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Original Articles

Cancer Risk and Mortality Patterns Among Silicotic Men in Sweden and Denmark

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Data from nationwide registry-based cohorts of patients hospitalized for silicosis in Sweden from 1965 to 1983 and Denmark from 1977 to 1989 were linked to national cancer registries in both countries and to mortality data in Sweden to evaluate the risk of cancer and other disorders among hospitalized silicotic patients. The overall cancer standardized incidence ratio (SIR) was 1.5 (95% confidence interval [CI], 1.3 to 1.7) in Sweden and 1.7 (95% CI, 1.2 to 2.3) in Denmark, primarily because of elevations in primary lung cancer in both Sweden (SIR, 3.1; CI, 2.1 to 4.2) and Denmark (SIR, 2.9; CI, 1.5 to 5.2). For Sweden, the all-causes standardized mortality ratio (SMR) was 2.0 (1.9 to 2.2). The SMR for all malignancies was 1.5 (1.2 to 1.7), primarily because of excesses of lung cancer (SMR, 2.9; CI, 2.1 to 3.9). The significant increase in mortality for all infectious and parasitic conditions (SMR, 11.2) was primarily due to tuberculosis (SMR, 21.8). Significant excesses in mortality from silicosis (SMR, 5.23), bronchitis (SMR, 2.6) and emphysema (SMR, 6.7) contributed to the elevation in nonmalignant respiratory deaths (SMR, 8.8), whereas excess mortality from musculoskeletal disorders (SMR, 5.9) was due to six deaths from autoimmune diseases. Despite limitations of the available data, our findings are consistent with previous reports indicating that silicotic patients are at elevated risk of lung cancer, nonmalignant respiratory diseases, tuberculosis, and certain autoimmune disorders.

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Silicosis is a chronic and incurable occupational lung disease caused by the inhalation of crystalline silica particles into the lungs. It has been described in a variety of occupational groups, including miners, stonecutters, sandblasters, foundry workers, and pottery and porcelain manufacturing workers. [1] Silicosis remains a public health concern [2] [3] because of continuing silica exposure and difficulties in diagnosis of the disease and its complications, notably tuberculosis. [3] [4] [5] [6] [7] In recent years, several reports have suggested an excess risk of lung cancer among silicotics, [5] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] although it has been difficult to disentangle the effects of silicotic lung disease from heavy exposure to silica, [20] and the possible confounding effects of cigarette smoking, radon, and other occupational carcinogens. [22] In addition, there are reports suggesting an association of silicosis with chronic respiratory diseases other than lung cancer or tuberculosis, particularly obstructive diseases such as chronic bronchitis and emphysema. [5] [21] [23] [24] [25] Furthermore, some studies have suggested an excess risk of certain autoimmune diseases, notably systemic sclerosis. [2] [24] [25] [26] [27] [28] [29] [30] To further investigate the relation of silicosis with various health outcomes, we used data from nationwide registry-based cohorts of patients hospitalized for silicosis in Sweden and Denmark and linked to national cancer and mortality registries.

Methods

Study Population

Included in the cohorts were persons hospitalized for silicosis in Sweden from 1965 through 1983

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(with discharge diagnoses coded using the Swedish version of the International Classification of Diseases seventh revision, or ICD-7, code 523.00, and eighth revision, or ICD-8, codes 515.00, 515.01, 515.05, 515.09) and in Denmark from 1977 through 1989 (with discharge diagnoses coded using the Danish version of ICD-8 code 515.09). Patients were identified from registries (nationwide for Denmark and including an increasing proportion of Swedish hospitals ranging from 65% to 85% between 1969 and 1983) listing hospitalizations reported annually to the centralized Swedish Inpatient and the nationwide Danish Hospital Discharge Registers. Each record in these registries includes the patient's unique national registration number, date of birth, dates of admission and discharge, discharge diagnoses, and surgical procedures. Subjects with multiple admissions during these time periods have multiple records.

The individual registration numbers (assigned to all Swedish residents a short time after birth) of the cohort of Swedish patients whose hospital discharge diagnoses included silicosis were linked to the Swedish Registry of Causes of Death, the Registry of the Total Population, The Registry of Population Migration, and the National Swedish Cancer Registry. Similarly, the cohort of hospitalized Danish silicotics was linked to the Danish Cancer Registry and the Central Population Register using the individual registration numbers. These record linkages provided information on the occurrence of incident cancers, death, or emigration for hospitalized silicotics. More detailed descriptions of the methods utilized for record-linkage studies have been reported. [31] [32] We initially identified 1886 personal identification numbers from Sweden and 404 from Denmark for silicotic patients. Records with incomplete or erroneous personal identification numbers and those with inconsistent dates uncovered during record linkage were excluded. Also excluded were those patients with concurrent diagnosis of asbestosis (17 in Sweden, seven in Denmark), and the small number of women diagnosed with silicosis (125 in Sweden, eight in Denmark).

There could be some overlap of our study population with those of previous studies that investigated

cancer incidence in occupationally exposed silicotic cohorts in Sweden and Denmark. [18] [33] [34] [35] Although the degree of overlap is not known, our study included five additional years of follow-up in Sweden and three in Denmark. As a result, more than one third of the lung cancer cases reported in our study are new and could not have been included in the previous cohort studies.

Follow-up for each cohort began after the first hospitalization in which a discharge diagnosis of silicosis was listed during the study period and continued until the date of the subject's death, emigration, or end of follow-up (December 31, 1989, for Sweden; December 31, 1990, for Denmark), whichever event occurred first. Person-years and events (deaths for the mortality analysis and cancer diagnoses for the cancer analysis) in the first year of follow-up (eg, persons who survived less than one year after their first hospital visit for silicosis; 423 in Sweden, 140 in Denmark) were excluded to minimize the potential for selection bias. The mortality analysis included 1130 Swedish men with silicosis, but no Danish cases, because mortality data were unavailable. The cancer incidence analysis involved 1052 Swedish men with silicosis (78 with prevalent cancer were dropped because the Swedish incidence rates used exclude second primary cancers) and 243 Danish men.

Statistical Analysis

The expected number of cancers (Sweden and Denmark) and the expected number of deaths (Sweden only) were calculated by multiplying the number of person-years for men by the appropriate national gender-, age-, calendar year-, and site-specific cancer incidence and mortality rates for each 5-year age group and calendar year of observation. Risks of cancer/mortality were estimated by computing standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs), defined as the ratio of the observed-to-expected numbers of cancers or deaths for all male silicotics combined and by age and length of follow-up. 95% confidence intervals (CIs) were computed assuming that the observed number follows a Poisson distribution. [36] The prevalence of selected hospital conditions among silicotics was assessed to explore associations revealed in the mortality analyses further. Each association was depicted as a risk ratio (RR), ie, the ratio of the rate of hospitalization for the condition in the silicosis cohort to the rate of hospitalization for the condition in each country (in Sweden based on the rate in participating hospitals). The RR calculation was cross-sectional, including events that occurred prior to silicosis as well as subsequent events.

Results

[Table 1](#) presents SIRs for Swedish and Danish men by major type of cancer. The overall cancer risk was elevated in both Sweden (SIR, 1.5; CI, 1.3 to 1.7) and Denmark (SIR, 1.7; CI, 1.2 to 2.3). The risk of respiratory cancers was elevated in both countries, mainly because of threefold elevations in primary lung cancer one or more years subsequent to first hospitalization for silicosis. These risks remained increased regardless of length of follow-up. Although the percentage of lung cancers with squamous cell histology was higher in Sweden (50%) than Denmark (27%), the cell type was unknown for approximately one third of lung tumors in each country. The other respiratory cancers were lung not specified as primary (two subjects) in Sweden, and one larynx

TABLE 1 -- Cancer Incidence Among Male Silicotic Patients in Sweden and Denmark: All Latency Periods Combined, Excluding the First 12 Months*

Type of Malignancy	Sweden †	Denmark

(ICD-7)	Obs	SIR	95% CI	Obs	SIR	95% CI
All Cancers (140 to 209)	169	1.5	1.3 to 1.7	35	1.7	1.2 to 2.4
Buccal cavity and pharynx (140 to 148)	3	1.1	0.2 to 3.2	0	0	
Digestive cancers (150 to 159)	39	1.2	0.9 to 1.7	11	2.1	1.1 to 3.8
Esophagus (150)	0	0		1	4.4	0.1 to 24.4
Stomach (151)	10	1.3	0.6 to 2.4	0	0	
Colon (153)	12	1.4	0.7 to 2.5	4	2.5	0.7 to 6.4
Rectum (154)	9	1.6	0.7 to 3.0	2	1.8	0.2 to 6.5
Liver (155)	5	1.5	0.5 to 3.5	2	8.3	0.9 to 30.0
Pancreas (157)	2	0.5	0.1 to 1.7	1	1.6	0.0 to 8.7
Respiratory cancers (160 to 164)	38	2.8	2.0 to 3.8	13	3.1	1.7 to 5.3
Lung (162)	36	3.1	2.1 to 4.2	11	2.9	1.5 to 5.2
Breast (170)	1	6.0	0.1 to 33.4	0	0	
Prostate (177)	40	1.3	0.9 to 1.8	3	1.0	0.2 to 3.0
Testis (178)	1	2.1	0.0 to 11.9	0	0	
Kidney (180)	5	1.2	0.4 to 2.9	0	0	
Bladder (181)	8	1.1	0.5 to 2.1	2	1.1	0.1 to 3.9
Melanoma (190)	3	1.7	0.3 to 5.0	0	0	
Non-melanoma skin (191)	6	1.4	0.5 to 3.0	2	0.7	0.1 to 2.5
†						
Brain and CNS (193)	2	1.0	0.1 to 3.5	0	0	
All hematopoietic	13	1.6	0.9 to 2.8	2	1.7	0.2 to 6.1

(200 to 205) §						
NHL (200, 202, 205)	4	1.4	0.4 to 3.7	0	0	
Multiple myeloma (203)	3	1.7	0.3 to 5.0	1	4.4	0.1 to 24.4
All leukemia (204)	6	2.1	0.8 to 4.6	1	1.9	0.0 to 10.3
CLL (204.0)	2	1.4	0.2 to 5.2	1	3.6	0.0 to 20.0
Not otherwise specified (199)	6	1.9	0.7 to 4.1	0	0	

* ICD, International Classification of Disease; Obs, observed; SIR, standardized incidence ratio; CI, confidence interval; CNS, central nervous system; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia.

† Excludes 78 silicotics with prevalent cancers. Second primary cancers are not included in the rates.

‡ Includes both squamous and basal cell in Denmark, but only squamous cell in Sweden.

§ Coded as ICD-8 codes 200 to 209 in Sweden, which includes polycythemia vera and myelofibrosis.

cancer and one pleural mesothelioma in Denmark. There was no significant excess of smoking-related non-lung cancers (ie, buccal cavity and pharynx, esophagus, stomach, pancreas, larynx, kidney, bladder). A greater than twofold excess was seen for all digestive cancers combined in Denmark (primarily because of increases of liver, esophagus, and colon cancers), whereas no significant excess was noted in Sweden (SIR, 1.2; CI, 0.9 to 1.7).

Mortality risks among Swedish men are shown in [Table 2](#). Approximately 70% of the cohort was deceased, with a median age at death of 74 years. A twofold increase in risk was observed for all causes of death, with approximately 41% due to circulatory diseases, 32% to respiratory diseases, and 15% to malignancies. The excess mortality from all malignancies combined was 50%, due mainly to a threefold excess of lung cancer and a 1.5-fold excess of prostate cancer. The SMR for all infectious and parasitic diseases was greater than 11-fold, mainly because of a 22-fold increase in tuberculosis. The median age at death from tuberculosis was 74 years (range, 58 to 86 years). Deaths from tuberculosis appeared to decrease over time, but the trend was not significant ($P = 0.23$). A review of computerized hospital diagnoses with silicosis revealed that 6.5% of Swedish patients (68 patients) and 5.8% of Danish patients (14 patients) in each country had tuberculosis coded as a discharge diagnosis on their medical record during the study period.

The SMR for nonmalignant respiratory diseases was close to ninefold, with 73% of deaths attributed to silicosis, which was associated with a 500-fold increased risk. In addition, twofold excesses were seen for obstructive lung diseases, including bronchitis and emphysema, but no increases were noted for pneumonia or asthma. A significant 40% excess mortality was observed for diseases of the circulatory system, with 73% of those deaths due to arteriosclerotic heart disease. However, a review of computerized hospital diagnoses for Swedish silicotics revealed that 88% of the silicotics with

arteriosclerotic heart disease had this diagnosis prior to the first hospitalization in which silicosis was recorded.

A nearly twofold elevation in mortality from digestive system diseases was due to gastric and duodenal ulcers and cirrhosis of the liver. Three of five Swedish silicotics dying of liver cirrhosis had an alcohol-related diagnosis mentioned on the computerized files of the medical record before 1983 or on the death certificates.

The sixfold excess mortality from musculoskeletal diseases was based on six deaths: three with rheumatoid arthritis, two with systemic lupus erythematosus (SLE), and one with Sjogren's syndrome. A review of Swedish computerized hospital diagnoses from 1965 through 1983 revealed 57 subjects with diagnostic codes of both silicosis and an autoimmune disorder, including 44 with rheumatoid arthritis (RR, 8.1; CI, 5.9 to 10.82), eight with SLE (RR, 23.8; CI, 10.3 to 47.0), and five with scleroderma (RR, 37.0; CI, 11.9 to 86.3). A similar review of computerized hospital diagnoses from 1977 through 1989 for Denmark revealed ten patients with both silicosis and

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TABLE 2 -- Mortality Risks Among Male Silicotic Patients in Sweden: All Latency Periods Combined, Excluding the First 12 Months

Cause of Death	Obs	SMR	95% CI
All Causes of Death	795	2.0	1.9-2.2
All malignancies	122	1.5	1.2-1.7
Stomach cancer	10	1.2	0.6-2.2
Colon cancer	7	1.1	0.4-2.2
Lung cancer	41	2.9	2.1-3.9
Prostate cancer	24	1.5	1.0-2.2
All infectious and parasitic conditions	28	11.2	7.4-16.1
Tuberculosis	24	21.8	14.0-32.4
Respiratory diseases	253	8.8	7.7-9.9
Silicosis	184	523	450-604
Bronchitis	12	2.6	1.3-4.6
Pneumonia	16	1.0	0.6-1.6
Emphysema	17	6.7	3.9-10.8
Allergic, endocrine, metabolic diseases	6	1.1	0.4-2.4
Diseases of nervous system and sense organs	3	0.9	0.2-2.6
Diseases of circulatory system	324	1.4	1.3-1.6
Chronic rheumatic heart disease	2	1.2	0.1-4.4

Arteriosclerotic heart disease	235	1.5	1.4-1.8
Other heart disease	29	1.8	1.2-2.6
Cerebrovascular disease	32	0.9	0.6-1.2
Arterial disease	16	1.2	0.7-1.9
Venous and thromboembolic disease	4	0.9	0.3-2.4
Digestive system diseases	21	1.8	1.1-2.7
Gastric and duodenal ulcers	8	2.5	1.1-4.9
Cirrhosis of liver	5	1.8	0.6 -4.2
Urinary disease	9	1.6	0.7 -3.1
Musculoskeletal diseases	6	5.9	2.2 -12.9
All external causes of death	13	1.0	0.5 -1.6

rheumatoid arthritis (RR, 8.3; CI, 4.0 to 15.3). No consistent temporal patterns were evident in terms of the dates of hospitalization for silicosis or for autoimmune disorders.

Discussion

These national incidence and mortality surveys in Sweden and Denmark are consistent with previous reports of an excess lung cancer risk among patients with silicosis, [5] [6] [10] [11] [12] [13] [20] [21] [23] including the recent meta-analysis of lung cancer mortality among silicotics by Smith et al [20] (relative risk, 2.2, CI, 2.1 to 2.4, based on a pooled estimate from 23 studies). Furthermore, the mortality data revealed excess deaths not only from silicosis, but also from tuberculosis, chronic obstructive lung diseases, and autoimmune diseases.

Our population-based cohort study had the advantage of nearly complete ascertainment of cancer incidence and mortality from various causes and absence of recall bias because diagnoses are derived from medical records and death certificates. However, several major limitations of the study need to be emphasized. Because only hospitalized patients were included, the study population probably had a disproportionate number of silicotics with more advanced disease that required hospital admission. Also, it seems likely that patients hospitalized for silicosis had other serious medical conditions or underlying risk factors (eg, smoking and drinking habits) for cancer or mortality, which may result in overestimation of the risks of certain diseases. [37] Review of medical records to confirm diagnoses, ascertain past medical history and medications used, or evaluate smoking and drinking habits was beyond the scope of this investigation. We also could not assess possible misclassification of the underlying cause on death certificates. Furthermore, no occupational exposure assessment was possible for silica or other agents in the workplace. Because a substantial proportion of the silica-exposed workers in Sweden work in mines, the potential exists for confounding by radon exposure, a recognized lung carcinogen. [38] Dates of onset of silicosis and other medical conditions such as autoimmune disease and tuberculosis could not be clearly determined to evaluate temporal sequence. In addition, the power to detect significant elevations in risk for most cancer sites may have been limited by the relatively small

size of the cohorts, although multiple comparisons may have led to some chance associations.

Although the elevated incidence and mortality rates we observed for lung cancer suggest a causal association with silicosis, it is important to note that the information available in the computerized registries did not permit us to evaluate important potential confounders such as cigarette smoking and exposure to radon and other occupational carcinogens. [12] [13] [16] Nevertheless, in previous studies of silicotics that adjusted for smoking, an excess risk of lung cancer has persisted. [5] [8] [9] [35] It has been more difficult to exclude an effect of other occupational exposures such as radon. [22] [39] Also, in our study and others, it has not been possible to disentangle the possible carcinogenic effects of silica exposure from the progression of histopathologic

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changes associated with silicosis, including impaired pulmonary function that may result in retention of lung carcinogens. [16] [40] Although most epidemiologic studies point to an excess risk of lung cancer among silicotics, the mechanisms are unclear, and evidence for the human carcinogenicity of silica has been designated as *limited* based on comprehensive evaluations by the International Agency for Research on Cancer. [12] [13]

The excess mortality from all infectious and parasitic conditions in our study was mainly due to tuberculosis, listed as the underlying cause for 3% of all deaths in the Swedish cohort. Approximately 6% of Swedish and Danish silicotics had a diagnosis of tuberculosis mentioned on their medical record. Two thirds of the silicotic patients with tuberculosis had it noted on or before the date of first hospitalization for silicosis. Although tuberculosis and silicosis may be diagnosed simultaneously because of increased medical surveillance, the predisposition to tuberculosis among patients with silicosis is well-established by numerous clinical and epidemiologic studies [4] [5] [7] [9] [18] [21] [23] as well as experimental investigations indicating that infections with *Mycobacterium tuberculosis* are augmented by the addition of silica dust. [41] Although the median age at death of tuberculosis, 74 years, was similar to that for the total cohort, the persistently high proportion of deaths from tuberculosis suggests the need for closer surveillance of silica-exposed patients to enable earlier diagnosis and treatment of tuberculosis. An important public health issue beyond the scope of our study is the potential for transmission of tuberculosis from infected study patients to family members and others in close proximity.

The excess mortality from nonmalignant respiratory diseases was primarily due to silicosis but extended to obstructive lung diseases of bronchitis and emphysema. Although information on smoking was unavailable in our study, an excess of obstructive lung disease has been noted in other studies of silicotics [9] [23] [40] and suggests a causal relation to silica and other occupational dusts, along with a susceptibility to pulmonary infections that require early and aggressive treatment.

A significant excess mortality from circulatory disease was also observed in our study, but this finding has not generally been seen in other mortality studies of silicotics. [9] [21] [23] [40] A non-causal association seems likely since a review of computerized hospital records for Swedish silicotics revealed that 88% of the diagnoses of arteriosclerotic heart disease antedated the first silicosis diagnosis during the study period. On the other hand, the excess mortality we observed for digestive diseases has been noted in previous studies of silicotics, [9] [21] [23] [40] including an elevated risk for cirrhosis of the liver. [23] Our findings are consistent with those of Merlo et al, [5] who reported that silicotics had excess mortality from digestive disorders, including alcohol-related liver disease.

The elevated mortality from musculoskeletal disorders in our study resulted from the autoimmune

diseases of rheumatoid arthritis, SLE, and Sjogren's syndrome. An association between silicosis and certain types of autoimmune disease, especially scleroderma and rheumatoid arthritis, has been described in clinical studies and prevalence surveys of silicotics, [2] [24] [25] [26] [27] [28] [29] [30] but not as yet in cohort studies. Caplan's syndrome, or "rheumatoid pneumoconiosis," is a severe pulmonary fibrosis that follows silica dust exposure among individuals with rheumatoid arthritis. [42] [43] Mechanisms underlying the syndrome are unclear, but it has been suggested that the rheumatoid state may predispose to the rapid progression of silicosis. [2] Further studies are obviously needed to clarify the relationship between silica exposure, silicosis, and autoimmune diseases.

In summary, nationwide registry-based cohort studies in Sweden and Denmark were undertaken to evaluate the risk of cancer and other disorders among hospitalized silicotic patients, compared with incidence and mortality rates in the general population. Despite limitations of the data, the excess of lung cancer seen in both incidence and mortality analyses provides further evidence that patients with silicosis are prone to lung cancer. The elevated mortality from tuberculosis and chronic obstructive lung disease is also consistent with previous studies of silicosis, whereas the excess deaths from certain autoimmune disorders highlights an area where further research is needed.

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