

Incidence of Malignant Disease in Biopsy-Proven Inflammatory Myopathy

A Population-Based Cohort Study

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Background: The validity and magnitude of an association between myositis and malignant disease continue to be debated. Such issues as the legitimacy of a myositis diagnosis and distinction among myositis subgroups in previous population-based studies remain unresolved.

Objective: To determine the risk for malignant disease in patients with biopsy-proven inflammatory myopathies.

Design: Population-based, retrospective cohort study.

Setting: Victoria, Australia.

Patients: 537 patients in whom a biopsy-positive idiopathic inflammatory myopathy was first diagnosed from 1981 through 1995.

Measurements: Standardized incidence ratios were calculated to compare the incidence of malignant disease in patients with inflammatory myopathy and the general population.

Results: A total of 116 cases of malignant disease were found in

104 patients. Seventy-four cases were identified concurrently with (within 7 days) or after diagnosis of myositis. The highest risk for malignant disease was associated with dermatomyositis (standardized incidence ratio, 6.2 [95% CI, 3.9 to 10.0]). The risk was also increased in polymyositis (standardized incidence ratio, 2.0 [CI, 1.4 to 2.7]), although the relative risk for malignant disease in dermatomyositis compared with polymyositis was 2.4 (CI, 1.3 to 4.2). An increased risk for malignant disease was also found in inclusion-body myositis (standardized incidence ratio, 2.4 [CI, 1.2 to 4.9]). The excess risk for malignant disease diminished with time (standardized incidence ratio, 4.4 [CI, 2.7 to 7.1] in the first year; 3.4 [CI, 2.3 to 5.1] between 1 and 3 years; 2.2 [CI, 1.3 to 3.9] between 3 and 5 years; and 1.6 [CI, 1.0 to 2.6] beyond 5 years [*P* for trend, 0.002]).

Conclusion: The risk for malignant disease is increased in biopsy-proven dermatomyositis and polymyositis and also appears to be increased in inclusion-body myositis.

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Although an association between polymyositis and dermatomyositis and malignant disease was first suggested in 1916 (1, 2), the validity and the magnitude of this association continue to be questioned (3–11). Clinical and methodologic factors that have hindered resolution of this question have included diagnostic suspicion and referral bias; the legitimacy of the diagnosis of myositis and, in particular, the distinction between polymyositis and dermatomyositis; studies with small samples and short duration of follow-up; and lack of an appropriate control group.

It is important to know for certain whether an increased risk for malignant disease exists, and the magnitude and duration of that risk. This knowledge may assist clinicians in making decisions about the need to follow patients for malignant disease, particularly conditions for which benefits of early treatment are proven. We performed a population-based retrospective cohort study to determine the risk for malignant disease in

patients with biopsy-proven idiopathic inflammatory myopathies.

METHODS

Identification of Biopsy-Positive Inflammatory Myopathy

We used the Victorian Neuropathology Service (which has reviewed all muscle biopsies performed in the state of Victoria, Australia, since 1981) to identify all patients in whom biopsy-positive idiopathic inflammatory myopathies were first diagnosed from 1981 through 1995. All muscle biopsy reports generated since 1981 were searched for key words that would identify all potential biopsy-positive inflammatory myopathies; these included the specific diagnostic labels *inflammatory myopathy*, *myositis*, *polymyositis*, *dermatomyositis*, *inclusion-body myositis*, *childhood myositis*, *focal necrotizing myositis*, and *connective tissue disease*. Reports were also searched for key words that suggested the presence of an inflam-

matory myopathy; these included *inflammation, inflammatory cells, lymphocytes, rimmed vacuoles, and myosinolysis*. One pathologist who was blinded to the biopsy reports subsequently reviewed all biopsies that were identified as including one or more key words in their reports.

Myopathies were categorized as “polymyositis,” “dermatomyositis,” “myositis associated with connective tissue disease,” “childhood myositis,” or “inclusion-body myositis” according to the pathologic criteria for inflammatory myopathies of Banker and Engel (12). In brief, in idiopathic polymyositis, normal sarcomere architecture is destroyed, with resultant loss of cross-striations in affected muscle fibers. Other changes include myophagia, segmental degeneration, and regeneration. The inflammatory cell infiltrate usually consists of lymphocytes with some reactive macrophages. The minimum criteria for classification as polymyositis were segmental degeneration with diffuse fascicular involvement and some inflammatory cells. Dermatomyositis is characterized by myosinolysis, floccular degeneration, and capillary loss in the perifascicular regions of the muscle fasciculi. Perifascicular atrophy and inflammatory cells may also be observed in these regions and in the adjacent interstitial connective tissue. Changes on electron microscopy include tubuloreticular inclusions in endothelial cells of blood vessels. The minimum criteria for classification as dermatomyositis were myosinolysis and perifascicular focus. Childhood dermatomyositis may also show a more focal ischemic lesion. The minimum criteria for classification as childhood dermatomyositis were those used for dermatomyositis or the presence of several contiguous degenerating fibers. The criteria for classification as inclusion-body myositis were partial myophagia and the presence of rimmed vacuoles, along with additional fiber atrophy and endomysial fibrosis. Patients younger than 16 years of age at diagnosis of myositis were considered to have childhood myositis.

Our earlier study established the validity of our method for identifying all biopsy-positive cases of idiopathic inflammatory myopathies in the state of Victoria, Australia (13). In that study, we used a dual search strategy to identify all newly diagnosed cases from 1989 through 1991. Review of all 1024 muscle biopsies performed during this period identified 103 cases that satisfied the pathologic criteria of idiopathic inflammatory myopathies. Hospital discharge diagnoses from all major

metropolitan and 12 minor metropolitan and rural Victorian hospitals in 1989 through 1991 were also reviewed, and identified cases of idiopathic inflammatory myopathies were verified by medical record review. No additional biopsy-positive cases were identified by hospital record search (13).

Identification of Malignant Disease

The demographic characteristics of all identified patients with biopsy-proven myositis were matched to the records of the Victorian State Cancer Registry. This registry includes details of all cases of malignant disease occurring in Victoria, apart from nonmelanocytic skin cancers. Notification of malignant diagnoses to the registry is mandatory by law, and almost complete ascertainment is achieved by notification from pathology laboratories and hospital medical record departments and by screening of death certificates. The *International Classification of Diseases*, ninth revision (ICD-9), is used to code the site of malignant disease (14), and the ICD-Oncology morphology rubrics are used to code histologic type (15, 16). At the time of the study, the registry was complete through 1997. We used the date of diagnosis of malignant disease as listed in the Victorian Cancer Registry in our analysis.

Identification of Deaths

The Australian Institute of Health and Welfare also matched the demographic details of all identified biopsy-proven cases of myositis to the National Death Index to identify all deaths up until the end of 1999.

The study was approved by the Ethics Committees of Monash University and the Anti-Cancer Council of Victoria.

Statistical Analysis

To estimate the risk for malignant disease, the analysis included all patients whose malignant disease was diagnosed concurrently with (within 7 days) or after diagnosis of myositis. Patients whose diagnosis of malignant disease predated their diagnosis of myositis by more than 1 week were included in descriptive statistics only. For patients with more than one malignant disease, only time to first malignant disease was considered unless the first case occurred before diagnosis of myositis and a subsequent independent case occurred after diagnosis of myositis (3 participants). A second analysis was

Table 1. Biopsy-Positive Myositis in Victoria, Australia, 1982–1991

Type of Myositis	Patients	Mean Age (Range)	Women	Cases of Malignant Disease
	<i>n</i>	<i>y</i>	%	<i>n</i> (%)
Overall	537	51.9 (1.2–88.9)	55	116 (22)
Polymyositis	321	57.1 (16.5–88.9)	57	58 (18)
Dermatomyositis	85	51.7 (17.4–84.7)	55	36 (42)
Inclusion-body myositis	52	63.4 (28.8–84.0)	40	12 (23)
Myositis associated with connective tissue disease	30	48.5 (22.6–73.0)	62	8 (27)
Childhood myositis	49	7.7 (1.2–15.8)	51	2 (4)

performed in which the first year of follow-up after diagnosis of myositis was excluded. Because data were complete only through 1997, any malignancies diagnosed after this time were excluded from the analysis.

Standardized incidence ratios for malignant disease were calculated for each myositis category, sex, and time since diagnosis by using the rates of malignant disease in the population of Victoria, Australia (17), stratified by age, sex, and calendar period (18). The standardized incidence ratio compares the incidence of malignant disease observed in the myositis cohort (or subgroup) with that expected if the cohort developed malignant disease at the same rates as the population of Victoria. A standardized incidence ratio greater than 1 indicates elevated incidence of malignant disease in the study cohort with myositis relative to the population.

Crude incidence curves were produced by using the Kaplan–Meier method. Internal comparisons of rates within myositis subgroups were made by performing Cox regression with age as the basic time scale and adjusting for time since diagnosis (<1, 1 to <3, 3 to <5, or >5 years after diagnosis of myositis). In addition, sex and calendar period were controlled for as stratification variables because of their nonproportionality of hazards. Interactions between terms were assessed by adding cross-product terms to the regression model and using the likelihood ratio test. No interactions were statistically significant at the 10% level. All analyses were performed by using Stata for Windows, version 6 (Stata Corp., College Station, Texas).

RESULTS

Five hundred thirty-seven patients with biopsy-positive idiopathic inflammatory myopathy were identi-

fied. Demographic characteristics are shown in Table 1. A total of 116 cases of malignant disease were identified in 104 patients (9 patients had 2 malignant conditions and 2 patient had 3 malignant conditions). The prevalence of malignant disease in each myositis diagnosis category ranged from 4% for childhood myositis to 18% for polymyositis and 42% for dermatomyositis. Seventy-four cases of malignant disease in 69 patients were diagnosed concurrently with or after myositis diagnosis. Another 6 cases of malignant disease were diagnosed in the 3 months before diagnosis of myositis. Figure 1 shows the duration of time between diagnosis of polymyositis and dermatomyositis and diagnosis of malignant disease. Twenty-six percent (15 of 58) of cases of malignant disease in polymyositis occurred before

Figure 1. Time between diagnosis of polymyositis (top) or dermatomyositis (bottom) and diagnosis of malignant disease.

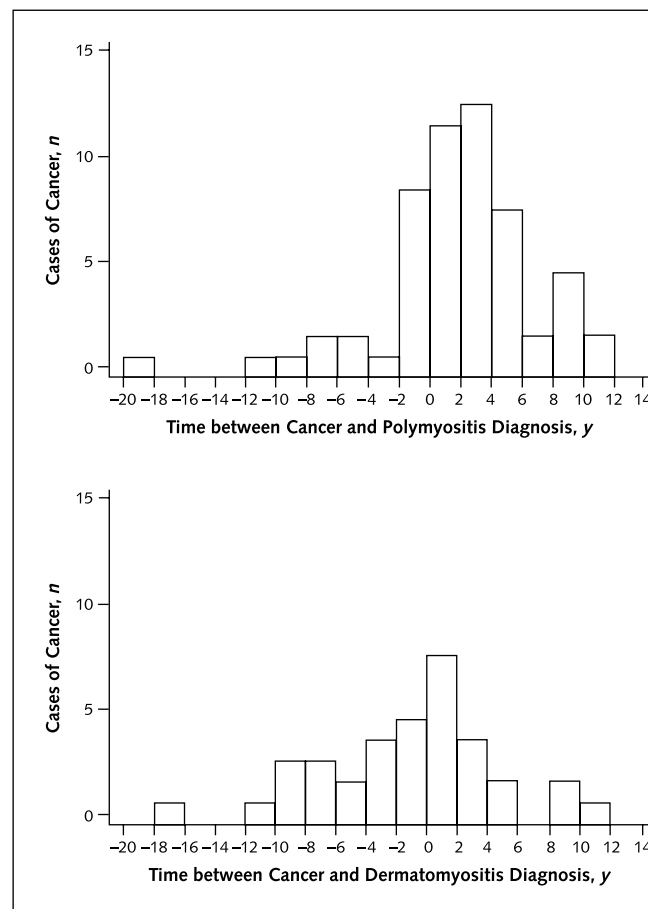


Table 2. Standardized Incidence Ratios for Malignant Disease Associated with Diagnosis of Myositis, Victoria, Australia, 1982–1997*

Variable	Follow-up	Observed Cases of Malignant Disease	Expected Cases of Malignant Disease	Standardized Incidence Ratio (95% CI)
	person-years			
Type of myositis				
Overall	3022.6	69	26.4	2.6 (2.1–3.3)
Polymyositis	1866.4	38	19.4	2.0 (1.4–2.7)
Dermatomyositis	415.8	17	2.7	6.2 (3.9–10.0)
Inclusion-body myositis	222.2	8	3.3	2.4 (1.2–4.9)
Myositis associated with connective tissue disease	134.9	4	0.88	4.6 (1.2–11.7)
Childhood myositis	383.3	2	0.069	29.0 (3.5–105)
Time since myositis diagnosis				
<1 y	463.1	17	3.9	4.4 (2.7–7.1)
1 to <3 y	826.5	24	7.0	3.4 (2.3–5.1)
3 to <5 y	628.2	12	5.5	2.2 (1.3–3.9)
≥5 y	1104.9	16	10.0	1.6 (1.0–2.6)
Sex				
Male	1293.0	36	14.4	2.5 (1.8–3.5)
Female	1729.6	33	12.0	2.8 (2.0–3.9)

* Only malignant diseases diagnosed concurrently with (within 7 days) or after diagnosis of myositis were included in the analysis.

diagnosis of polymyositis, compared with 53% (19 of 36) of cases of malignant disease in dermatomyositis.

Follow-up beyond 7 days before diagnosis of myositis was complete for 502 patients. The median follow-up was 5.3 years (range, 0.1 days to 15.7 years). When data from the first year after myositis diagnosis were excluded, 445 patients had a median follow-up beyond 1 year of 5.0 years (range, 41 days to 14.7 years).

The overall risk for malignant disease in idiopathic inflammatory myopathy was increased (standardized incidence ratio, 2.6 [95% CI, 2.1 to 3.3]) (Table 2). Risk for malignant disease was also increased within each subgroup of myositis. This risk was highest in dermatomyositis (standardized incidence ratio, 6.2 [CI, 3.9 to 10.0]) but was also increased in polymyositis (standardized incidence ratio, 2.0 [CI, 1.4 to 2.7]). An increased risk for malignant disease was also found in inclusion-body myositis (standardized incidence ratio, 2.4 [CI, 1.2 to 4.9]), myositis associated with connective tissue disease (standardized incidence ratio, 4.6 [CI, 1.2 to 11.7]), and childhood myositis (standardized incidence ratio, 29.0 [CI, 3.5 to 105.0]).

A decreasing trend in excess risk for malignant disease was observed in the years after diagnosis of myositis (standardized incidence ratio, 4.4 [CI 2.7 to 7.1] in the first year; 3.4 [CI, 2.3 to 5.1] between 1 and 3 years; 2.2 [CI, 1.3 to 3.9] between 3 and 5 years; and 1.6 [CI, 1.0 to 2.6] beyond 5 years) (Table 2). Excess risk for ma-

lignant disease was seen in both men and women (standardized incidence ratio, 2.5 [CI, 1.8 to 3.5] and 2.8 [CI, 2.0 to 3.9]).

When the analysis was performed after excluding malignancies that were identified concurrently with and in the first year after diagnosis of myositis, the overall risk for malignant disease was still increased (standardized incidence ratio, 2.3 [CI, 1.8 to 3.0]) (Table 3). The risk was increased in polymyositis (standardized incidence ratio, 1.8 [CI, 1.3 to 2.6]), dermatomyositis (standardized incidence ratio, 4.3 [CI, 2.3 to 8.1]), and inclusion-body myositis (standardized incidence ratio, 2.7 [CI, 1.3 to 5.6]) (Table 3).

We calculated the relative risk for malignant disease when all cases of malignant disease occurring within 7 days of myositis diagnosis were included (Table 4). After adjustment for age, sex, calendar period, and time since myositis diagnosis, the relative risk for malignant disease in dermatomyositis compared with polymyositis was 2.4 (CI, 1.3 to 4.2). The adjusted relative risk for malignant disease was higher in the first 3 years after diagnosis of myositis than at any later time, and the risk decreased with increasing time since diagnosis of myositis (relative risk, 2.5 [CI, 1.2 to 5.3] for <1 year vs. ≥5 years; 2.5 [CI, 1.3 to 4.9] for 1 to <3 years vs. ≥5 years; and 1.2 [CI, 0.6 to 2.5] for 3 to <5 years vs. ≥5 years [*P* for trend = 0.002]).

Sites and types of malignant disease are shown in

Table 5. We were unable to determine whether the risk for any individual type of malignant disease was increased compared with the general population because of the small numbers of individual malignancies.

DISCUSSION

We found an overall increased incidence of malignant disease in both men and women with idiopathic inflammatory myopathies. The overall risk was highest in the first 3 years after diagnosis of myositis than at any later time. Although a trend toward decreased excess risk for malignant disease with increasing time since diagnosis of myositis was observed, risk was still increased 5 years after diagnosis of myositis. The increased incidence of concurrent and subsequent malignant disease was found in both polymyositis and dermatomyositis, although the relative risk was higher in dermatomyositis (2.4 [CI, 1.3 to 4.2]) after adjustment for age, sex, and time since myositis diagnosis.

We addressed several methodologic and clinical issues that have limited the ability to draw firm conclusions from previous studies. First, our population-based cohort study avoids referral bias and selective follow-up, which may have affected the results of earlier studies performed predominantly in hospital or specialized settings. We identified all patients with newly diagnosed biopsy-positive disease from a central neuropathology service and verified the diagnoses by review of pathology. We previously established the validity of this method for identifying all biopsy-positive cases of idiopathic inflammatory myopathy in the state of Victoria (13).

The Victorian Cancer Registry is considered to be complete for all cases of malignant disease, apart from nonmelanocytic skin cancers. At the time of completion of our study, registration was complete through 1997;

we may therefore have underestimated the true incidence of malignant disease because of the relatively short follow-up in persons in whom myositis was diagnosed toward the end of the study period.

Second, although other studies have had a population-based cohort design (7, 9, 10), they used national hospital discharge databases to identify patients with myositis. This method of identification relies on accurate coding of discharge diagnoses. Sigurgeirsson and colleagues (7) identified diagnoses of polymyositis and dermatomyositis by using ICD-7 and ICD-8 statistical coding from the Swedish national hospitalization registry. They reviewed the records of 69 of 788 patients identified as having myositis and found that 7% of these patients probably had neither polymyositis nor dermatomyositis, and a further 20% were categorized as probably having either dermatomyositis or polymyositis. Thus, some patients with unconfirmed myositis were included, and some patients with myositis may have been missed. Chow and associates (9) identified patients in a similar manner from the Danish Central Hospital Discharge Register from ICD-8 codes for dermatomyositis and polymyositis and were unable to verify diagnoses of their registry-based data. Airio and coworkers (10) reviewed the medical records of 627 of 731 patients with an ICD-8 code of polymyositis or dermatomyositis in the Finnish national hospital registry from 1969 through 1985. More than one third of these patients (226 of 627 [36%]) were excluded from further study because they had neither polymyositis nor dermatomyositis. Previous studies examining whether diagnostic coding in administrative databases accurately reflects physician diagnosis recorded in the medical records for other medical conditions have found varying degrees of discordance (19–22).

Table 3. Standardized Incidence Ratios for Malignant Disease, Excluding the First Year of Follow-up after Diagnosis of Myositis

Type of Myositis	Follow-up	Observed Cases of Malignant Disease	Expected Cases of Malignant Disease	Standardized Incidence Ratio (95% CI)
	<i>person-years</i>	<i>n</i>	<i>n</i>	
Overall	2559.6	52	22.5	2.3 (1.8–3.0)
Polymyositis	1585.6	31	16.8	1.8 (1.3–2.6)
Dermatomyositis	353.1	10	2.3	4.3 (2.3–8.1)
Inclusion-body myositis	174.8	7	2.6	2.7 (1.3–5.6)
Myositis associated with connective tissue disease	111.8	2	0.75	2.7 (0.3–9.7)
Childhood myositis	334.3	2	0.062	32.2 (3.9–117.0)

Table 4. Adjusted Relative Risk for Malignant Disease, by Type of Myositis and Time since Diagnosis

Risk Factor	Adjusted Relative Risk (95% CI)*
All malignant disease diagnosed within 7 days of myositis diagnosis included	
Diagnosis	
Polymyositis	1.0 (referent)
Dermatomyositis	2.4 (1.3–4.2)
Time since diagnosis of myositis	
≥5 y	1.0 (referent)
3 to <5 y	1.2 (0.6–2.5)
1 to <3 y	2.5 (1.3–4.9)
<1 y	2.5 (1.2–5.3)
Malignant disease diagnosed in the first year after myositis diagnosis excluded	
Diagnosis	
Polymyositis	1.0 (referent)
Dermatomyositis	1.8 (0.8–3.7)
Time since myositis diagnosis	
≥5 y	1.0 (referent)
3 to <5 y	1.3 (0.6–2.8)
1 to <3 y	2.8 (1.5–5.6)

* Adjusted for myositis subgroup, sex, age, calendar period, and time since myositis diagnosis.

All have emphasized the need to verify data obtained from administrative databases by medical record review. Identification of patients with myositis on the basis of positive muscle biopsy eliminates this concern.

Third, we assembled an inception cohort based on date of first muscle biopsy. We considered this to be a fairly uniform point in the clinical course of myositis, on the basis of published series showing that the first symptoms of myositis usually occur within 1 year of diagnosis (23, 24). Although patients in our setting are routinely admitted to hospital for muscle biopsy, no data from previous studies are available to verify that use of national hospital discharge databases to identify patients with myositis identifies a group of patients at a common time point in their disease.

Fourth, we used a strict definition of idiopathic inflammatory myopathy that was based on histologic criteria (12). Earlier studies used the 1975 criteria of Bohan and Peter (25) for diagnosis of myositis (3, 4, 7, 10, 11). These criteria do not necessarily require histologic confirmation of diagnosis. Rather, they rely on the presence of at least three of the following four criteria to be considered definite or probable: proximal muscle weakness; increased serum creatine kinase level; confirmatory electromyogram; and confirmatory muscle biopsy, in addition to a rash indicative of dermatomyositis. Be-

cause histologic confirmation is not required in this system of criteria, previous studies may have included some patients without myositis and excluded some patients with true myositis. In the Finnish population-based study (10), 90 of 627 (14%) patients were excluded after medical record review because they did not fulfill the diagnostic criteria of Bohan and Peter, although the exact reasons for exclusion were not reported, and 49 of 311 (15%) patients with myositis who were included did not have histologic confirmation of diagnosis.

Previous studies have also been criticized because the criteria of Bohan and Peter are now regarded as unacceptable for distinguishing between polymyositis and dermatomyositis, since typical histologic features of dermatomyositis can be seen in patients with no or mild rash (26). By classifying our patients on histologic grounds, we reduced the risk for misclassification of polymyositis and dermatomyositis.

Because we used a biopsy-based definition of inflammatory myopathy, however, we probably did not identify all cases of inflammatory myopathy. Although most physicians who manage inflammatory myopathies in our setting would routinely perform a muscle biopsy if this diagnosis was suspected (13), a small subset of people with inflammatory myopathies would probably never have been referred for biopsy because of very mild or clinically undetected myopathy. Some persons with other severe conditions, very sick persons, and patients in whom myositis was a component of another connective tissue disease may also never have been referred for muscle biopsy. In addition, some patients with inflammatory myopathy, which is often patchy and focal in nature, may have had a negative result on muscle biopsy. Because our study was retrospective, we may also not have identified all malignancies; only a prospective study would address these specific issues.

We chose to analyze our data from the clinical perspective of whether risk for malignant disease is increased in patients with newly diagnosed myositis. We therefore included all cases of malignant disease that occurred concurrently with (within 7 days) or after diagnosis of myositis. However, over the study period (1981 to 1997), the proposed association between myositis and malignant disease was common knowledge, and this may have led to investigation specifically for occult malignant disease. Zantos and colleagues (8) sug-

Table 5. Site or Type of Malignant Disease, by Myositis Subgroup*

Polymyositis		Dermatomyositis		Inclusion-Body Myositis		Myositis Associated with Connective Tissue Disease		Childhood Myositis at/after Myositis Diagnosis
At/after Myositis Diagnosis	Before Myositis Diagnosis	At/after Myositis Diagnosis	Before Myositis Diagnosis	At/after Myositis Diagnosis	Before Myositis Diagnosis	At/after Myositis Diagnosis	Before Myositis Diagnosis	
Lung (8)*	Breast (5)	Head and neck (3)	Bladder (4)	Lung (2)	Bladder (1)	Lung (1)	Breast (1)	Head and neck (1) Cervix (1)
Breast (6)	Non-Hodgkin lymphoma (2)	Lung (3)	Breast (3)	Lip (2)	Colorectal (1)	Breast (1)	Hairy-cell leukemia (1)	
Chronic lymphocytic leukemia (4)	Colorectal (1)	Ovary (2)	Colorectal (3)	Kidney (1)	Ovary (1)	Chronic myelogenous leukemia (1)	Melanoma (1)	
Prostate (2)	Head and neck (1)	Colorectal (2)	Prostate (2)	Colorectal (1)	Prostate (1)	Colorectal (1)	Polycythemia rubra vera (1)	
Melanoma (2)	Lung (1)	Cervix (2)	Cervix (1)	Non-Hodgkin lymphoma (1)				
Non-Hodgkin lymphoma (2)	Melanoma (1)	Stomach (1)	Hodgkin lymphoma (1)	Chronic lymphocytic leukemia (1)				
Bladder (2)	Myelodysplasia (1)	Breast (1)	Meningioma (1)					
Colorectal (2)	Breast (male) (1)	Prostate (1)	Non-Hodgkin lymphoma (1)					
Ovary (2)	Esophagus (1)	Non-Hodgkin lymphoma (1)	Ovary (1)					
Head and neck (2)	Ovary (1)	Uterus (1)	Head and neck (1)					
Uterus (2)			Stomach (1)					
Pancreas (1)								
Unknown (1)								
Kidney (1)								
Stomach (1)								
Mesothelioma (1)								
Cervix (1)								
Esophagus (1)								
Myeloma (1)								
Ependymoma (1)								

* The number of cases of the condition appears in parentheses.

gested that preclinical malignant diseases that are likely to be detected by intensive surveillance will be discovered within the first year of diagnosis of myositis. We addressed this potential for diagnostic suspicion bias by performing a second analysis in which malignancies detected in the first year after diagnosis of myositis were excluded; overall increased risk for malignant disease was still observed.

The early increased risk for malignant disease after diagnosis of myositis is not likely to be explained by an effect of immunosuppressant therapy on this risk. However, unlike Chow and associates (9), who reported no excess risk after the first 2 years following diagnosis of myositis in long-term survivors of polymyositis or dermatomyositis, we found an excess risk for malignant disease above that of the general population that was still evident 5 years after diagnosis of myositis. Some of this late excess risk may be the result of long-term effects of immunosuppressant therapy.

We also found an increased risk for concurrent and subsequent malignant disease in inclusion-body myositis (standardized incidence ratio, 2.4 [CI, 1.2 to 4.9]). Case

reports of inclusion-body myositis and malignant disease have been published (27, 28), and Lotz and colleagues (29) reported that 15% (6 of 40 patients with inclusion-body myositis) had malignant disease. This proportion compares to our finding of 23% (12 of 52 patients).

We found an increased risk for malignant disease in myositis associated with connective tissue disease, although the number of patients was small and the results were no longer significant if data from the first year after diagnosis of myositis were excluded. These results should therefore be interpreted with caution. We also observed an apparent increased risk for malignant disease in childhood myositis, although the number of patients was small and all types of childhood myositis (polymyositis, dermatomyositis, and myositis associated with connective tissue disease) were analyzed together.

Our study does not address the question of whether asymptomatic patients should be screened for malignant disease in this initial period of increased risk. From a clinical perspective, it may be reasonable to advise that asymptomatic patients be screened for diseases for which early detection and treatment have been shown to im-

prove patient outcome: for example, cervical, breast, and colorectal cancers (30). Other investigators have suggested that it may be reasonable to perform screening if factors that might be predictive of malignant disease, such as epidermal necrosis in dermatomyositis or lack of response to steroids, are present (31–34).

Another reason to screen asymptomatic patients might be if successful treatment of malignant disease leads to improvement in myositis. Improvements in myositis with anticancer therapy and flares associated with progression of malignant disease have been reported (29, 35–37), but the lack of controlled studies precludes drawing inferences about causality from these observations.

We could not ascertain which malignancies were clinically obvious and which were detected by screening. Previous studies have generally found that the yield of intensive search for occult malignant disease is low (3, 4, 38–42), although cases of neoplasms being uncovered only after a systematic search have been reported (43). Some malignancies, such as ovarian cancers, may be difficult to detect even with initial and frequently repeated evaluations (34).

In summary, we performed a population-based cohort study of the association between idiopathic inflammatory myopathy and malignant disease, based on identification of patients with myositis from a centralized muscle pathology service. By including patients with known myositis on strict pathologic grounds, we ensured the legitimacy of the diagnosis (compared with previous studies that used hospital discharge diagnostic codes, which may not accurately reflect the diagnosis). We could also therefore distinguish polymyositis from dermatomyositis on histologic rather than clinical criteria and could thus draw firmer conclusions about the association between malignant disease and each of these distinct entities. We verified that risk for concurrent and subsequent malignant disease is increased in both polymyositis and dermatomyositis. We also established that although this risk for malignant disease is highest in the first 3 years after diagnosis of myositis compared with any later time, the risk is still apparent 5 years after diagnosis of idiopathic inflammatory myopathies. The risk for malignant disease was also increased in inclusion-body myositis, a finding that needs verification in other studies.

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