and Cw3. B8 was also fairly common, as in other Nordic countries (90).

Grönhagen-Riska et al. investigated a familiy with sarcoidosis and Crohn's disease and found the haplotypes B8/DR3 in all affected patients (91).

There are no other reports regarding HLA types in Finnish sarcoidosis patients.

2.5.3. Genetics of sarcoidosis in Hokkaido

In the1980s several studies on HLA types in sarcoidosis were published in Japan. In the studies by Kunikane et al. (92) and Abe et al. (93) the commonest HLA types in sarcoidosis populations were DRw52 and DRj5. The presence of HLA-DRj5 was shown to be associated with a poor outcome (93). Ina et al. showed that patients with HLA-DRw52 and-DR5 had earlier onset of sarcoidosis but a better outcome than patients with HLA-DRw8 (94).

Tachibana et al. also found that HLA-DRw52 was common in Japanese sarcoidosis patients but -B8 and -DR3 were rare (95). Ishihara et al. found no significant correlations on analysing HLA-DM polymorphism and allelic variation of the TAP2 gene in relation to susceptibility to sarcoidosis (96, 97).

2.6. Angiotensin-converting enzyme gene polymorphism and sarcoidosis

The angiotensin-converting enzyme (ACE) gene is polymorphic. A non-sense DNA fragment can be present or absent (98). The polymorphism is located in intron 16. ACE itself therefore does not differ in relation to genotype but polymorphism accounts for 47% of total enzyme levels (98). The genotype is divided into three types: insertion homozygotes (II), deletion homozygotes (DD), and heterozygotes (ID). Serum ACE activity has been found to be significantly higher in DD individuals than in II individuals, in healthy control subjects and in patients with sarcoidosis (99-101). No significant difference has been found in allele distribution between controls and sarcoidosis patients (99-101). ACE polymorphism therefore does not predispose to the disease.

There are differences in prevalences of the D and I alleles between ethnic groups (98-102). This may be interesting from a sarcoidosis epidemiological point of view.

2.6.1. Angiotensin-converting enzyme gene polymorphism and sarcoidosis in Finland and Japan

There have been no studies on the ACE gene polymorphism in the Finnish population.

In caucasians, the D allele appears dominant. I/D ratios of 0.41/0.59 (98), 0.45/0.55 (102) and 0.49/0.60 (100) have been reported.

In Japanese individuals, the I allele is dominant: I/D ratios of 0.67/0.33 in control subjects and 0.61/0.39 in sarcoidosis patients have been reported by Furya et al. (101), and 0.65/0.35 in controls and 0.62/0.38 in sarcoidosis patients by Tomita et al. (99). There are also some indications that Japanese sarcoidosis patients with the ACE DD genotype have a more prolonged disease than patients with other genotypes (99).

3. AIMS OF STUDY

Literature reports indicate that incidences and prevalences, clinical pictures of and outcomes in sarcoidosis differ between Finland and Japan. The overall aim of the study was to investigate sarcoidosis in two well-defined populations of similar sizes living in similar climatological enviroments (the Mjölbolsta Hospital cathment area in southern Finland, and Hokkaido, a northerly island of Japan), in which, in addition, incidences and prevalences of tuberculosis were similar during the study period, to determine whether reported differences were real or could be explained by differences in classification, terminology or diagnostic procedures.

Aim of Study I: To asses whether reported differences in prevalences and incidences of sarcoidosis between Finland and Hokkaido were real.

Aim of Study II: To describe and compare the clinical pictures of sarcoidosis in Finland and Hokkaido.

Aim of Study III: To compare the prognoses in pulmonary sarcoidosis in Finland and Hokkaido.

Aim of Study IV: To determine incidences and prevalences of familial sarcoidosis in Finland and Hokkaido and to analyse types of associations reported.

Aim of Study V: To describe the HLA pattern in Finnish sarcoidosis patients and compare it with the HLA pattern in sarcoidosis patients in Japan.

Aim of Study VI: To determine ACE genotypes in Finnish sarcoidosis patients and to evaluate prognoses in patients with different ACE genotypes.

4. SUBJECTS AND METHODS

4.1. Study populations and designs of studies I-VI

Study I

To calculate incidences and prevalences of sarcoidosis in Finland and Hokkaido, the following procedures were performed: In 1984 a seventh nationwide survey on sarcoidosis in Japan was carried out by the Intractable Disease Research Committee of the Japanese Ministry of Health and Welfare. The survey involved of two stages. In the first, hospitals with 200 or more beds were asked to report numbers of sarcoidosis patients visiting their hospitals in 1984. In the second stage physicians in the hospitals were asked to provide clinical information about individual patients with verified diagnoses of sarcoidosis. Raw data stored by the Japan Sarcoidosis Committee on magnetic tape were made available to the study group.

In Finland, hospitals are requested to report on all patients discharged. Permission was obtained to use official health statistics for 1984 which included a diagnosis of sarcoidosis (1969 WHO codes 135,97 and 135,99) and patients birth dates. All hospitals in which patients with proven sarcoidosis had been seen in 1984 were approached. After obtaining permission, hospital records were evaluated using the Japanese case-report forms as a model. In all, 99.5% of patient records were made available. Both series of patients included both hospitalized and out-patients. However, in 1984 most patients with suspected sarcoidosis were hospitalized for diagnostic purposes.

In Hokkaido, Finnish members of the project team made themselves acquainted with the Japanese classification of and diagnostic criteria for sarcoidosis. The same criteria were then applied and identical information collected in both countries. Diagnosis was to be based on one or other of the following criteria: a) a chest-radiography finding of BHL with or without parenchymal shadows and a histological finding in at least one organ

showing noncaseating epithelioid cell granulomas; b) a histological finding as above in combination clinical symptoms or signs compatible with sarcoidosis, but a normal chest radiograph; c) a chest-radiography finding with BHL, with or without parenchymal shadows and a typical clinical picture; d) symptom-free patients with typical chest-radiography findings exhibiting gradual spontaneous regression during a sufficiently long follow-up period and exclusion of other lung diseases. Similarity of interpretation of chest radiographs in Finland and Japan was carefully checked.

Prevalence was defined as number of cases with active sarcoidosis during 1984, irrespective of year of diagnosis. Incidence was number of new cases diagnosed in 1984.

In relation to Hokkaido series the number of patients was estimated using established methods (103, 104).

Study II

To compare the clinical pictures of sarcoidosis in Finland and Hokkaido two hospital materials were evaluated:

During the period 1955-1987, 571 patients with sarcoidosis were seen at the Mjölbolsta Hospital, Finland. From 1964 to 1988, 686 sarcoidosis patients were admitted to the Sapporo Hospital of the Hokkaido Railway Company. Within their respective areas these two hospitals have been the units to which patients with suspected sarcoidosis have been referred throughout the years concerned.

To facilitate comparison of the two populations, two of the Finnish investigators participated for three months in clinical work in Sapporo. This background allowed patient data to be evaluated identically in Finland and Japan, focusing on diagnostic criteria, symptoms and findings ont diagnosis (thoracic and extrathoracic), and on results of biopsy procedures and laboratory investigations.

The diagnostic criteria used were the same as in the 1984 incidence and prevalence in Finland and Hokkaido.

Acceptability of diagnosis of sarcoidosis: Three hundred and seventy-eight of the 571 Finnish patients (66%) and 293 of the 686 Hokkaido patients (43%) had biopsy-proven diagnoses of sarcoidosis. Diagnosis of sarcoidosis in relation to the other patients was based on clinical picture and chest-radiography findings. Diagnoses of sarcoidosis in Japanese patients with only eye involvement could be accepted if there were also concomitant increase in serum ACE activity and/or lysozyme concentrations. All

Japanese sarcoidosis patients had been routinely checked by an ophthalmologist. Numbers of patients with sarcoidosis defined according to the various diagnostic criteria are shown in Table VI.

Results of tuberculin skin tests were also compared. In Finland titrated PPD skin tests were performed, starting with 1 or 2 TU. If the test was negative, 10 TU were used. In Japan 0.05µg of PPD in a 1:2000 solution (corresponding to 2.5 TU) was the initial concentration used followed by 0.25µg, if necessary (12.5 TU). A 5 x 5 mm induration was considered to represent a positive reaction.

Results of biochemical laboratory tests such as concentrations of serum lysozyme (S-LZM), serum calcium (S-Ca), total serum proteins (S-prot) and serum gamma-globulin (S-γ-glob), and serum ACE and serum alkaline phosphatase (S-Afos) activities were recorded. The peripheral blood picture, including haemoglobin level (B-Hb), leukocyte count (B-leuk), lymphocyte count (B-lymph), thrombocyte count (B-thromb) and erythrocyte sedimentation rates (ESR) were checked. Numbers of values within and outside corresponding reference ranges were noted. Laboratory test results for the two series were transformed to standard units before statistical analysis. Laboratory test methods in the two countries were, however, not compared.

Results of lung-function tests recorded related to forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLco).

Study III

To allow assesment of differences in prognoses in pulmonary sarcoidosis in Finland and Japan, data relative to of 563 Finnish and 579 Hokkaido patients who had been hospitalized because of pulmonary sarcoidosis were carefully re-evaluated. Only 437 Finnish and 457 Japanese patients with initial chest radiographic changes and positive biopsy findings were selected for further review. It should be noted that the patients included in this comparison were not identical with those in studies I and II. Characteristics of these patients are recorded in Table VII. Factors such as age, sex, initial chest-radiographic finding, and presence or absence of extrapulmonary lesions were investigated. Five-year follow-up data were recorded and differences over time between Finnish and Japanese patients were assessed on a yearly basis.

Table VI:
Numbers and percentages of patients according to diagnostic criteria in Finnish and Hokkaido hospital series.

Hospital	HP+ CR+ CP+	HP+ CR- CP+	HP- CR+ CP+	HP- CR- CP+	HP- CRm CP+	Total
Mjölbolsta	374 (65%)	4 (1%)	188 (33%)	5 (1%)	0	571 (100%)
Sapporo	268 (39%)	25 (4%)	277 (40%)	97 (14%)	19 (3%)	686 (100%)

HP= Histopathology, CR= Chest radiograph, CP= Clinical picture, m= missing

Table VII:
Characteristics of Finnish and Japanese patients with biopsy-proven radiographic pulmonary sarcoidosis

	Finland		Hokkaido	
	No. of patients	**Percentage**	**No. of patients**	**Percentage**
iobox.fisaijai Total no. of patients	437	100	457	100
Female	254	58.1	234	51.2
Male	183	41.9	223	48.8
Mean age, years (SD)	41.9 (12.9)		28.4 (13.7)	
Stage I	191	43.7	309	67.6
Stage II	186	42.6	125	27.4
Stage III	58	13.3	23	5.0
Stage IV	2	0.4	0	0
Erythema nodosum	101	23.1	0	0
Extrapulmonary sarcoidosis*	197	45.0	244	53.4
Symptom-free patients	215	49.3	261	57.1

* Excluding patients with erythema nodosum

Study IV

To determine the incidence and prevalence of familial sarcoidosis in Finland and Hokkaido, the 1984 series and the two hospital series from Finland and Hokkaido were used. Relatives having the same disease were identified, and the nature of the relationship noted. Clinical pictures of and outcomes in familial and non-familial cases in the two areas were compared.

Study V

The HLA pattern in Japanese sarcoidosis patients is known (94, 95). To determine the HLA pattern in Finnish sarcoidosis patients we studied 20 consecutive patients (9 men and 11 women) with sarcoidosis in the Mjölbolsta Hospital. Sixteen had positive biopsy findings showing non-caseating granulomas. Diagnosis in the other 4 patients was based on typical clinical pictures (with EN), chest radiography findings and biochemical results (high S-ACE activity and/or high S-LZM concentrations). All patients exhibited changes in their chest radiographs on presentation: nine exhibited stage-I changes, seven stage-II changes and four had stage-III changes. Duration of sarcoidosis at the time of investigation varied from 0.5 to 12 years. Fourteen of the patients were still suffering from active disease.

We used published data relating to 10,000 subjects in the national bone-marrow-donor registry (90) for relating porposes. Both controls and patients were representative of the whole country because of the homogeneity of the Finnish population.

Associations between HLA types and the commonest symptoms (dyspnoea, erythema nodosum), chest-radiographic findings and good or less favourable outcome were also evaluated. For HLA typing 30-ml samples of heparinized peripheral blood were obtained. Mononuclear cells were then isolated using Lymphoprep (Nyegaard and Co A/S, Oslo, Norway) density-gradient centrifugation. HLA class-I and class-II were determined using standard microlymphocytotoxicity methods. The local panel of antisera were complemented with commercial sera from Biotest (Dreieich, Germany) and results confirmed using a panel from the Eleventh International Histocompatibility Workshop. HLA loci A, B, C, DR and DQ were studied. However, because of the small number of patients antigen subtypes were not included in the final analysis. The 50 broad specifities determined were: HLA-A 1, 2, 3, 9, 10, 11, 19, 28; HLA-B 5, 7, 8, 12, 13, 14, 15, 16, 17, 18, 21, 22, 27, 35, 37, 40, 47, w4, w6; HLA-C 1 to 7; HLA-DR 1 to 10 plus 51, 52, 53 and HLA-DQ 1 to 4.

Left-over cells were stored for subsequent DNA extraction. After analysing serological results Cw* alleles were determined using the PCR-SSP method employed at the Twelvfth International Histocompatibility Workshop, with purchased primers (Merck, through Kebo Lab Co, Helsinki) made like those based on and supplied for the Workshop [Bunce & Welsh (105)]. To exclude the possibility of inadequacies in the HLA-typing serological and DNA typing were performed in 88 routinely HLA-typed miscellaneous patients.

Sudy VI

Whole-blood samples were obtained from 59 Finnish sarcoidosis patients and 70 control subjects. The sarcoidosis blood samples were taken from consecutive, known patients (followed up for one to 23 years) visiting the hospital's out-patient department for scheduled visits. The blood samples were stored at -70° C until shipped to Sapporo, Japan, for analysis.

Patient characteristics on diagnosis according to ACE genotype are shown in Table VIII. There were 42 female and 17 male patients. All

Table VIII:
Patient characteristics on diagnosis according to ACE genotype.

	Genotype II	**Genotype ID**	**Genotype DD**	**Total**
Women	7	23	12	42
Men	2	9	6	17
Biopsy +	6	20	15	41
Steroid treatment	5	19	11	35
Pulmonary findings:				
Stage 0	0	1	1	2
Stage I	5	17	5	27
Stage II	2	10	8	20
Stage III	2	4	3	9
Extrapulmonary findings:				
Erythema nodosum	3	4	4	11
Peripheral lymph node	0	7	2	9
Skin	2	6	3	11
Eyes	1	7	2	10
Other*	4	7	6	17
Hypercalcemia	1	3	1	5

* Including spleen, liver, kidney, heart, CNS and parotid gland

exhibited chest radiographic changes. Twenty-seven patients had radiographic stage-I lesions, 20 patients stage-II lesions. Thirty-one patients (53%) had extrapulmonary sarcoidosis manifestations other than EN, which had occurred in 11 patients. Detection of ACE-gene polymorphism: A 287 base-pair I/D polymorphism in intron 16 of the ACE gene was examined using the polymerase chain reaction (PCR), as previously described (101). Briefly, two primers, sense oligo 5‘CTGGAGACCACTCCCATCCTTTCT3‘ and anti-sense oligo 5‘GATGTGGCCATCACATTCGTCAGAT3‘, were synthesized to amplify the polymorphic fragment. Reactions were performed using 10 pmol of each primer in a final volume of 50µl containing 100 ng of genomic DNA, 3 mM $MgCl_2$, 50 mM KCl, 10 mM Tris-HCl, pH 8.4, 0.1 mg/ml gelatin, 0.5 mM of each deoxynucleotide triphosphate (dNTP), 1 unit of Taq polymerase (Perkin Elmer Cetus, Norwalk, USA). The DNA was amplified for 30 cycles as previously described (106). PCR products were subjected to electrophoresis in agarose gels and visualized by the sizes of bands, as previously described (107).

Determination of outcomes in sarcoidosis: Outcomes were evaluated after observation periods of one, 2, 3, 5 and more than five years following diagnosis. Outcome was classified as good if the chest radiograph had become normal within 2 years, no signs of extrapulmonary sarcoidosis were detectable, and biochemical markers of sarcoidosis activity (S-ACE, S-LZM, serum $ß_2$-microglobulin concentrations and S- and U-Ca levels) were normal. Outcome was classified as poor if after 5 years of follow-up infiltrates remained visible on chest -radiography, and impaired lung function (FVC, DLco) and/or active extrapulmonary disease in combination with increased levels of one or more biochemical markers of sarcoidosis activity had been found. The outcome in patients who did not fulfil the above criteria was classed as intermediate. Such patients might have achieved a normal status after 2 to 5 years of follow-up, or infiltrates might have remained visible on chest radiography with borderline signs of disease activity.

4.2. Statistical methods

Study I

Distributions of frequencies and percentages were calculated for all qualitative variables and other variables divided into classes.

Comparison between the Finnish and Hokkaido series with respect to class-divided variables was undertaken using cross-tables and calculating x^2-values. Significances of differences were tested using the x^2 -test. A p value of less than 0.01 was taken to indicate significance. The same methods were used to compare groups of patients with respect to distribution of quantitative and class-divided variables.

Arithmetic means and standard deviations were calculated for quantitative variables. Differences between means were tested using the t-test and analysis of variance. A p value of less than 0.01 was taken to indicate significance. Adjusted incidences and prevalences were calculated taking the Finnish population in 1984 as the standard population.

Adjusted incidences and prevalences for Hokkaido were derived from the age-adjusted Finnish population multiplied by age-adjusted rates in Hokkaido, divided by the total Finnish population.

Study II

Frequency distributions were calculated for all qualitative variables and for other variables divided into classes. In some cases distributions were described using charts. Dependence between variables was assessed by calculating contigency coefficients. The chi-squared test was used to test f or independence between variables, and in comparing groups of patients with respect to qualitative variables.

Quantitative variables were described by calculating the arithmetic means and standard deviations. Distributions of quantitative variables were also described by drawing histograms.

Since reference values were different in the two hospitals, laboratory test results were transformed to facilitate comparison. Laboratory values (expressed in SI units) were standardized relative to individual reference ranges by deducting the low reference limit from the value found. The standardized value is independent of any units. Unit were subsequently restored expressing reference ranges in international units. All statistical comparisons were made using the transformed values, in the case of ESR.

Differences between groups were tested for significance using Student's t-test and one-way analysis of variance. Dependences between quantitative variables were studied and significances tested using the Pearson correlation coefficient. The significance level used in significance testing was 0.01. Distributiosn of symptoms in the various age groups were tested using Spearman's rank-correlation test.

Study III

Frequency distributions were calculated for all qualitative variables and for other variables divided into classes. In some cases distributions were described by means of charts.

Dependence between qualitative variables was studied by preparing contingency tables and computing Pearson contigency coefficients. The chi-squared test was used to test for independence between variables, and comparing groups of patients in respect of qualitative variables.

Quantitative variables were described by calculating the arithmetic means and standard deviations. Distributions of quantitative variables were also studied by means of histograms.

Differences between groups were tested for significance using the t-test and one-way analysis of variance. Dependences between quantitative variables were studied and the significances tested using the Pearson correlation coefficient. Contingency tables and the chi-squared test were used to study how the results of different tests could be used to predict the development of sarcoidosis after diagnosis. A p value less than 0.01 was considered to indicate significance.

Study IV

Familial and non-familial cases in Finland and Hokkaido were compared using the chi-squared test, the Mann-Whitney U-test and Student's t-test.

Study V

The chi-squared test was used in comparing the HLA frequencies between patients and controls; p values were multiplied by 41 (the number of HLA specificities compared) to obtain a corrected p value (p_c).

Fisher's exact test was used to find associations between HLA and clinical parameters. Odds ratios were calculated using the formula RR = ad/bc, where a = number of patients with given HLA antigen, b = number of patients without it, c = number of control subjects with it and d = number of controls without it.

Study VI

Significances of differences in allele and genotype frequencies between control subjects and sarcoidosis patients were tested using chi-squared test. Odds ratios were calculated to estimate relative risk of sarcoidosis, and analyses were carried out using logistic regression models adjusted for sex and/or age.

5. RESULTS

5.1. Incidences and prevalences of sarcoidosis in Finland and Hokkaido, Japan. (Study I)

Incidences and prevalences of sarcoidosis

Evaluation of Finnish statistics for 1984 showed that there were 1378 patients who met the diagnostic criteria for sarcoidosis. Five hundered and fifty-seven had been diagnosed in 1984. Sixty-two per cent of all Finnish patients had had histological verification of their disease. On the basis of these numbers the crude prevalence of sarcoidosis in Finland in 1984 was 28.2 per 100,000 and the annual incidence 11.4 per 100,000. Since all Finnish hospitals with sarcoidosis patients in 1984 were approached and the response rate was almost 100%, the figures given must be very close to the true incidence and prevalence of sarcoidosis in Finland.

In the Hokkaido survey in 1984, 288 patients met the diagnostic criteria for sarcoidosis. Forty-six were diagnosed in 1984. Of the Hokkaido patients, 78.4% (on the basis of 208 patients for whom data was available) had histological evidence of the disease.

The crude prevalence of sarcoidosis in Hokkaido was 5.1 per 100,000 and the annual incidence 0.8 per 100,000. As only hospitals with 200 or more beds had been approached and the response rate was 53.5%, true incidence and prevalence figures had to be estimated. Estimated true prevalence was 7.2 per 100,000 and incidence 2.8 per 100,000.

Age-adjusted prevalences and incidences in Finland and Hokkaido are shown in Fig. 1 and 2. The prevalence and the incidence were significantly higher for Finland.

Age-adjusted prevalences and incidences are shovnn in Table IX. The difference in prevalence as well as in incidence is high between Finland and Hokkaido the age-adjusted figures are similar to the crude figures.

Table IX:
Age-adjusted incidences and prevalences of sarcoidosis in Finland and Hokkaido

		Finland	Hokkaido
Incidence per 100,000	Male	9.0	0.8
	Female	13.8	0.9
	Total	11.5	0.9
Prevalence per 100,000	Male	22.0	4.9
	Female	34.4	7.0
	total	28.4	5.0

Fig. 1:
Age-adjusted prevalences of sarcoidosis in Finland and Hokkaido in 1984.

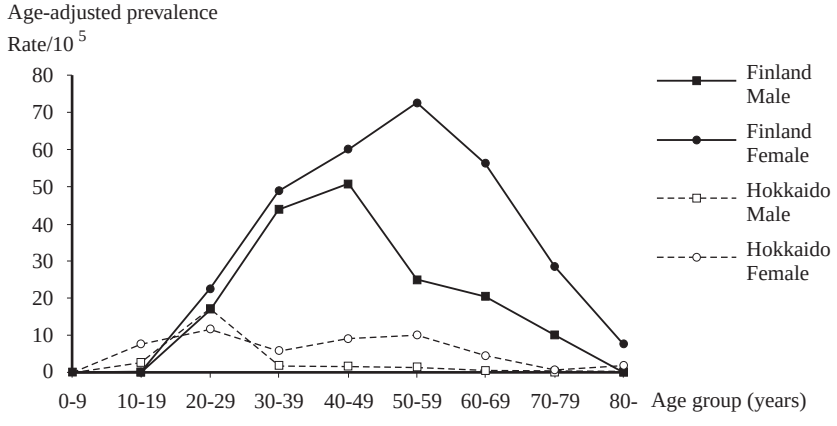
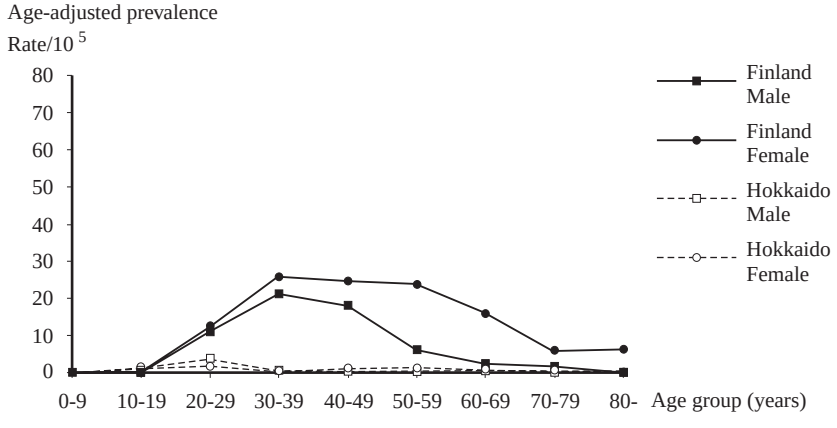


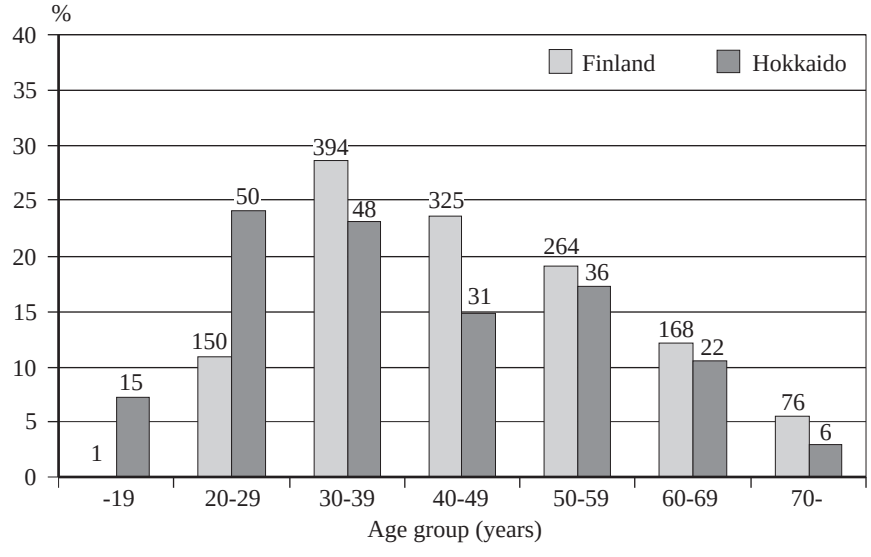
Fig. 2:
Age-adjusted incidences of sarcoidosis in Finland and Hokkaido in 1984.



Sex and age distributions

The number of female patients in the Finnish series was 868 (63%), in Hokkaido 193 (67%). The male/female ratios were therefore similar. The Hokkaido patients were younger at the time of diagnosis. Mean age (SD) was 40.2 (16.1) years as compared with 45.0 (13.7) years for the Finnish patients. This difference is statistically significant ($p < 0.001$). Median ages were 38 and 44 years, respectively. Age distributions are shown in Fig. 3.

Fig. 3:
The age distributions of sarcoidosis patients in Finland and Hokkaido in the 1984 surveys.



5.2. Mode of presentation of sarcoidosis in Finland and Hokkaido (Study II)

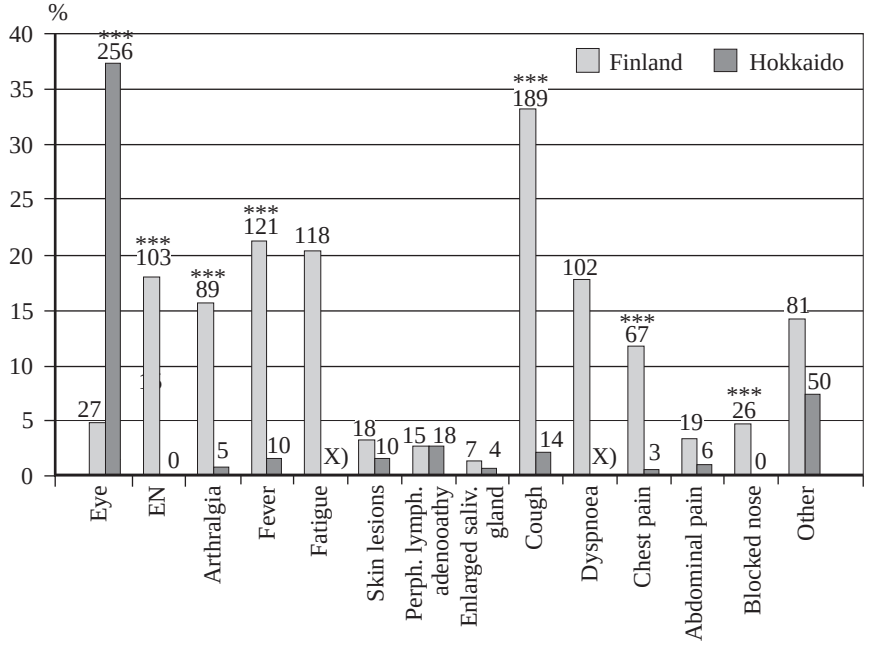
Presenting symptoms

Fifty per cent of Finnish patients and 51% of Hokkaido patients were symptom-free.

In symptomatic patients in Finland the commonestt symptoms were cough [189 patients (21%)], fatigue [118 (21%)], EN [102 (18%)], arthralgia [89 (16%)] and chest pain [67 patients (12%)]. Only 27 (5%) had eye symptoms.

In Hokkaido, the main presenting symptoms were eye symptoms [245 patients (41%)], enlarged peripheral lymph nodes [18 patients (4%)], cough [14 patients (3%)] and fever and skin symptoms [10 patients (2%).] Symptoms leading to a diagnosis of sarcoidosis are recorded in Fig. 4. In Finland, the percentage of symptom-free patients per age group increased significantly with age ($p < 0.001$) The opposite was found in Hokkaido ($p < 0.001$) (Table X).

Fig. 4:
Presenting symptoms of sarcoidosis patients in the Finnish (Mjölbolsta) and Hokkaido (Sapporo) hospital series.



X) Not recorded, *** < 0.001

Table X:
Numbers of sarcoidosis patients in Finnish (A) and Hokkaido (B) hospital series grouped by age and sex, and numbers of symptom-free patients at time of diagnosis.

A:

Age group	Male	Female	Total	Symptom-free patients	Percentage of symptom-free patients
Years	No. (%)	No. (%)	No. (%)	No.	
0 - 9	0 (0)	0 (0)	0 (0)	0	0
10 - 19	1 (0.5)	2 (0.5)	3 (0.5)	2	67
20 - 29	54 (23)	51 (15)	105 (18)	24	23
30 - 39	100 (43)	83 (25)	183 (32)	86	47
40 - 49	48 (20)	80 (24)	128 (22)	80	63
50 - 59	19 (8)	64 (19)	83 (15)	48	58
60 - 69	10 (4)	44 (13)	54 (9)	30	56
70 -	3 (1)	12 (3.5)	15 (2.5)	14	93
Total	235 (100)	336 (100)	571 (100)	284	50

B:

Age group	Male	Female	Total	Symptom-free patients	Percentage of symptom-free patients
Years	No. (%)	No. (%)	No. (%)	No.	
0 - 9	7 (2)	5 (1)	12 (2)	8	67
10 - 19	88 (28)	83 (22)	171 (25)	96	56
20 - 29	149 (48)	104 (28)	253 (37)	121	48
30 - 39	26 (8)	45 (12)	71 (10)	23	32
40 - 49	19 (6)	59 (16)	78 (11)	26	33
50 - 59	13 (4)	51 (14)	64 (9)	16	25
60 - 69	7 (2)	22 (6)	29 (4)	6	21
70 -	1 (0.5)	7 (2)	8 (1)	4	50
Total	310 (100)	376 (100)	686 (100)	300	44

Age and sex distribution and smoking habits

On diagnosis the mean age (SD) of Finnish sarcoidosis patients was 47 (14.5) years as compared with 30 (15.4) years in Hokkaido ($p < 0.001$). There was a female predominance in both series: 59% in Finland, 55% in Hokkaido.

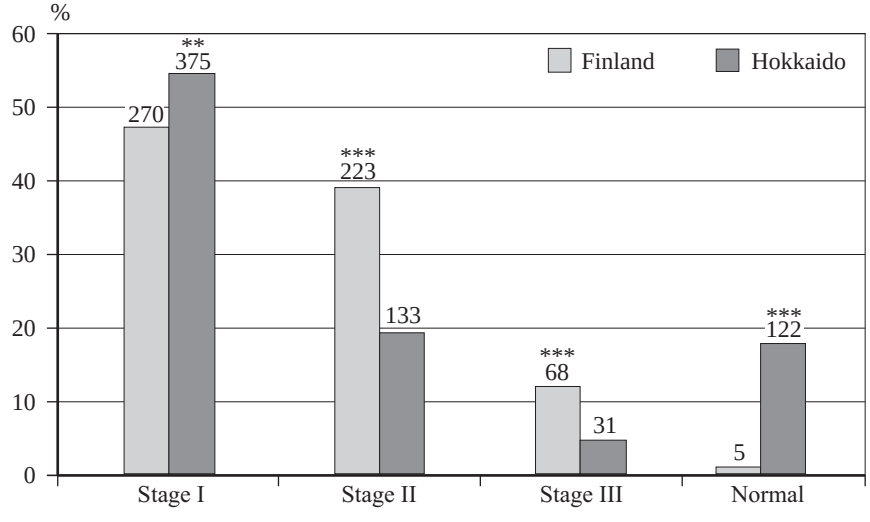
In patients below 40 years of age, there were significantly more men ($p < 0.001$) in both series: 67% of all male patients versus 41% of all female patients in the Finnish series, 86% of all male patients versus 63% of all female patients in Hokkaido.

Twenty-eight per cent of the Japanese patients were smokers as compared with only 16% of the Finnish patients ($p < 0.001$).

Intrathoracic and extrathoracic findings

On diagnosis chest-radiography findings were different in the two series. In the Finnish series, stage-I changes were found in 48% of patients as compared with 57% in the Hokkaido series ($p < 0.01$). Stage-II lesions were seen in 39% of Finnish patients and 20% of Hokkaido patients. Stage-III changes were found in 12% of Finnish patients and 5% of Hokkaido patients ($p < 0.001$). On diagnosis, only 1% of Finnish patients but 19% of Hokkaido patients had normal chest radiographs. The Hokkaido patients had only eye and/or skin lesions on presentation. Distributions of chest-radiography findings are shown in Fig. 5.

Fig. 5: Chest radiographic findings on diagnosis of sarcoidosis in the Finnish (Mjölbolsta) and Hokkaido (Sapporo) series.

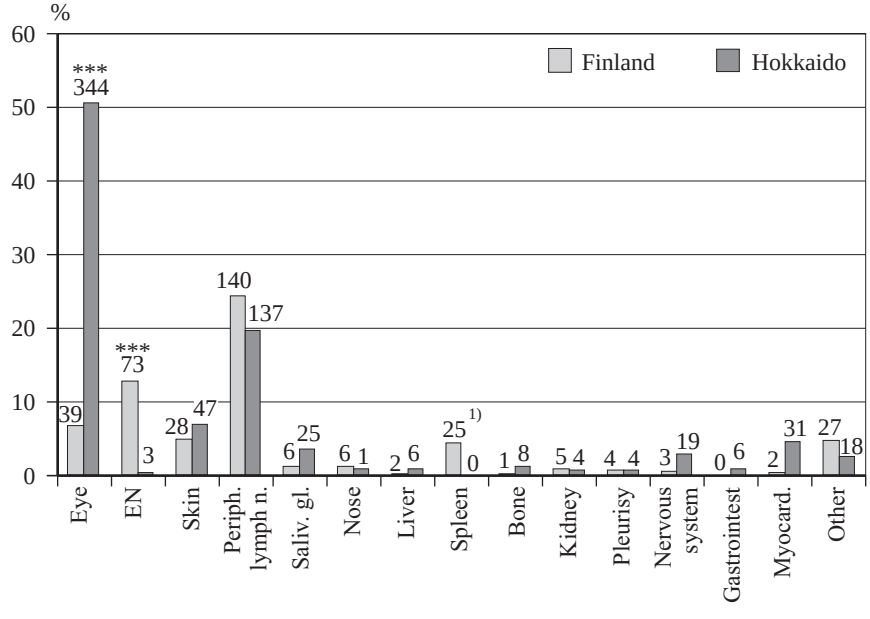


** p < 0.01, *** < 0.001

On diagnosis the commonest extrapulmonary lesions in the Finnish series were peripheral lymphadenopathy [140 patients (25%)], EN [73 patients (13%)], eye lesions [39 patients (7%)] (most often diagnosed by an ophthalmologist), skin lesions [28 patients (5%)] and splenic involvement (fine-needle aspiration biopsy) [25 patients (4%)].

In Hokkaido, the commonest extrapulmonary finding on presentation was an eye lesion, seen in 344 patients (50%). The difference in prevalence of ocular lesions between Finnish and Hokkaidoan patients was significant ($p < 0.001$). The second commonest extrapulmonary lesion in Hokkaido was lesions the of peripheral lymph nodes, in 137 patients (20%), similar to the Finnish figures. The other lesions reported in Hokkaido were skin lesions [47 patients (7%)], myocardial lesions [31 patients (5%)], findings in salivary glands [25 patients (4%)] and in the nervous system [19 patients (3%)]. EN was found in only three patients. The difference in prevalence of EN between the Hokkaidoan and Finnish series was statistically significant ($p < 0.001$). Extrapulmonary findings are summarized in Fig. 6.

Fig. 6: Extrapulmonary findings of sarcoidosis in the Finnish (Mjölbolsta) and Hokkaido (Sapporo) hospital series.



*** $p < 0.001$, [1]) Positive fine-needle aspiration biopsies

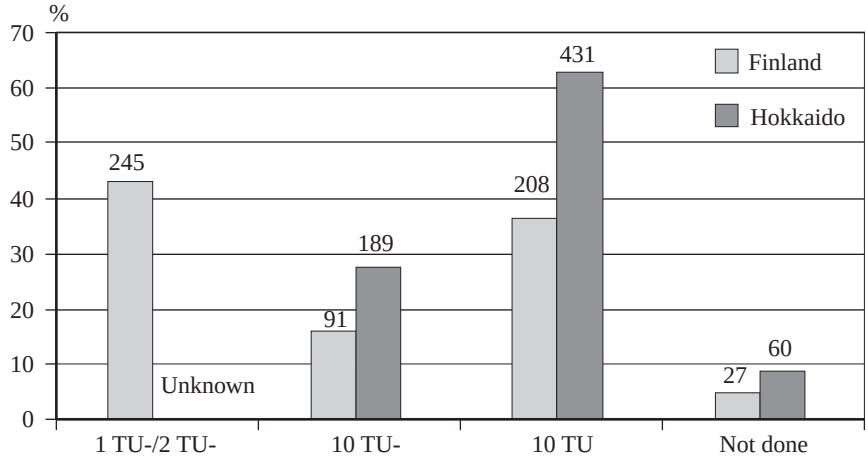
Tuberculin skin test

In Finland 245 patients tested positive for 1 or 2 TU (43%), and 91 patients tested positive for 10 TU (16%). Two hundered and eight patients tested negative for 10 TU (36%). No testing was undertaken in 27 patients.

The Hokkaido patients were divided into skin-test positive (189 patients, 28%) and skin-test negative (431 patients, 63%) depending on their reactivity to 12.5 TU. Sixty-six Hokkaido patients were not tested.

The number of skin-test-negative patients was higher in Hokkaido than in Finland but the difference was not statistically significant. Results of the tuberculin skin tests on diagnosis are summarized in Fig. 7.

Fig. 7: Results of tuberculin skin tests on diagnosis of sarcoidosis in the Finnish (Mjölbolsta) and Hokkaidoan (Sapporo) hospital series.



Lung function and clinical laboratory tests

Forced vital capacities (FVC), forced expiratory volumes in one second (FEV1) and diffusion capacities (DLco) as percentages of predicted normal values (mean, SD) were normal in both series; FVC 98% (16.6%) in Finland and 101.6% (16.8%) in Hokkaido; FEV1 96.0% (18.8%) in Finland and 83.4% (9.1%) in Hokkaido; and DLco 94.4% (16.8%) in Finland and 88.6% (34.0%) in Hokkaido. The difference in FEV1 values between the two series is statistically significant ($p < 0.001$) but the differences in FVC and DLco values between are not. The spirometric reference values have not remained the same over time, in Finland or Hokkaido.

In clinical laboratory test results the following statistically significant differences were found in relation to mean values between the two series: the Finnish mean values for ESR, S-ACE, S-prot and S-Afos were higher than the Hokkaido mean values ($p < 0.0001$ for each). Hokkaido means were higher for S-LZM ($p < 0.0001$) and S-Ca ($p < 0.001$). No statistically significant differences were found in relation to haemoglobin levels and blood leukocyte counts. Thrombocytes were counted in only a few Hokkaido patients.

5.3. Outcome in pulmonary sarcoidosis in Finland and Hokkaido (Study III)

The results of the five-year follow-up study of 437 Finnish and 457 Hokkaido biopsy-proven sarcoidosis cases with pulmonary sarcoidosis are presented in terms of percentages of normalized chest radiographs.

All patients

Percentages of normalized chest radiographs in the two series of patients with biopsy-proven sarcoidosis are shown in Table XI and Fig. 8. Within one year 46% of Japanese patients, but only 16% of Finnish patients had a normal chest radiographs. After five years of follow-up the corresponding figures were 73% and 40%. The differences between the two series are significant at all times ($p < 0.001$).

Fig. 8: Development of chest-radiography findings over 5 years after diagnosis in all Finnish patients (Mjölbolsta Hospital) and Hokkaido patients (Sapporo Tetsudo Hospital).

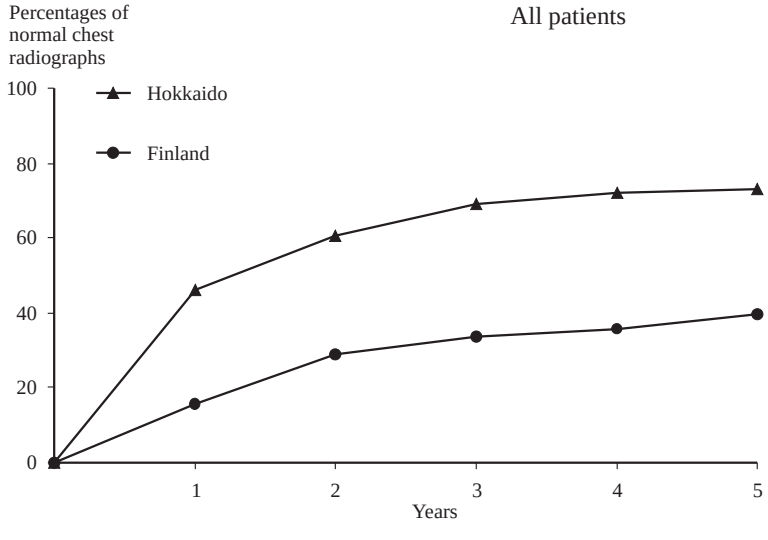


Table XI:
Percentage of patients in Finnish and Hokkaido hospital series experiencing normalization of chest radiographs during five years of follow-up

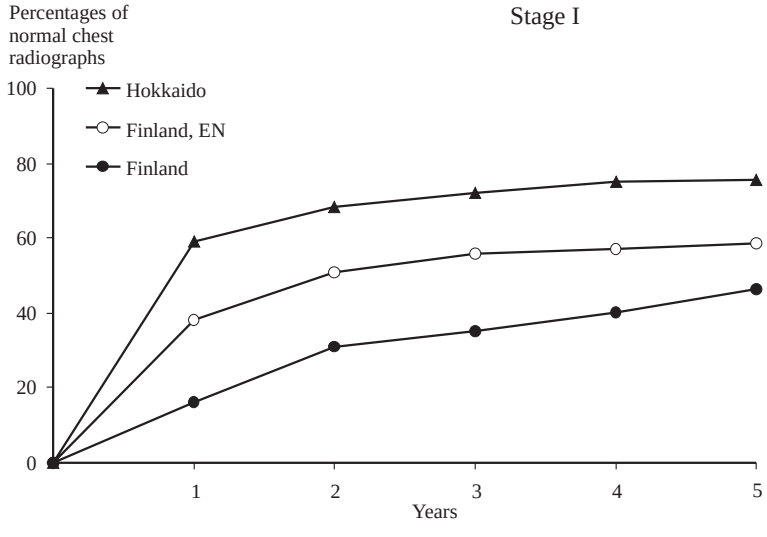
	Follow-up (years)					
	No. of patients	**1**	**2**	**3**	**4**	**5**
All patients						
Finland	437	15.6***	29.1***	33.6***	35.9***	39.6***
Hokkaido	457	46.2	60.6	69.1	72.2	73.1
Female patients						
Finland	254	16.9***	30.3***	35.8***	39.0***	42.1***
Hokkaido	234	44.9	58.1	66.2	70.1	70.9
Male patients						
Finland	183	13.7***	27.3***	30.6***	31.7***	36.1***
Hokkaido	221	47.5	63.2	72.2	74.4	75.3
Age < 30 years						
Finland	91	18.7***	35.2***	39.6***	40.7***	42.9***
Hokkaido	323	51.7	67.8	76.2	79.6	79.9
Symptom-free patients						
Finland	215	11.6***	23.3***	26.5***	27.9***	32.6***
Hokkaido	261	51.5	76.0	73.6	76.6	77.4
Erythema nodosum patients						
Finland	101					
Pulmonary stage I	63	38.1	50.8	55.8	57.1	58.7
Pulmonary stage II	38	18.4	44.7	44.7	47.4	52.6
Hokkaido	0					
Pulmonary stage I						
Finland	191	16.2***	31.0***	35.2***	40.1***	46.5***
Hokkaido	309	59.2	68.3	72.2	75.1	75.7
Pulmonary stage II						
Finland	186	11.8*	25.8***	31.2***	32.3***	35.5***
Hokkaido	125	22.4	48.8	68.0	72.0	72.8
Pulmonary stage III						
Finland	58	12.1	20.7	24.1	24.1	24.1
Hokkaido	23	0	21.7	34.8	34.8	39.1
Extrapulmonary lesions present						
Finland	197	13.7***	25.9***	30.5***	32.0***	34.0***
Hokkaido	244	41.4	53.7	64.8	67.2	68.0

Statistically significant differences between the groups are shown by means of asterisks: *** = $p < 0.001$, * = $p < 0.05$

Patients with initial stage-I radiographic findings

On diagnosis, 142 Finnish patients had stage-I lesions when patients with EN were excluded. After a follow-up of one year 16% of patients had a normal chest radiograph, after five years 47%. In Hokkaido, 309 patients initially had stage-I lesions. After one year of follow-up 59% of the patients had developed a normal chest radiograph, after five year 76%. The differences in chest radiographic normalization rates between the two series are significant ($p < 0.001$) at all times. Normalization of chest radiographs in Finnish and Hokkaido patients with initial stage-I changes during five year of follow-up is shown in Table XI and Fig. 9.

Fig. 9: Percentages of normalized chest radiographs in patients with initial stage-I disease in Finnish and Hokkaido hospital patients, including Finnish patients with EN, during five years of follow-up.

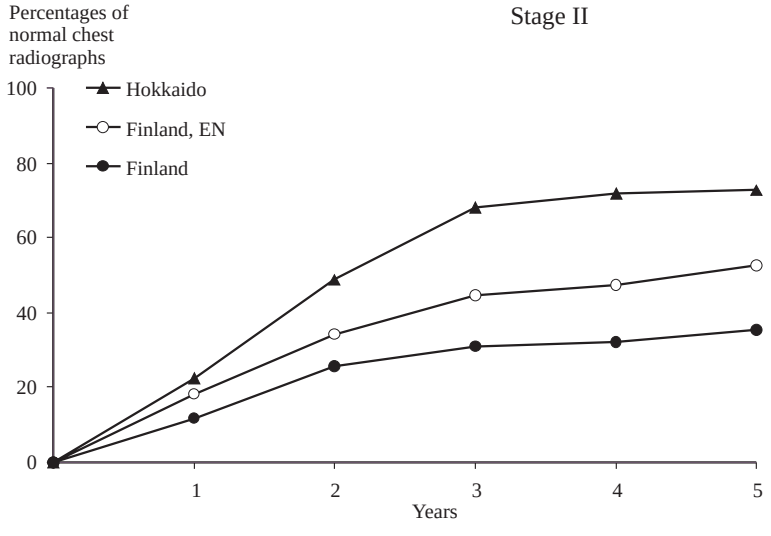


During the 5-year follow-up, 20% of Finnish patients and 14% of Hokkaido patients with initial stage-I findings developed parenchymal changes. Twelve per cent of Finnish stage-I patients and 5% of Hokkaido patients still had parenchymal lesions after five years of follow-up.

Patients with initial stage-II changes

One hundered and eighty-six of the Finnish patients and 125 of the Hokkaido patients had initial stage-II changes in their chest radiographs. After one years of follow-up 12% of Finnish patients and 22% of Hokkaido patients ($p = 0.013$) had normal chest radiography findings, after five years of follow-up, 36% of Finnish patients and 73% of Hokkaido patients had normal chest radiography findings ($p < 0.001$). Reversion to normal chest-radiography findings with time is recorded in Table XI and Fig. 10.

Fig. 10: Percentages of normalized chest radiographs in patients with initial stage-II disease in Finnish and Hokkaido hospital patients, including Finnish patients with EN during five years of follow-up.



Patients with initial stage-III changes

Fifty-eight Finnish and 23 Japanese patients had initial stage-III lesions. Findings in 24% of Finnish patients and 35% of Japanese patients became normal during five years of follow-up. The difference is not statistically significant. Developments with time are shown in Table XI.

Patients with initial stage-I radiographic findings and erythema nodosum

Sixty-three of the Finnish patients had initial stage-I chest-radiography changes and exhibited EN on diagnosis or had a history of EN a few weeks

prior to diagnosis of sarcoidosis. In 51% chest radiography findings became normal during a follow-up period of two years, in 59% after a 5-year follow-up period. The difference in outcome between Finnish sarcoidosis patients with and without EN is significant ($p < 0.001$). Both regarding normalization of chest radiographs in patients with initial stage-I changes and EN are recorded in Table XI and Fig. 9. No EN patient developed parenchymal lesions during follow-up.

No Hokkaido sarcoidosis patient presented with EN. EN occurred during follow-up in three patients. Comparison of outcomes between Finnish and Hokkaido patients with EN was not possible because of the small number of Hokkaido EN cases.

Patients with initial stage-II radiographic findings and erythema nodosum
Thirty-eight Finnish patients had EN and stage-II chest radiographic findings. After one, 2, 3, 4 and 5 years, 18%, 34%, 45%, 47% and 53% of patients, respectively, had normal chest radiography findings. Outcomes in stage-I and stage-II patients with EN are not statistically significantly different. Both regarding normalization of chest radiographs in patients with initial stage-II changes and EN are recorded in Table XI and Fig. 10.

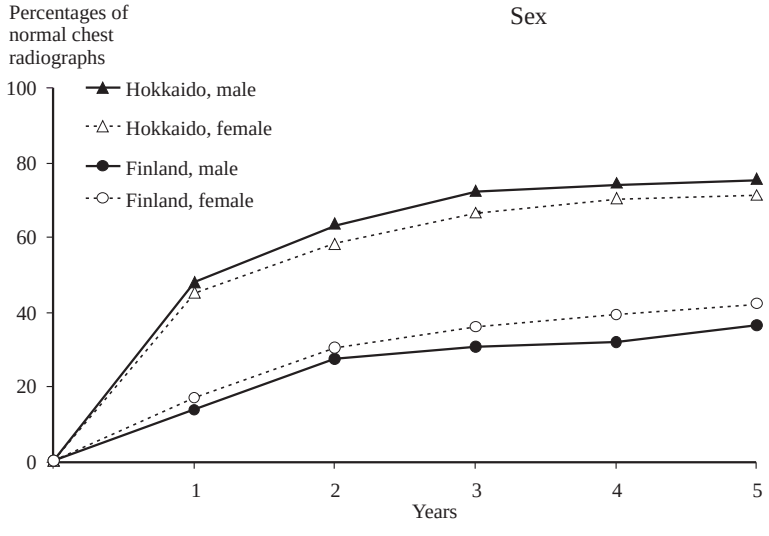
Influence of age on prognosis
The two series of patients were first divided into subgroups of these below and above 30 years of age. In the Finnish series, there were 91 patients in the younger age group, 346 patients in the older. Pulmonary radiographic changes did not develop significantly differently between the two age groups. In Hokkaido there were 323 patients in the younger are group, 123 in the older. Significantly lower percentages of Hokkaido patients more than 30 years of age than younger patients had normal chest radiographs ($p < 0.001$ at all times during follow-up).

The younger Hokkaido patients exhibited a significantly higher rate of normalization of chest radiographs during the five years of follow-up than Finnish patients ($p < 0.001$) (Table XI). The same was true for all Hokkaido and Finnish patients and for Hokkaido and Finnish patients with initial stage-I findings. For Hokkaido and Finnish patients with initial stage-II findings the differences between the two groups are not significant after one and two years of follow-up, but differences are statistically significant ($p < 0.001$ after three, four and five years of follow-up). Numbers of patients with initial stage-III findings were too few to allow meaningful comaprisons.

Influence of sex on outcome

Forty-two per cent of Finnish female patients and 71% of Hokkaido female patients, and 36% of Finnish male patients and 75% of Hokkaido male patients developed normal chest radiographs during five years of follow-up. There were no statistically significant differences between the sexes in Finland and Hokkaido. However, the differences between Finnish and Japanese patients are statistically significant for both female and male patients ($p < 0.001$). Developments in chest-radiography findings according to sex are recorded in Table XI and Fig. 11.

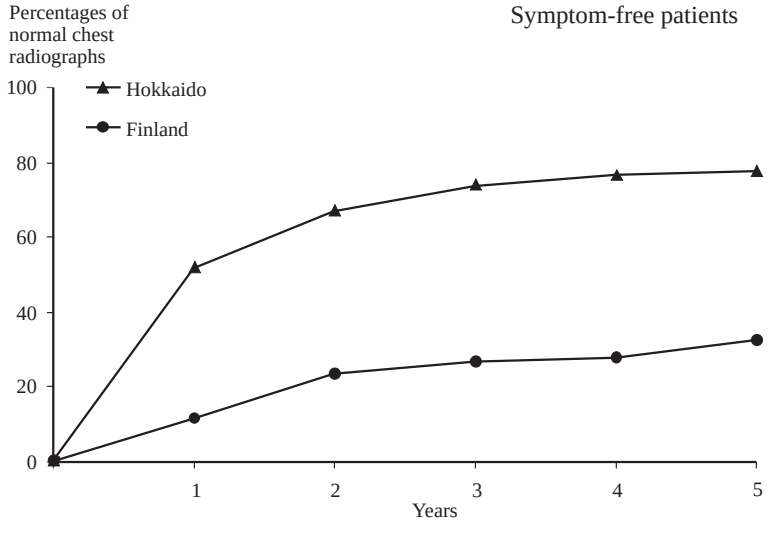
Fig. 11: Percentages of normalized chest radiographs according to sex in Finnish and Hokkaido hospital patients during five years of follow-up.



Influence of presenting symptoms on outcome

Two hundered and fifteen Finnish patients and 261 Hokkaidoan patients with pulmonary sarcoidosis presented without symptoms. During the first year of follow-up, 12% of the Finnish patients and 52% of Hokkaido patients developed normal chest radiographs. After five years of follow-up, 28% and 77%, respectively, had developed normal chest radiographs. Differences in percentages of patients with normal chest radiography findings between the two series were significant at all times ($p < 0.001$). The influence of symptoms on outcome is summarized in Table XI and Fig. 12.

Fig. 12: Percentages of normalized chest radiographs in patients without symptoms on diagnosis in Finnish and Hokkaido hospital patients during five years of follow-up.



Influence of extrapulmonary findings on outcome

Extrapulmonary lesions were initially diagnosed in 298 Finnish patients (68%) and 244 Hokkaido patients (53%). Excluding the 101 Finnish patients with EN who have been discussed separately there were 197 Finnish patients with extrapulmonary lesions. After five years of follow-up, 34% of these Finnish patients and 68% of the Hokkaido patients with initial extra-pulmonary lesions had developed normal chest radiographs. The difference is significant ($p < 0.001$). Follow-up data are recorded in Table XI.

In Finland, 42% of patients without extrapulmonary lesions developed normal chest radiographs. This percentage is higher than the 34% for patients with extrapulmonary findings. The difference is not statistically significant ($p < 0.1$). The corresponding percentages for Hokkaido were 76 (patients without extrapulmonary lesions) and 68 (patients with extrapulmonary lesions). This difference is significant ($p < 0.05$). Normalization in Hokkaido patients without eye sarcoidosis was also statistically significantly better than that in patients with eye sarcoidosis. After one year of follow-up 41% of patients with ocular lesions had normal chest radiographs compared with 51% of patients without ($p = 0.05$). After five years the corresponding percentages were 67 and 79, respectivly ($p = 0.01$).

Influence of treatment on outcome

As previously mentioned disease severity differed between untreated and treated groups of patients. In Finland 136 patients (31%) received treatment, in Hokkaido 106 patients (23%). Indications for commencement of treatment with corticosteroids, and treatment regimens, were similar in Finland and Hokkaido. In most cases, extrapulmonary manifestations alone or with pulmonary findings were the reason for starting treatment. Pulmonary sarcoidosis without extrapulmonary manifestations was treated only if there was radiographic evidence of progression of infiltrates during follow-up, or there was obvious impairment on the basis of diffusion capacities and spirometric volumes. In Finland 87 patients (47% of stage-II or stage-III patients) in Hokkaido 51 patients (41%) received treatment on this basis. Patients exhibiting stage-I radiographic changes alone, without extrapulmonary manifestations, were not usually treated. Comapisons of pulmonary radiographic findings for treated and untreated Finnish and Hokkaido patients revealed statistically significantly better development in the latter ($p < 0.001$).

Completely normal chest radiographs were significantly commoner in all untreated patients than in treated patients (p values between < 0.01 and < 0.001 one to five years of follow-up). These findings are, however, of limited interest, as treatment always had been given in non-random fashion and to patients with more severe disease. Chest radiographic findings that were not completely normal were neverthless better in steroid-treated patients with stage-II to stage-III pulmonary findings as the sole indication for starting treatment (p values between < 0.01 and < 0.001 after one to five years of follow up) than in untreated patients.

5.4. Familial sarcoidosis in Finland and Hokkaido (Study IV)

Prevalence of familial sarcoidosis and family relationships

In the 1984 surveys, 1378 Finnish patients with a diagnosis of sarcoidosis and 208 Hokkaidoan patients were seen in hospital. Fifty Finnish and 9 Hokkaido patients had family members who had also had sarcoidosis. In the two Mjölbolsta and Sapporo Hospitals, 571 Finnish and 686 Hokkaido patients were diagnosed as having sarcoidosis. Twenty-seven the Finnish

patients and 20 of the Hokkaido patients had family members who had had sarcoidosis. These results give prevalences of familial sarcoidosis in Finland of 3.6 to 4.7%, in Hokkaido of 4.3 to 2.9%.

There were 13 sibling pairs and 12 parent-child pairs in the Finnish hospital series. The corresponding figures for Hokkaido were nine and six, respectively. There were no cousins in the Finnish series but two in the Japanese series. There were two nieces or nephews in the Finnish series, three in the Japanese series. Family relationships are shown in Table XII.

Table XII:
Frequencies of occurence of different family relationships in Finnish (Mjölbolsta) and Hokkaido (Sapporo) hospital series.

Type of relationship	**Mjölbolsta (27 families) Number of cases; (per cent)**		**Sapporo (20 families) Number of cases; (per cent)**	
Sibling:	26	(46)	18	(45)
Sister-sister	6		4	
Brother-brother	2		4	
Brother-sister	18		10	
Parent-child:	26	(46)	12	(30)
Mother-child	16		12	
Mother-child-sister	3		0	
Father-child	4		0	
Father-child-grandchild	3		0	
Cousins	0	(0)	4	(10)
Others	4	(7)	6	(15)
Nieces	2		4	
Nephews	2		2	
Total	**56**		**40**	

Clinical picture and outcome

The familial cases in the two hospital series were compared with the rest of the sarcoidosis cases. Statistics and clinical pictures relating to Finnish and Japanese familial sarcoidosis cases are recorded in Table XIII. Six of the Finnish familial patients (22%) and 96 of the non-familial Finnish sarcoidosis patients (18%) had EN. In Hokkaido, only three EN cases occurred, all among non-familial sarcoidosis patients. Eye involvement was commoner in Hokkaido sarcoidosis patients: There were eight familial (20%), 336 non-familial cases (51%) ($p < 0.001$). The corresponding Finnish figures for eye envolvement were one and 26.

Table XIII:
Statistics relating to and clinical picture in patients with familial sarcoidosis in hospital series of 571 Finnish patients (Mjölbolsta) and 686 Hokkaido patients (Sapporo).

	Mjölbolsta		Sapporo	
	Familial	**Non-familial**	**Familial**	**Non-familial**
No. of families	27		20	
No. of cases	56	544	40	646
Female/ male ratio	0.9	1.5	1.4	1.2
Age (years)	39.5	41.6	35.9	30.0
Chest X-ray:				
Stage I	14	256	38	315
Sttage II	9	216	1	136
Stage III	4	64	1	33
Extrathoracic findings				
Erythema nodosum	6	96	0	3
Eye findings	1	26	8	336

Familial cases in the two countries had slightly less favourable outcome (normalization of chest radiographs) during five years of follow-up than non-familial cases. No statistically significant differences were found between familial and non-familial series in either Finland or Japan but familial and non-familial sarcoidosis patients in Hokkaido had statistically significantly better outcome than patients in Finland.

5.5. Association between sarcoidosis and HLA-B7, -Cw7 and -DR2 in a Finnish sarcoidosis population (Study V)

HLA pattern in sarcoidosis patients
The study involved 20 consecutive patients with a diagnosis of sarcoidosis in the Mjölbolsta Hospital. The control population consisted of 10,000 Finnish-bone marrow donors. Statistically significant excesses in frequencies of HLA-B7 ($p = 0.002$), -Cw7 ($p = 0.0002$, $p_c < 0.01$) and DR2 ($p = 0.0003$, $p_c = 0.012$) were found in sarcoidosis patients. HLA-B7, -Cw7 and -DR2 coincided in 10 patients.

Frequencies of HLA-A2, -B8, -B22 and -DR3 were higher but not statistically significantly in sarcoidosis patients than in controls. HLA-B27 and -Cw4 were less common in sarcoidosis patients than in controls but not statistically significantly.

The odds ratio (OR) relating to the excess of HLA-Cw7 was 5.1 (95% confidence interval 2.3 - 11.5), that for the deficit of HLA-B27 0.3 (95% confidence interval 0.2 - 0.5).

To confirm the findings Cw* typing for 18 DNA samples was also performed. Cw*07 was found in 13 sarcoidosis patients (72%), two of whom were serologically Cw7 negative. One clearly Cw7 seropositive sarcoidosis patient was Cw*07 negative. In 88 control subjects who had been routinely HLA-typed serological and DNA typing revealed Cw7Cw*07 in 41 cases, and Cw*07 alone in two cases. Two uncertain Cw7 findings were Cw*07 negative.

HLA antigens and clinical picture (unpublished data)

Statistically significant associations were found between EN and HLA-B8 in four of six cases ($p = 0.037$) and -DR3 in four of six cases ($p = 0.0279$). The other common symptom, dyspnoea, was not found to be HLA-associated.

HLA antigens, chest radiography findings and outcome (unpublished data).

Ten of the 20 sarcoidosis patients had normal chest radiography findings after follow up for one to two years. Eight of them had HLA-B7, an excess ($p = 0.069$) as compared with the other 10 patients (three B7 positives). In three other patients radiography findings were normal within one further follow-up year. None was HLA-B7 positive. After four years of follow-up the radiographic findings were normal in 13 patients. In the remaining patients the active disease persisted for longer. Both chest-radiographiy changes (stage-I to stage-III) and high levels of biochemical markers of sarcoidosis activity remeined. No statistically significant associations were found between less favourable outcomes of sarcoidosis and persistance of chest-radiographic findings and HLA types. No associations were found between the most prevalent HLA types, Cw7 and DR2, and chest-radiography findings and outcome of sarcoidosis.

5.6. Association of angiotensin-converting enzyme DD gene with poor outcome in Finnish sarcoidosis patients (Study VI)

ACE genotype frequencies are shown in Table XIV. Frequencies of the D allele were higher in controls and sarcoidosis patients than frequencies of the I allele (0.51/0.49 and 0.58/0.42 respectively), but the differences were not statistically significant.

Table XIV:
ACE genotype and allele frequencies in Finnish sarcoidosis patients and controls.

	Female		**Male**		**Total**	
	Patients N = 42	**Controls N = 47**	**Patients N = 16**	**Controls N = 23**	**Patients N = 59**	**Controls N = 70**
Genotype frequency						
DD (%)	12 (29)	14 (30)	6 (38)	5 (22)	18 (31)	19 (27)
ID (%)	23 (55)	23 (49)	9 (56)	11 (48)	32 (54)	34 (49)
II (%)	7 (17)	10 (21)	2 (13)	7 (30)	9 (15)	17 (24)
Odds ratio*	1.17		3.08		1.45	
95% CI	0.41-3.32		0.50-18.9		0.60-3.49	
P values	0.77		0.22		0.41	
Allele frequency						
D	0.56	0.54	0.625	0.46	0.58	0.51
I	0.44	0.46	0.375	0.54	0.42	0.49
P values	0.82		0.14		0.32	

* :Ratio of DD + ID to II. CI: Confidence interval

Outcomes in sarcoidosis patients according to ACE genotype are shown in Table XV. Only two of 18 patients with the DD genotype had favourable outcomes. In three the outcome was classed as intermediate. Patients with good outcomes were compared with patients in whom outcomes were poor or intermediate. A good outcome was statistically significantly less common in patients with the DD genotype than in patients with the II and ID genotypes ($p < 0.05$). Thirteen of the 18 DD patients had poor outcomes. This ratio is statistically significantly different from corresponding ratios relating to patients with II or ID genotypes ($p < 0.01$).

Table XV:
Outcomes in Finnish sarcoidosis patients by ACE genotypes.

	Genotype		
Outcome	**II**	**ID**	**DD**
Good	4	12	2
Intermediate	4	8	3
Poor	1	12	13
Total	9	32	18

Erythema nodosum: Eleven patients (4 DD, 4 ID and 3 II) had had EN, a sign that outcome is likely to be good. The three patients with the II genotype and three of the four patients with the ID genotype had good outcomes. Three of the four EN patients with the DD genotype had poor outcomes. The difference between the DD patients and the II and ID patients are statistically significant ($p < 0.05$).

6. DISCUSSION

Study populations and methods

The system used to calculate incidences and prevalences of sarcoidosis in Finland and Hokkaido were different. For many Japanese, annual chest radiographic examinations had been compulsory. The first nationwide epidemiological sarcoidosis survey was performed in Japan in 1960. Others have followed. Sarcoidosis has been found more often in Hokkaido than other parts of Japan. Hosoda et al. (25) found the incidence of sarcoidosis in Hokkaido to be 4.8 per 100,000. In Kyushu, the main southerly island of Japan, it was only 0.5 per 100,000. This regional difference in Japan has persisted. A national survey in 1984 resulted in prevalence figure (non-adjusted for age) of 1.5 per 100,000 for Japan as a whole but 5.0 per 100,000 for Hokkaido. Annual incidence was 0.3 per 100,000 in Japan as a whole but 0.7 per 100,000 in Hokkaido (12). In Hokkaido, only hospitals with 200 beds or more were asked to report numbes of sarcoidosis patients visiting them in1984. True incidences and prevalences therefore had to be estimated (103, 104).

In Finland, mass radiographic surveys have been performed only every third year. Possibilities of finding sarcoidosis cases have therefore been more limited in Finland than in Japan. However, according to reports at international conferences on sarcoidosis the incidence and prevalence of sarcoidosis in Finland has always been much higher than in Japan (Tables II-III). Finnish prevalences for sarcoidosis as high as 102 per 100,000 have been reported (9). The true difference may therefore have been under-estimated.

Although Japanese incidence and prevalence figures are partly estimated and the Finnish system for finding the cases has been different from that in Japan, the results of this comparative study confirm that there are substantial differences in incidences and prevalences of sarcoidosis between Hokkaido and Finland. The differences are real, since differences in diagnostic procedures and classifications can be excluded, even though raw data could not be checked for all patients in Hokkaido.

Validity of diagnosis

To study the clinical picture and course of sarcoidosis, and the occurrence of familial sarcoidosis in Finland and Hokkaido, two large hospital series (Mjölbolsta 571 patients, Sapporo 686 patients) were evaluated in similar ways by members of our study group. Identical diagnostic criteria were used. These are described on pp. 30 to 31. They are based on papers by Hiraga and Hosoda (108, 109). The clinical pictures presented by patients differed greatly in the two countries. Ocular sarcoidosis was prevalent in Japan. In 1984, 44% of Japanese male patients and 59% of female patients had eye lesions (12). Findings in present Sapporo series were similar. If a patient meets at least two of the three criteria compatible with sarcoidosis (histological verification, chest-radiography findings, typical clinical picture) a diagnosis of sarcoidosis is obviously reasonable. However, reliability of diagnosis in Sapporo Hospital patients on the basis of typical clinical picture alone (visual disturbances and/or findings) has been questioned (110). In such a situation, increases in S-ACE and/or S-LZM have been shown to be of diagnostic value (111, 112). These biochemical markers were used as supportive tools in our Japanese work. In previous studies, patients with ocular sarcoidosis have usually had abnormal chest-radiography findings. However, when ocular lesions are present, chest-radiography changes may not be evident, or may have resolved (37, 113). In our study, a number of patients with only ocular symptoms/changes on presentation subsequently developed chest-radiographic lesions later, according to oral information provided by a member of the Japanese study team. Hilar/mediastinal lymphadenopathy was also verified by CT scanning of patients with normal chest radiography findings. On the basis of follow-up information and high values for serum markers of activity the diagnoses of sarcoidosis in Sapporo patients exhibiting only typical clinical pictures are therefore considered reliable.

Age and sex distribution

The results of the 1984 series indicated that the sex distribution of sarcoidosis did not differ significantly between Finland and Hokkaido. Findings in the two hospital series and in previous studies in Finland and Japan have been similar (1, 6, 8).

One noteworthy feature is that sarcoidosis patients in Finland were significantly older at the time of diagnosis than patients in Hokkaido. In previous Japanese studies (12, 25, 28) the age group 20-29 years has been largest. In the largest Finnish study (8), the age group 30-39 years was

largest. In Swedish and Danish series (18), and in most sarcoidosis studies elsewhere (1), younger age groups have been largest. The age distribution in Finland, with predominance of patients more than 30 years of age, is therefore exceptional. The reason is unknown. The more effective and frequent screening system in Japan may result earlier detection of the disease.

Environmental factors, and dietary and smoking habits

It has been suggested that mycobacterial infection can lead to sarcoidosis (114, 116). Incidences and prevalences of tuberculosis in Finland and Hokkaido at the time of our study, and earlier have been similar. Differences in exposure to mycobacteria therefore probably do not explain the differences in incidences and prevalences of sarcoidosis between the two countries.

It has also been suggested that climate features (7f) and exposure to pine pollen (116) can lead to sarcoidosis. The climates in Finland and Hokkaido are similar (13). No correlation between distribution of pine forests and cases of sarcoidosis has been found in Finland (22) or Japan (117). It is therefore unlikely that such enviromental factors could explain differences in incidences and prevalences of sarcoidosis.

Dietary habits in Japan differ from those in Finland. The Japanese eat more fish and vegetables, Finns eat mainly meat, and fewer green vegetables. In a Japanese case-control study a low intake of green vegetables has been shown to be associated with sarcoidosis (118). Since our study was retrospective we were unable to evaluate whether dietary habits had any effect.

Smoking habits differ between Finland and Hokkaido. The Japanese smoke more than Finns. Published data suggest that smoking can reduce the risk of suffering from sarcoidosis (119, 120) but there is also a report claiming no protective effect (121). Full information about the smoking habits of the sarcoidosis patients in the 1984 surveys in Finland and Hokkaido is lacking. However, they could partly explain the differences in incidences and prevalences of sarcoidosis.

Differences in clinical pictures and chest-radiographic findings

It has has been shown that race affects the incidence and prevalence, clinical picture and course of sarcoidosis (1, 32, 49). The clinical picture of sarcoidosis has been shown to differ in Finland and Japan (1, 6, 14). This was also found in our study, although a number of similarities were found between patients in the hospital series in these two countries.

Forty-four per cent and 50% of patients were symptom-free at time of diagnosis in the Finnish and Hokkaido series, respectively. In the largest Finnish study previously reported, 39% of patients were diagnosed following by routine chest-radiographic examinations (8). In previous Japanese studies, mean percentage of symptom-free patients was similar (around 50%) but percentages ranged from 15 to 80 depending on age and sex (28). Because of the differences in performance of mass-radiographic surveys in the two countries (annual mass-radiographic surveys in Japan every year, in Finland every third year), the percentage of symptom-free patients in Finland could in reality have been still higher.

The most important difference between the Finnish and Hokkaido hospital series relates to symptoms on presentation. Finnish patients often had cough with fever, arthralgia and EN. The latter was never seen as a presenting symptom in the Hokkaido series but appeared during a follow-up period of five years in three cases. Many Hokkaido patients had eye symptoms, but these were rare in Finnish patients. The reasons for the differences are unknown but genetics may have some influence, as discussed below. Unknown antigen differences, may be another explanation.

No statistically significant difference in percentages of patients exhibiting tuberculin-skin-test positivity was found between the two hospital series. This was to be expected, since percentages of tuberculin-skin-test-negative subjects are similar, 10%, in the general populations in the areas concerned (29, 122). BCG vaccination systems have also been similar. In Japan all newborn infants are BCG-vaccinated at age 3 months. In Finland, vaccination takes place during the stay in the maternity hospital.

Results of lung-function tests (FVC, FEV1, DLco), expressed as percentages of predicted values, were within normal ranges in both hospital series. The lower percentage relating to FEV1 in Sapporo indicates that the patients there were probably, more obstructed. The explanation may lie in the fact that smokers were commoner in the Sapporo patients than in the Finnish patients.

Chest-radiographic findings at time of diagnosis were commoner and more serious in the Finnish series than in the Hokkaido series. Only 1% of Finnish patients had normal chest-radiographic pictures as compared with 19% of Japanese patients. Fifty-one per cent of Finnish patients but only 17% of Hokkaido patients had stage-II or stage-III findings in their chest radiographs. Frequencies and types of changes in chest radiography findings in previous studies were similar (8, 18). In a Japanese study (12), the

percentage of sarcoidosis patients exhibiting no chest-radiography changes was lower than in our study.

Differences in outcome in pulmonary sarcoidosis

Although it would appear possible to diagnose sarcoidosis clinically without biopsy in Finnish patients with EN and stage-I to stage-II pulmonary findings, and in Japanese patients with ocular manifestations and stage-I to stage-II disease, in our study we included only patients with positive tissue-biopsy findings supporting clinical diagnosis of sarcoidosis. After careful re-evaluation of all hospital data very few re-classifications were undertaken. Normalization of chest radiographs occurred significantly oftener and more rapidly in Japanese stage-I and stage-II sarcoidosis patients than in Finnish patients. Finnish findings resemble findings in Scandinavian studies (40, 123). In Japanese sarcoidosis studies rates for clearance of chest radiographs have been found to be similar to those in Japan in our study (11, 57, 59). Clearance of chest-radiography findings was overall significantly better in Japanese patients than in Finnish pateints. EN in patients with sarcoidosis has been widely associated with a good outcome (8, 40, 54, 123). EN is more prevalent in Scandinavian and other European sarcoidosis patients than in patients elsewere (1, 18, 124). An association has been shown between EN and the histocompatibility antigen HLA-B8 (85). HLA-B8 is extremely rare in the Japanese population. This could explain the rarity of EN in our Japanese series. The Japanese patients have a different HLA background (95). Patients with good outcomes often have a genotype including HLA-DRw5 (94). In the our study, there was no EN on diagnosis in the Japanese patients, but 18 to 23% of Finnish patients had EN. Neverthless, overall, outcome in Japanese stage-I patients were better than outcomes in Finnish patients with EN. These facts suggest that EN alone is not indicative of a favourable outcome in sarcoidosis. There are reports of poor outcomes in sarcoidosis patients with EN (54, 83).

In previous studies, age has been discussed as a prognostic factor. It has been shown that patients below 30 years of age (57, 59) or 40 years of age (8, 54, 123, 125) had a better outcomes than older patients. In our study, age was a factor in relation to Japanese patients. In the younger age group, 80% exhibited normalization of chest-radiography findings. In the Finnish series the difference in outcomes between younger and older patients was not statistically significant.

The influence of sex on the incidence and prevalence, and outcome in sarcoidosis has been discussed in a number of papers (8, 54, 57, 59, 123).

No marked differences have been found. In our study, sex did not significantly affect outcome. There were no significant differences between the sexes in the Finnish or Japanese series. The widely cited view that female sex is associated with a good prognosis (45) was not supported by the results of our study.

Results of previous studies indicate that sarcoidosis patients with extrathoracic lesions (excluding EN) have more severe disease and poorer outcomes (3, 8, 40, 94, 1232) than patients without extrapulmonary manifestations. In a study in Finland, this was found to be true in relation to patients symptom-free on diagnosis but not patients with initial symptoms, including EN (125). In a Japanese study, a correlation was observed between less favourable outcomes and the presence of extrapulmonary disease manifestations (57). In our study after five years of follow-up of the two hospital series, Japanese patients were found to have experienced better outcomes overall than Finnish patients. The presence or absence of extrapulmonary lesions did not significantly influence the development of chest-radiography findings in Finnish patients. Japanese series patients without extrapulmonary lesions experienced normalization of chest radiographs significantly more often than patients with extrapulmonary manifestations. Our two series of patients included sufficient numbers of three types of extrapulmonary manifestation to allow their influences on development of pulmonary findings to be assassed. The extrapulmonary manifestations were peripheral lymphadenopathy in both countries, EN in Finland and ocular sarcoidosis in Japan. Other extrapulmonary lesions were too infrequent to allow their influence on outcome in pulmonary sarcoidosis to be assessed. Patients with peripheral lymphadenopathy experienced pulmonary radiography development similar to those in patients without enlarged lymph nodes, in both countries. Finnish patients with EN had better outcomes than patients without EN, in agreement with previous observations (8, 54). The percentage of Japanese patients with ocular sarcoidosis experiencing normalization of chest-radiography findings was significantly lower than in patients with no ocular or other extrapulmonary lesions, also in agreement with previous findings (11).

Treatment with corticosteroids did not account for the difference in outcome between Finnish and Japanese patients. Normalization of chest radiography findings was significantly commoner in untreated patients in Finland and Japan. However, severity of sarcoidosis differed greatly between untreated and treated groups of patients. There was no random allocation to treatment with corticosteroids or lack of it in Finnish or Japanese

patients. Comparison of outcomes in pulmonary sarcoidosis between patients treated and not treated with corticosteroids is therefore meaningless. In patients with parenchymal lesions as an indication for treatment with corticosteroids improvement was fastest in treated patients.

Influences of ethnic and genetic factors on incidence and prevalence, clinical picture and outcome in sarcoidosis

It has been suggested that genetics may be important in sarcoidosis. In different ethnic groups incidences and prevalences of sarcoidosis are very different (1). About 500 cases of sarcoidosis with familial connections have been published. The prevalence of familial sarcoidosis has shown to be higher than prevalence of sarcoidosis in the background population (61, 62). The histocompatibility system has been shown to be related to the clinical picture and outcome in sarcoidosis but seldom to susceptibility to sarcoidosis (83, 126, 127, 128). There have been thoughts that a recessive autosomal (65) or heterogenic heredity (64) may be a background factor in sarcoidosis.

The populations of Finland and Hokkaido are different ethnically. They may therefore have different genetic susceptibilities to sarcoidosis. There are also studies showing differences in incidences and prevalences of sarcoidosis, and in prevalence of familial sarcoidosis between different ethnic groups (31, 67). Some human leukocyte antigens have been found more often than expected in patients with sarcoidosis (7g, 73, 74, 75). Other studies have shown that some HLA types protect against sarcoidosis (79). In Japan the commonest HLA types in the sarcoidosis population are HLA-A1, -Bw46, -Cx46, -DRw8, -DRw9 and -DRw52, HLA-DRw52 being the most prevalent (94, 95). There have been no previous HLA studies in sarcoidosis patients in Finland but a case report on a family has shown an association between HLA-B8/DR3 and patients with sarcoidosis or Crohn's disease (91). However, individuals with Löfgren's Syndrome (sarcoidosis with EN and BHL, which is common in Finland and Scandinavia), most often have the HLA-B8 (3, 40, 54). In Japan HLA-B8 is almost nonexistent. In our study on HLA and sarcoidosis, an association between susceptibility to sarcoidosis and HLA-Cw7 and -DR2 was found. It cannot therefore be excluded that genetic differences influence incidence and prevalence of sarcoidosis although the mechanism of heredity is not yet clear. On the other hand heredity is probably not the only factor leading to sarcoidosis.

It has been found in previous studies that the clinical picture of sarcoidosis varies widely between ethnic groups (1, 14). In our study,

patients in the two hospital series were of different race. Their heredity and HLA backgrounds therefore differed. In our study on HLA and sarcoidosis in Finland frequencies of B8 and DR3 were twice as high and almost twice as high, respectively, in the sarcoidosis population than in the controls, but there was no statistically significant association with susceptibility to sarcoidosis, nor was there an association between HLA-B8 and DR3 and good outcome. In Sweden, a study has shown a high prevalence of HLA-B8 (67%) and -DR3 (90%) in sarcoidosis patients, with an association between EN and favourable outcome (83). Another recent Swedish study has shown an association between good outcome and HLA-DR17(3) (87). In two Japanese studies DRw52 has been found to be the most prevalent HLA type, and to be associated with a favourable outcome. In Japan, HLA-B8 and -DR3 are extremely rare (94, 95). EN and arthralgy, usually associated with these HLA types, are also rare in Japan.

On the basis of histopathological and chest radiography findings, sarcoidosis must be considered to be the same disease in Finland and Hokkaido. However, symptoms on diagnosis, mode of presentation and clinical picture vary considerably between Finland and Hokkaido. The reasons for the differences are unknown but difference in heredity may be important.

It has been shown that both HLA-B8 and -DR3 are associated with good outcome. Berlin et al. have shown in 122 sarcoidosis patients that those with HLA-DR17(3) had significantly better outcomes within 2 years than those with HLA-DR14(6) or -DR15(2) (87). There are also other studies relating to HLA types that indicate of a poor outcome in sarcoidosis e.g. in Italy HLA-DR5 (89). Japanese studies have, however, shown that HLA-DR5 may be associated with good outcome (94, 95). In our study on HLA and sarcoidosis, the association between HLA-B7 and good outcome (unpublished data) was almost statistically significant.

In our follow-up study of patients in the two hospital series, EN as a presenting symptom was not seen in Hokkaido but was seen in 18% of Finnish patients. The outcomes in Hokkaido stage-I patients were nevertheless better overall than outcomes in Finnish patients with EN. This suggest that occurrence of EN does not mean the outcome will always be favourable as already stated on page 64. There are also reports of poor outcomes in sarcoidosis patients with EN (54, 83).

The results of our study on ACE gene polymorphism may partly explain the poorer outcomes in Finnish sarcoidosis patients than in Japanese patients. Patients with the DD genotype had poorer outcomes than the

others. In our study and in previous studies (98-102), Caucasians had the D allele more often than Japanese subjects. In Japanese studies the DD genotype was found to be present in lower percentages of sarcoidosis patients (38% and 39%) (99 101) than in our study (58%).

Despite the differences in incidences and prevalences, clinical pictures and outcomes of sarcoidosis in Finland and Hokkaido, prevalences of familial sarcoidosis were similar in both areas. According to results of Japanese studies (94, 95) and our study on HLA and sarcoidosis in Finland, HLA patterns and ACE genotypes differ between Finnish and Hokkaido sarcoidosis patients (99, 101). The most important reasons for differences between sarcoidosis in Finland and Hokkaido appear to be the racial and genetic. The inheritance pattern of sarcoidosis appears complex but remains unresolved.

7. SUMMARY AND CONCLUSIONS

Finland and Hokkaido resemble each other in a number of respects. The four-season climates, with cold winters and cool summers are similar. Incidences and prevalences of tuberculosis are also similar. The two areas have populations of similar sizes. The populations are, however, of different race. The Japanese eat fish oftener than the Finns. Prevalence of smokers is higher in Japan than in Finland. Studies in Finland and Japan have shown differences in incidences and prevalences and clinical pictures of sarcoidosis.

To asses whether reported differences relating to sarcoidosis between Finland and Hokkaido are real, or could be explained by differences relating to classification, terminology or diagnostic procedures, comparative studies were performed. Information was collected identically for both areas, and cases were evaluated by a joint team.

Results relating to two series of sarcoidosis patients in both areas were studied: 1) sarcoidosis patients from the 1984 surveys in Finland (n = 1378) and Hokkaido (n = 208), to determine incidences and prevalences of sarcoidosis and 2) patients from Mjölbolsta Hospital in Finland (n = 571) and Sapporo Hospital (n = 686) to asses clinical pictures of sarcoidosis in the areas concerned.

Outcomes were determined from 5-year follow-up data relating to patients with biopsy-proven pulmonary sarcoidosis (437 Mjölbolsta Hospital cases, 457 Sapporo Hospital cases).

In all series familial sarcoidosis cases were also evaluated. To try to improve understanding of the heredity of sarcoidosis, 20 Finnish sarcoidosis patients, and their HLA phenotypes were stdied.

ACE genotypes in 59 Finnish sarcoidosis patients and 70 controls were determined. Outcomes in sarcoidosis in patients with the II, ID or DD genotypes were established.

1. The incidence and prevalence of sarcoidosis were higher in Finland than in Hokkaido: crude annual incidences were 11.4 and 2.8 per 100,000 inhabitants and crude prevalences 28.2 and 7.2 per 100,000 inhabitants, respectively. The Hokkaido sarcoidosis patients were younger than the Finnish patients. Mean ages were 40 and 45 years, respectively.

2. Half of the patients in Finnish and Hokkaido hospital series were first diagnosed via mass-radiographic surveys. In patients diagnosed on the basis of symptoms these varied considerably. In Finnish patients cough, fever, general malaise, dyspnoea and EN were prevalent. In Hokkaido patients eye distubances were commonest. Fewer than a half of the Finnish patients but more than half of the Hokkaido patients exhibited bilateral hilar lymphadenopathy as an initial radiographic finding (stage-I). Stage-II and stage-III changes were more often seen in Finnish patients than in Hokkaido patients. Normal chest radiographs were very seldom seen in Finnish patients but occurred in almost 20% of Hokkaido patients.

3. Normalization of chest-radiography changes in patients with biopsy-proven sarcoidosis occurred in 40% of Finnish patients and 73% of Japanese patients. Of the 191 Finnish and 309 Japanese patients with stage-I sarcoidosis, 47% and 76%, respectively, experienced normalization of chest-radiography findings during five years of follow-up. The Finnish series included patients with EN, of whom 59% experienced normalization. Of 186 Finnish and 125 Japanese patients with initial stage-II disease, 36% and 73%, respectively, experienced normalization of chest-radiography findings during follow-up. There was no significant difference in percentages of the 58 Finnish 23 and Japanese patients with initial stage-III chest radiography changes who experienced normalization. Sex did not influence outcome in sarcoidosis. Age had no influence in the Finnish series but Japanese patients below 30 years of age had significantly better outcomes than older patients. There were extrapulmonary findings in 298 Finnish and 244 Japanese patients. After follow-up for five years, 34% of Finnish patients (excluding the 101 patients with EN) and 68% of Japanese patients had normal chest radiographs.

4. Prevalences of familial sarcoidosis on the basis of the 1984 surveys and the hospital series were 3.6 to 4.7% in Finland, 4.3 to 2.9% in

Hokkaido. In both series sibling-sibling and mother-child relationships predominated.

5. Statistically significant associations between frequencies of HLA-Cw7, -DR2 and -B7 and sarcoidosis patients were seen in Finnish patients compared with healthy Finnish controls. In Japanese studies, HLA-DRw52 has shown to be commonest in Japanese with sarcoidosis but B8 is very rare. Patients with HLA-DRw52 and -DR5 have been shown to have better outcomes.

6. In Finns, ACE genotypes (II, ID, DD) did not statistically significantly differ in frequency of occurrence between patients and controls. Statistically significantly more patients with the DD genotype had poor outcomes than patients with the II and ID genotypes. Patients with Löfgrens Syndrome (stage-I chest-radiography changes and EN) and the DD genotype also had poor outcomes. In Japanese studies the I allele has shown to be dominant in the population. An association between less favourable outcome in sarcoidosis and the ACE DD genotype has also been demonstrated.

Differences in incidences and prevalences, clinical pictures and outcomes in sarcoidosis between Finland and Hokkaido were marked. Differences in racial background obviously at least partly explain the findings. Certain HLA gene combinations (haplotypes) may in particular serve as markers for gene(s) affecting the clinical expression of sarcoidosis and how it originates. This could explain the differences in clinical pictures and outcomes between Finnish and Hokkaido sarcoidosis patients. The ACE genotype may also be a prognostic marker in sarcoidosis. The low frequency of occurrence of ACE gene allele D in Japan could partly explain why outcomes in Japanese with sarcoidosis are better than in Finns with sarcoidosis.

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