

# Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study

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## Summary

**Background** Dermatomyositis and polymyositis are associated with cancer, but previous nationwide studies have not had sufficient cases to test the association between myositis and specific cancer types. Our aim was to investigate the risk of specific cancer types in individuals with dermatomyositis and polymyositis.

**Methods** We did a pooled analysis of published national data from Sweden, Denmark, and Finland. All patients with dermatomyositis and polymyositis ( $\geq 15$  years old) were identified by discharge diagnosis from the Swedish National Board of Health (1964–83), Danish Hospital Discharge Registry (1977–89), and Finnish National Board of Health (1969–85). Personal details were matched to national cancer registries, to identify all cases of cancer up to 1987 in Sweden, 1995 in Denmark, and 1997 in Finland, and to national death registries for the same periods. We calculated standardised incidence ratios (SIR) for individual cancer sites for dermatomyositis and polymyositis separately, using national cancer rates by country, sex, age, and date.

**Findings** We identified 618 cases of dermatomyositis, of whom 198 had cancer. 115 of the 198 developed cancer after diagnosis of dermatomyositis. This disease was strongly associated with malignant disease (SIR 3.0, 95% CI 2.5–3.6), particularly ovarian (10.5, 6.1–18.1), lung (5.9, 3.7–9.2), pancreatic (3.8, 1.6–9.0), stomach (3.5, 1.7–7.3), and colorectal (2.5, 1.4–4.4) cancers, and non-Hodgkin lymphoma (3.6, 1.2–11.1). 137 of the 914 cases of polymyositis had cancer, which developed after diagnosis of polymyositis in 95. Polymyositis was associated with a raised risk of non-Hodgkin lymphoma (3.7, 1.7–8.2), and lung (2.8, 1.8–4.4) and bladder cancers (2.4, 1.3–4.7). In both dermatomyositis and polymyositis, risk of malignant disease was highest at time of myositis diagnosis.

**Interpretation** Our results provide evidence that dermatomyositis is strongly associated with a wide range of cancers. The overall risk of malignant disease is also modestly increased among patients with polymyositis, with an excess for some cancers.

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## Introduction

Previous epidemiological studies have shown an increased rate of cancer in people with dermatomyositis and polymyositis.<sup>1–4</sup> However, these studies have had too few myositis cases with each cancer type to examine the associations with specific cancers.<sup>1–4</sup> Paraneoplastic syndromes such as Eaton-Lambert syndrome, limbic encephalitis, and cerebellar ataxia are mediated by cancer-associated antibodies and are usually linked with particular cancer types.<sup>5</sup> Identification of an association with specific cancer types would both enhance our understanding of the causes of myositis and help to identify appropriate diagnostic workup for cancer screening in affected patients.<sup>6</sup> Epidemiological studies and case series of dermatomyositis and polymyositis suggest an association with ovarian, lung, and gastric cancers in the former disease.<sup>1,7,8</sup>

Our aim was to investigate risk of specific cancer types in dermatomyositis and polymyositis by pooled analysis of published national data from Sweden, Denmark, and Finland. We studied cancers that arose before and after development of myositis.

## Methods

### Patients

We used data from three published studies.<sup>1–3</sup> Additionally, more recent follow-up data were available from Denmark and Finland. Only patients in hospital who had polymyositis and dermatomyositis were included. Each country has a cancer registry to which reporting of cancers is mandatory for treating physicians and pathology and haematology laboratories. All cancers were classified according to the International Classification of Diseases (ICD-7). Each country records all deaths. The cancer registries of the three countries have been validated, and have over 95% completion rates.<sup>9–11</sup>

In Sweden, all adults ( $\geq 15$  years) with dermatomyositis and polymyositis were identified by discharge diagnosis from the National Board of Health, with ICD-7 codes 710.00, 710.01, and 726.30 from 1964 to 1968, and ICD-8 codes 716.00 and 716.10 from 1969 to 1983. Patients with myositis were matched to the cancer registry to identify cases of cancer diagnosed in 1987, and unique personal identification numbers were issued. To provide information on censoring after myositis, personal identification numbers were matched to the Cause-of-Death Registry, which includes information on all deaths whether they took place in Sweden or elsewhere. Two dermatologists reviewed a random sample of 10% (76) of hospital records of patients diagnosed with myositis who were classified according to Bohan and Peter's criteria.<sup>12</sup> This system defines polymyositis as an inflammatory myositis with no rash, and dermatomyositis as an inflammatory myositis with dermatological features (including heliotrope rash, scaly erythematous rash over dorsum of hands, or involvement of the knees, elbows, and medial malleoli, face, neck, and upper torso). Of those reviewed, 72% (50) were classified as definitely, and 20% (14) as probably, having either dermatomyositis or polymyositis.

In Denmark, all adults ( $\geq 15$  years) with dermatomyositis or polymyositis were identified by discharge diagnosis (ICD-8 codes) from the hospital registry between 1977 and 1989. A unique personal identification number was issued, and all those with myositis were linked to the national cancer registry to identify all cases of cancer until 1995. Myositis patients were also matched to the Central Population Register, which contains information about death and migration of all residents.

In Finland, all adults ( $\geq 15$  years) with dermatomyositis or polymyositis were identified by discharge diagnosis (ICD-8 codes) from the National Board of Health between 1969 and 1985. The medical records of each patient with a myositis diagnosis were requested, and a rheumatologist reviewed those available (89%, 627). Of these records, 50% (311) of cases were excluded because of incorrectly classified disease or failure to fulfil Bohan and Peter's diagnostic criteria.<sup>12</sup> The remaining patients were issued with personal identifiers, which were subsequently matched to the national cancer registry and the national mortality files of Statistics Finland until 1997.

### Analysis

Our main aim was to determine risk of developing cancer after diagnosis of myositis. For this analysis, patients diagnosed with dermatomyositis or polymyositis before age 15 years were excluded. Patients with non-melanoma skin cancer were also excluded, because this cancer type is reported differently in the three Nordic countries. Finally, in-situ cancers were excluded from the Swedish and Danish data sets because these cancers are not included in the national rates. In-situ cancers (apart from skin and cervix) were included in the Finnish data. Second and subsequent cancers that constituted the first cancer diagnosed after myositis were included. We established the number of years of follow-up for each patient with myositis, beginning at the date of diagnosis and ending at the date of censorship—ie, date of diagnosis of cancer, death, or end of follow-up period.

We examined the association between dermatomyositis and polymyositis and all cancer types combined and specific types of cancer individually with standardised incidence ratios (SIR)—ie, the number of cancer cases that arose among dermatomyositis or polymyositis patients divided by the expected number of cancer cases according to national age-specific, sex-specific, and period-specific cancer rates. Because certain histological subtypes of cancer share the ability to produce substances that cause paraneoplastic syndromes, we assessed the risk of histological types of cancer developing in myositis. We used three broad categories: squamous carcinomas (head and neck cancers, oesophageal cancer, and carcinoma of the cervix), adenocarcinomas (stomach, colorectal, pancreas, thyroid, breast, ovary, uterus, and prostate), and haemopoietic and lymphatic malignant diseases (non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and leukaemia). Categories for squamous carcinomas and adenocarcinomas were based on the most common histological type at each cancer site. Lung cancers were not included in any of these categories, since histology was unknown for a substantial proportion of cases in the Swedish and Danish data sets, and this site has equally common histological subtypes.

To assess whether associations varied according to time after myositis diagnosis, we divided follow-up into three periods: 1 year or less; 2–5 years, and more than 5 years. A further analysis was done to assess the risk of malignant disease among those aged between 15 and 44 years and 45

years and over at myositis diagnosis, separately for dermatomyositis and polymyositis.

Cancers identified before diagnosis of myositis were classified according to cancer site (ICD-7 codes), and by numbers of years before diagnosis of myositis. To provide an estimate of the risk of cancer in myositis patients in the 2 years before myositis diagnosis, we calculated SIRs by observed and expected cancers in all myositis patients in two periods: 0–11 and 12–23 months before myositis diagnosis. Only people surviving cancer could be diagnosed with myositis; thus, the expected rates had to be adjusted for cancer survival. To make this adjustment, risks were divided by Finnish site-specific cancer survival rates.<sup>13</sup> For relative risks at 0–11 and 12–23 months before diagnosis of myositis, we used 6 and 18 month survival rates, respectively, and made this survival adjustment for relative risks significantly ( $p < 0.05$ ) raised in non-adjusted analyses.

### Results

We identified 618 patients with dermatomyositis (Sweden  $n=329$ , Denmark  $n=218$ , Finland  $n=71$ ) and 914 with polymyositis (Sweden  $n=389$ , Denmark  $n=350$ , Finland  $n=175$ ). The mean age at diagnosis of dermatomyositis was 55.6 (SD 18.4) years for men and 55.4 (17.1) for women, and for polymyositis was 56.2 (16.2) for men, and 57.5 (16.3) for women. Among those with dermatomyositis, a total of 198 cancers were identified, of which 115 developed after diagnosis. Among those with polymyositis, 137 cancers were identified, of which 95 developed after diagnosis.

#### Association between dermatomyositis and polymyositis, and cancer

For all cancer types, there was a three-fold increase in risk of malignant disease after diagnosis of dermatomyositis. The SIRs for men and women with dermatomyositis were 3.3 (95% CI 2.5–4.4) and 2.8 (2.2–3.6), respectively. Since SIRs were almost the same for sex-neutral cancers, results for men and women were combined (table 1). The highest risks after diagnosis of dermatomyositis were for ovarian, lung, pancreatic, stomach, and colorectal cancers, and for lymphomas. However, the relative risk of many other malignant diseases was also raised. Polymyositis increased risk of cancers by 30%. The SIR for the entire follow-up for polymyositis was 1.4 (95% CI 1.0–1.8) for men and 1.2 (0.9–1.6) for women. The greatest increased risks were for non-Hodgkin lymphoma and lung and bladder cancers. By contrast with

Cancer type (ICD-7 code)	Dermatomyositis (n=618)		Polymyositis (n=914)	
	Number	SIR (95% CI)	Number	SIR (95% CI)
All (140–205)	115	3.0 (2.5–3.6)	95	1.3 (1.0–1.6)
Oesophagus (150)	1	2.9 (0.4–20.8)	1	1.3 (0.2–9.4)
Stomach (151)	7	3.5 (1.7–7.3)	1	0.3 (0.04–1.9)
Colorectal (153, 154)	12	2.5 (1.4–4.4)	10	1.1 (0.6–2.0)
Pancreas (157)	5	3.8 (1.6–9.0)	1	0.4 (0.1–2.7)
Lung, trachea, and bronchus (162)	19	5.9 (3.7–9.2)	20	2.8 (1.8–4.4)
Breast (170)	12	2.2 (1.2–3.9)	12	1.4 (0.8–2.5)
Cervix (171)	2	2.7 (0.7–10.8)	0	0 (0–2.9)
Ovary (175)	13	10.5 (6.1–18.1)	2	1.1 (0.3–4.2)
Prostate (177)	5	1.8 (0.8–4.4)	4	0.6 (0.2–1.6)
Kidney (180)	2	1.7 (0.4–6.7)	4	1.5 (0.6–3.9)
Bladder (181)	3	1.8 (0.6–5.6)	9	2.4 (1.3–4.7)
Non-Hodgkin lymphoma (200)	3	3.6 (1.2–11.1)	6	3.7 (1.7–8.2)
Hodgkin's lymphoma (201)	1	5.9 (0.8–42.0)	0	0 (0–11.1)
Myeloma (203)	1	1.5 (0.2–10.5)	2	2.1 (0.5–8.5)
Leukaemia (204)	2	2.6 (0.7–10.5)	2	1.4 (0.3–5.4)

Table 1: Standardised incidence ratios (SIR) and 95% CIs for cancer after diagnosis of dermatomyositis or polymyositis

	Squamous*		Adenocarcinoma†		Haematological and lymphatic‡	
	Number	SIR (95% CI)	Number	SIR (95% CI)	Number	SIR (95% CI)
<b>Dermatomyositis</b>						
Men	4	8.1 (3.0–21.6)	15	2.6 (1.6–4.3)	4	4.0 (1.5–10.6)
Women	3	2.3 (0.7–7.1)	40	3.4 (2.5–4.6)	3	2.1 (0.7–6.5)
<b>Polymyositis</b>						
Men	2	1.6 (0.4–6.4)	10	0.6 (0.3–1.2)	5	2.3 (0.9–5.5)
Women	1	1.0 (0.7–1.6)	20	1.0 (0.7–1.6)	5	2.2 (1.0–5.5)

\*Includes head and neck cancers and oesophageal and cervical cancer. †Includes stomach, colorectal, pancreas, thyroid, ovarian, breast, and prostate cancer. ‡Includes non-Hodgkin lymphoma, Hodgkin's lymphoma, myeloma, and leukaemia.

Table 2: Standardised incidence ratios (SIR) and 95% CIs for cancers of different histological type in dermatomyositis and polymyositis

dermatomyositis, there was no increased risk of ovarian, colorectal, stomach, or pancreatic cancers (table 1).

#### Association between histological types of cancer and myositis

We examined whether or not myositis was associated with specific histological subtypes (table 2). In dermatomyositis, although adenocarcinomas were the most common type of cancer recorded, there was an increased risk associated with all histological types. Risk of squamous cell cancers and adenocarcinomas was not increased in patients with polymyositis; however, risk of haematological and lymphatic malignant diseases was increased two-fold.

#### Length of follow-up and risk of cancer

The risk of cancer was highest within the first year of myositis diagnosis, and dropped substantially thereafter (table 3). In those with polymyositis, the risk fell to expected rates 5 years after diagnosis; however, the risk in dermatomyositis did not return to expected population values for most cancers. The risks of ovarian, pancreatic, and lung cancer remained high up to 5 years after diagnosis of dermatomyositis, and the increased risk of pancreatic and colorectal cancer extended past the 5 years follow-up. The risk of non-Hodgkin's lymphoma was increased in the first year but not subsequently.

#### Age and risk of cancer

Although there was a raised risk of malignant disease in people aged 15–44 years at time of dermatomyositis diagnosis (SIR 2.2, 95% CI 1.1–4.2), and in those aged 45 and older (3.1, 2.6–3.7), the number of cancers

recorded after diagnosis in the younger age group was small (nine cancers in 153 patients). There was no increase in the risk of cancer in patients diagnosed with polymyositis aged 15–44 years (SIR 1.2, 95% CI 0.5–2.6), but a small increased risk of malignant disease in those aged 45 years and older (1.3, 1.1–1.6) was recorded.

#### Cancers arising before diagnosis of myositis

Of cancers diagnosed before dermatomyositis, most preceded myositis by 2 years or less (71%). By contrast, most cancers were diagnosed greater than 5 years before polymyositis diagnosis. In the year before diagnosis of dermatomyositis, 43 cancers were recorded (adjusted SIR 9.8, 95% CI 7.3–15.3). Lung (43.2, 26.1–71.7), ovarian (28.6, 10.7–76.1), colorectal (10.5, 7.7–23.3), and breast cancers (10.7, 5.1–22.5) were associated with increased adjusted risks. In the 1–2 years before dermatomyositis diagnosis, 16 cancers were recorded, giving an adjusted SIR of 4.6 (95% CI 2.8–8.7). In polymyositis patients, 11 cancers were seen in the year before diagnosis (1.6, 0.9–2.9), and only risk of lung cancer was increased (4.4, 1.4–13.6). In the 1–2 years before polymyositis diagnosis, three cancers were recorded, giving an adjusted SIR of 0.5 (0.2–1.7).

#### Discussion

We have confirmed that both dermatomyositis and polymyositis are associated with an increased risk of malignant disease, but that this risk is substantially greater for dermatomyositis. The cancers most strongly associated with dermatomyositis are ovarian, lung, gastric, colorectal, and pancreatic cancers, and non-Hodgkin's lymphoma. However, there was also an association with a broad range of other malignant diseases. In patients with polymyositis, there was a raised risk of lung and bladder cancers, and non-Hodgkin's lymphoma. Our results emphasise that dermatomyositis and polymyositis are different diseases, in respect of the magnitude of risk and types of associated malignant disease.

Our study is one of the largest of its kind, and has allowed us to estimate fairly precisely specific cancer risks. To assess the relations between specific cancer types and myositis a large population sample is needed, because dermatomyositis and polymyositis are rare, and individual cancer types uncommon. Despite our use of data from three countries, the number of cancer cases in each category was small, underscoring the difficulty of epidemiological studies in rare diseases.

Type of cancer	0–1 year follow-up		2–5 years follow-up		>5 years follow-up	
	Number	SIR (95% CI)	Number	SIR (95% CI)	Number	SIR (95% CI)
<b>Dermatomyositis</b>						
All	55	13.5 (10.4–17.6)	30	2.5 (1.7–3.5)	30	1.4 (1.0–2.0)
Stomach	6	27.5 (12.4–61.3)	0	0 (0–4.7)	1	1.9 (0.3–13.3)
Colorectal	4	8.6 (3.2–22.8)	2	1.2 (0.3–5.0)	6	2.3 (1.03–5.1)
Pancreas	1	7.1 (1.0–50.4)	2	4.1 (1.03–16.5)	3	4.1 (1.3–12.6)
Lung	10	28.3 (15.2–52.5)	5	4.7 (2.0–11.4)	4	2.2 (0.8–5.9)
Non-Hodgkin lymphoma	3	42.3 (13.6–131.0)	0	0 (0–12.3)	0	0 (0–6.2)
Breast	5	9.9 (4.1–23.8)	4	2.4 (0.9–6.3)	4	1.3 (0.5–3.4)
Ovary	9	72.0 (37.5–138.4)	3	7.3 (2.4–22.6)	1	1.5 (0.2–10.6)
Prostate	3	9.6 (3.1–29.7)	0	0 (0–3.2)	2	1.4 (0.4–5.6)
<b>Polymyositis</b>						
All	19	2.6 (1.6–4.0)	40	1.5 (1.1–2.1)	36	0.9 (0.6–1.3)
Colorectal	0	0 (0–3.3)	6	1.8 (0.8–4.1)	4	0.8 (0.3–2.2)
Pancreas	2	7.5 (1.9–30.1)	0	0 (0–3.2)	0	0 (0–2.2)
Bladder	1	2.7 (0.4–18.8)	5	3.8 (1.6–9.0)	1	0.5 (0.1–3.7)
Lung	2	2.3 (0.6–9.3)	10	3.4 (1.8–6.4)	6	1.4 (0.7–3.2)
Non-Hodgkin lymphoma	2	12.6 (3.2–50.3)	1	1.8 (0.3–12.7)	2	2.2 (0.6–8.8)
Breast	1	1.3 (0.2–8.9)	5	1.7 (0.7–4.0)	6	1.3 (0.6–2.8)

Table 3: Standardised incidence ratios (SIR) and 95% CIs of cancer by year after diagnosis of myositis

We have shown an increase in risk of malignant disease in the period around diagnosis of myositis suggesting that heightened surveillance for cancer is likely at this time, resulting in some detection bias. However, in dermatomyositis, the raised risk of malignant disease persisted through all years of follow-up, which suggests that detection bias would explain only a small part of this association, and that a true link with cancer does exist. The clustering of cancer cases before diagnosis of myositis further suggests that the association is not merely a result of increased cancer surveillance after this diagnosis. Also, a previous analysis of the Swedish data set indicated that mortality due to cancer was increased in individuals with dermatomyositis, which would not be affected by better diagnosis of malignant disease.<sup>1</sup>

The small overall magnitude of association in polymyositis, the increased risk in the first year after polymyositis diagnosis, and the reduced risk after 5 years of follow-up all suggest that detection bias could account for a large part of the recorded association in polymyositis. A previous meta-analysis of case-control and cohort studies of myositis and malignant disease showed no increase in cancer detection before diagnosis of polymyositis, despite a raised risk after diagnosis.<sup>14</sup> Misclassification of dermatomyositis cases as polymyositis could also contribute to this apparent high risk in polymyositis.

We assessed the case records according to Bohan and Peter's criteria.<sup>12</sup> This classification has been criticised because diagnosis of dermatomyositis is based both on the presence of a rash and myositis.<sup>15</sup> More recent evidence shows that changes in muscle characteristic of dermatomyositis can take place with little or no rash being evident.<sup>16</sup> The only cohort study to classify myositis on the basis of histological diagnosis, and therefore less likely to have misclassified dermatomyositis as polymyositis, showed a small but significant increased risk of malignant disease in polymyositis.<sup>4</sup> Furthermore, cancers with increased risk in polymyositis differ from those in dermatomyositis. Therefore, a small increased risk of malignant disease in polymyositis seems likely.

Dermatomyositis is probably a paraneoplastic event in some patients. Ovarian, lung, and colorectal cancers were diagnosed frequently both before and after diagnosis of dermatomyositis, suggesting that these could be candidate cancers associated with the disease. Dermatomyositis has been noted to improve after treatment of cancer, with recurrence of muscle weakness taking place at relapse of malignant disease, further suggesting a paraneoplastic origin.<sup>17,18</sup> There also seem to be differences in clinical features of dermatomyositis associated with malignant disease. Patients with cancer-associated dermatomyositis are more likely to have normal creatinine kinase values and digital vasculitis, and less likely to have myositis-specific autoantibodies than those without cancer.<sup>19,20</sup> Generally, paraneoplastic features are associated with certain histological types of cancer;<sup>5,6</sup> however, different cancers seem to be associated with dermatomyositis. Although we noted an increased risk of cancers diagnosed before dermatomyositis, the method of calculation, by expected cancer survival, was imprecise.

Our results also suggest that the common assumption that malignant disease is a feature only in older people developing dermatomyositis is incorrect.<sup>21</sup> Although the absolute number of cancer cases is small, the risk of malignant disease is increased even in dermatomyositis patients aged 45 or younger.

Our study is based on information from three Nordic countries with little ethnic diversity, suggesting that our

results are mainly relevant to whites. However, case series indicate that other types of cancer might be commonly associated with myositis among Asians.<sup>22</sup>

A limitation of registry-based data is the possibility of some misclassification of myositis. Although a subset of case records in Sweden and all those in Finland, were reviewed, no Danish case records were inspected; however, when we did analyses excluding Danish data, results remained unchanged. Additionally, there could be a small group of patients misclassified with dermatomyositis or polymyositis rather than other forms of muscle disease, which would mean that the calculated risks of malignant disease are underestimated.

Amyopathic dermatomyositis has been identified,<sup>21</sup> but any such cases are unlikely to have been included in our study. Although there are case reports of amyopathic dermatomyositis associated with malignant disease,<sup>23,24</sup> there are no population data on the increased risk of cancer for this subtype of dermatomyositis.

The importance of our study lies partly in its implications for the malignant disease workup of myositis patients, which could potentially reduce mortality in these individuals. Rheumatology textbooks and reviews cite personal experience and scant data on the cancer types associated with dermatomyositis and polymyositis in their recommendations for investigation of malignant disease.<sup>20,25,26</sup> Consequently, recommendations vary widely, and range from advising careful clinical examination and routine laboratory screening,<sup>25</sup> to extensive invasive investigations.<sup>20</sup> In view of the increased risk of ovarian, lung, gastric, colorectal, pancreatic, and breast cancer, and non-Hodgkin lymphoma, our findings suggest that, in addition to routine examination and laboratory screening, chest computed tomography (CT) scan, faecal blood testing, abdominal ultrasound or CT scan; mammography, pelvic CT scan, or ultrasound, and gynaecological examination, are justified in those with dermatomyositis. Since the risk of malignant disease remains high for many years after diagnosis, vigilance needs to be maintained. Even if mortality is not prevented, or survival prolonged, for these malignant diseases, disability from myositis could be alleviated if cancers are detected and treated early enough. In those with polymyositis, investigation should be targeted to the commonest sites of cancer (including lung, bladder, and non-Hodgkin's lymphoma).

#### Contributors

Catherine Hill and Yuqing Zhang were responsible for study design and execution, and analysis and interpretation of results. Bardur Sigurgeirsson, Lene Mellemkjaer, Eero Pukkala, and Antti Airio recorded data and helped with analysis and interpretation of results. Stephen Evans contributed to data analysis and David Felson provided the conceptual basis for the study. All authors were involved in writing the manuscript.

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