Association between exposure to crystalline silica and risk of sarcoidosis

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Abstract

***Objectives*—The possibility of an association between exposure to silica and autoimmune diseases has recently come under discussion. In the following case-referent study, a cohort exposed to diatomaceous earth and cristobalite provided an opportunity to evaluate such an exposure with reference to sarcoidosis.**

***Methods*—The inhabitants of a district served by a single healthcare centre and a hospital formed the study base. A diatomaceous earth plant is located in this community and the medical institutions are responsible for primary and secondary health care of the population. Cases of sarcoidosis were identified from the hospital records according to certain clinical, radiological, and histological criteria. Referents were selected randomly from the population of the district. Information on exposure to crystalline silica, cristobalite, was obtained by record linkage of the cases and referents with a file which included all present and past workers at the diatomaceous earth plant and those who had worked at loading vessels with the product from the plant.**

***Results*—Eight cases of sarcoidosis were found, six of which were in the exposed group. Of the 70 referents, 13 were exposed. The odds ratio (95% confidence interval) was 13.2 (2.0 to 140.9).**

***Conclusion*—The odds ratios were high and there were some indications of a dose-response relation which will hopefully encourage further studies. To our knowledge this is the first study to indicate a relation between sarcoidosis and exposure to the crystalline silica, cristobalite.**

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Keywords: diatomaceous earth; cristobalite; case-referent study

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Although the aetiology of sarcoidosis is unknown, pulmonary sarcoidosis is mediated by an intensive cellular immune response at sites of disease activity.[1] Sarcoidosis is a benign phenomenon which often is only incidentally discovered, as it tends to exhibit few symptoms and thus goes undiscovered and may clear up by itself without treatment. The diagnosis of sarcoidosis is based on clinical symptoms and signs, and pathological changes which are compatible with sarcoidosis when other diseases have been excluded.

A working group under the auspices of the International Agency for Research on Cancer (IARC) has recently evaluated carcinogenicity from crystalline silica inhaled in the form of quartz or cristobalite and reclassified these as carcinogenic to humans, which is an upgrade from their previous classification as probably carcinogenic.[2]

In a recent communication the relation between exposure to silica and some autoimmune diseases was discussed,[3] with specific reference to systemic sclerosis, rheumatoid arthritis, lupus, and chronic renal disease. The authors present some plausible mechanisms for such an association from the medical literature and they urge that further studies be carried out on exposure to silica and autoimmune conditions.

Over 10 years ago we presented what was then little more than an indication that sarcoidosis seemed to be more common in a cohort exposed to crystalline silica in the form of cristobalite.[4] This cohort consisted of workers employed in a plant processing diatomaceous earth who had previously been studied for the risk of lung cancer.[5] The plant is located in the northern part of Iceland and the health surveillance of the workers was conducted at a local, community based, primary healthcare centre. This situation was considered ideal for evaluating the relation between sarcoidosis and exposure to diatomaceous earth and cristobalite in a case-referent study.

Material and methods

The population of the district (about 4500 people), which is served by the healthcare centre and the hospital in the town of Husavik, functioned as the study base. The people were identified in the National register, which by law, must be kept at the Statistical Bureau of Iceland and consists of everyone who has lived in Iceland since 1951. The healthcare centre and the hospital, which are the only medical institutions in the district, are responsible for the primary and secondary health care of the population of the district, including the workers at the diatomaceous earth plant on Lake Myvatn.

Table 1 Characteristics of the cases

Cases	*Age at diagnosis*	*Sex*	*Symptoms at diagnosis*	*Histology*	*x Ray stage*
1	23	Male	Yes	Yes	II
2	34	Female	Yes	Yes	III
3	34	Male	No	Yes	III
4	42	Male	No	Yes	III
5	32	Male	No	Yes	I
6	25	Female	Yes	No	I
7	52	Female	No	Yes	II
8	42	Female	Yes	Yes	0

Table 2 Years of exposure, number of years from first exposure to diagnosis, year of diagnosis and accumulated hours at exposed work

Cases	Start of exposure	Last year of exposure	First exposure to diagnosis (y)	Year of diagnosis	Accumulated hours at work
1	1973	1973	1	1974	680
2	1970	1977	4	1974	396
3	1967	1981	10	1976	21120
4	1973	1981	10	1982	16040
5	1975	1978	10	1984	348
6	—	—	—	1989	0
7	1987	1992	6	1992	10720
8	—	—	—	1993	0

Diatomaceous earth is material composed of siliceous skeletons of microscopic plants, diatoms, large deposits of which are found on the bottom of Lake Myvatn. The deposits are several metres thick and are pumped up from the lake and into the plant. The material is then dried using geothermal water and sieved. On further processing by flux-calcination, which forms the principal part of the process, a large portion of the diatomaceous earth is transformed from an amorphous state to a crystalline form, which is up to 70% cristobalite and 1%–2% quartz.[6]

Information on the cases of sarcoidosis was obtained from the files of the healthcare centre and the hospital. Those selected had to meet three of the following five criteria: (*a*) show pulmonary or general symptoms, (*b*) show parenchymal or lymph node changes on chest *x* ray films, (*c*) have a histopathological diagnosis compatible with sarcoidosis, (*d*) include erythema nodosum, and (*e*) report the benign course of the disease, with regression of pulmonary and other symptoms and signs. All cases selected were to meet this last criterion. All cases except one fulfilled the third criterion and that case had erythema nodosum. The histology is characterised by non-caseating epithelioid granulomas, but there are no pathognomonic features, thus the importance of the benign course (the fifth criterion). The characteristics of the cases are shown in table 1. The referents were drawn randomly from the population of the district from the National register.

Table 3 All cases and referents according to exposure to diatomaceous earth and cristobalite and cases not discovered at routine health check up, incidental cases, odds ratio (95% CI)

	Exposed		Odds ratio	95% CI
	Ever	Never		
All cases:				
Cases	6	2		
Referents	13	57	13.2	2.0 to 140.9
Incidental cases:				
Cases	4	2		
Referents	13	57	8.8	1.1 to 102.5

Table 4 Cases which were not discovered at routine examinations and referents according to exposure to diatomaceous earth and cristobalite

	Exposure (h)		
	⩾1000	<1000	Never
Cases	1	3	2
Referents	1	12	57
Odds ratios	28.5	7.1	(1)
95% CIs	0.24 to 2271.5	0.7 to 90.5	

We did not stratify on age, however, the age range of the cases determined the age section of the population register used to draw the referents. Permission to carry out the study was obtained from the Data Protecting Commission.

The cases and referents were record linked with a file which included all present and past workers of the diatomaceous earth plant and those who had worked at loading the finished product from the plant aboard transport vessels.[5] This was possible through the 10-digit personal identification number unique for every Icelander; the same number is used in the National register. In this way it could be ascertained whether cases and referents had been exposed to diatomaceous earth and crystalline silica. The diatomaceous earth plant started operations in 1967. In accordance with a request from the public health authorities in Iceland the management of the plant keeps files on every worker at the plant. The files included information on when the workers started and stopped different job tasks in the plant. Payrolls were available for those who had worked at loading vessels. Thus it was possible to obtain information on how many hours each worker had been exposed.

As the result of another initiative of the health authorities the workers at the plant underwent annual health check ups at the healthcare centre in Husavik; however, chest *x* ray films were only done every second or fifth year since 1980. In general the exposed workers were not considered to have more respiratory symptoms than others and those loading vessels were not included in the health check ups. No case of silicosis has yet been diagnosed among the present or past workers.

Records of personal samples of respirable cristobalite showed considerable variation according to the person's tasks and location within the factory.[6] The dust measurement of personal samples from the year 1978 showed mean values of 0.6, 0.3, 0.2, and 0.1 mg/m^3 of respirable cristobalite for packers, oven operators, maintenance men, and cleaners, respectively. The average value for those loading transport vessels was 0.3 mg/m^3 according to measurements from 1978. It is assumed that the working conditions have improved since then, yet the mean values of the content of respirable cristobalite in personal samples was 0.02 mg/m^3 in loading and 0.05, 0.002, 0.01, and 0.06 mg/m^3 for packers, oven operators, maintenance men, and cleaners, respectively, in the year 1981.[6] The threshold limit value for respirable cristobalite is 0.05 mg/m^3, according to the threshold limit value list in Iceland.[7]

Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated according to Fisher's exact test.[8] Sarcoidosis is a disease which can pass unnoticed without symptoms and therefore it is possible that cases among the exposed group were only found because of the annual health examinations. To eliminate this possible bias it was decided, after analysing all the cases, to restrict the subsequent analysis of the material to those which were not discovered at the routine health examinations.

Results

A total of eight cases were found, six of which had been exposed to diatomaceous earth and cristobalite at work. The six exposed cases were distributed into different job categories so no particular job seemed at increased risk. Exposure information and year of diagnosis of the cases are shown in table 2.

Of the 70 referents 13 had been exposed. The OR (95% CI) for all the cases and referents are shown in table 3. In table 3 the OR (95% CI) are shown after restricting the study to those cases which were not discovered at the annual health examinations. The OR was still high.

Table 4 shows the cases not found at annual health examinations and referents classified into exposure categories according to accumulated number of hours of exposure: those who had worked $\geqslant$1000 hours, those who had worked <1000 hours, and those who had never been exposed to diatomaceous earth at work. The only case who had worked >1000 hours had indeed worked >10 000 hours. As the numbers are low, the calculations give us wide 95% CIs. None the less, the ORs were high, and increased with longer exposure.

Discussion

The ORs were increased for those who had been exposed to diatomaceous earth and cristobalite and there was an indication of a dose-response relation. However, as there are few cases the results are handicapped by wide 95% CIs.

Although it was not the purpose of this study to find the annual incidence of sarcoidosis in the health district concerned, this can be estimated on the basis of the number of inhabitants, the number of years observed, and the number of cases, producing an annual incidence of 9.3/100 000. This is far higher than the annual incidence of sarcoidosis for the whole population of Iceland, which in the year 1978 was estimated to range from 0.5–2.7/100 000.[9]

The main strength of the study is that the exposure history was obtained by record linkage of a joint file of cases and referents with a file of all exposed people, which in turn was obtained from employment lists from the factory and payrolls from the shipping agency. The file of the exposed workers was gathered entirely independently of the diagnosis of the cases. In this record linkage we used the personal identification number which everyone in Iceland has. Thus the information on exposure was obtained independent of subjective evaluation or memory of the cases and referents, or of the doctors who were responsible for the diagnosis and treatment of the cases, or of those performing the study.

The referents were selected randomly from the population from which the cases were diagnosed. For this purpose we used the National register, and the inhabitants of the district served by the healthcare centre and hospital of Husavik formed the study base. Thus the method ensures that the referents are representative of the exposure rate in the population.

The discussion of the biological plausibility of a relation between exposure to silica and autoimmune conditions has already been mentioned[3] but the medical literature on silica and sarcoidosis is scant. Cutaneous silica granuloma, which is different from cutaneous sarcoidosis, is known to develop in old scars contaminated with silica in crystalline or vitreous form.[10 11] The suggestion has been made that only granulomatous infiltration of an old scar should be considered as scar sarcoidosis when this is present along with other manifestations of sarcoidosis.[11] According to a paper by Eggelmeijer *et al*[11] most patients with scar sarcoidosis were found to have siliceous material in the infiltrations, thus there are striking similarities between scar sarcoidosis and silica granuloma. In the light of this, the description of a patient in whom silica granuloma progressed into scar sarcoidosis is of interest.[12]

It has been postulated that silica granulomas represent a delayed hypersensitivity response[13] and it has also been suggested that silica may act in a manner similar to beryllium and zirconium, in causing a delayed hypersensitivity reaction which may result in a histological picture identical to that of sarcoidosis.[14] Previously the clinical, histological, and radiological similarities between beryllium disease and sarcoidosis have been discussed[15] and the importance of the knowledge of occupational exposure to beryllium has been stressed.[15] The coexistence of these two diseases is thought to be very unlikely and the importance of increased tissue content of beryllium in lung and mediastinal lymph nodes has been reported.[15] On the contrary, the coincidence of silicosis and sarcoidosis has been reported in a communication from Germany in a case series,[16] in which the pathogenesis of both diseases is discussed.[17] This communication by Hubener *et al* also refers to several other case reports on the association of silicosis and sarcoidosis.[16]

Exposure to crystalline silica has been suggested to have an effect on the immune system, which has drawn attention to the possible association of exposure to silica and autoimmune diseases.[3] Whether the immunological role of silica may be the explanatory link in the pathogenesis of the carcinogenic properties of silica or not, will certainly continue to be the focus of future research.[18]

A recent study has shown that the risk of sarcoidosis was statistically associated with men enlisted in the United States Navy to aircraft carriers.[19] The study was initiated by a man who asked whether his sarcoidosis diagnosed in 1974 may have been associated with environmental exposure during his service in the navy. The diagnosis was based on a chest radiograph indicating bilateral hilar adenopathy without parenchymal disease and non-caseating granulomata on lymph node biopsy. He related his symptoms to his work of grinding antiskid materials from aircraft carrier decks during the preceding two years. In 1987 pneumoconiosis was diagnosed in this patient after mineral dust deposits were identified in a lung biopsy and the mineral dust deposit were attributed to the same work exposure aboard the aircraft

carrier.[19] The report does not give the precise nature of the mineral concerned.[19]

If the association between exposure to diatomaceous earth or cristobalite and sarcoidosis is causal, it is an addition to our constantly increasing knowledge on the complicated effect of silica on human health and will further intensify the demand for control of exposure.

In conclusion we have found an increased risk of sarcoidosis among those workers exposed to diatomaceous earth and cristobalite. There is a biological plausibility for such an association and the finding is interesting in view of the fact that the assessment of the carcinogenic property of cristobalite has been upgraded recently.

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1 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomed journals. *JAMA* 1993;**269**:2282-6.
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