Heliyon 10 (2024) e33883

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Cancer and pulmonary fibrosis risks in patients with dermatomyositis and polymyositis: A retrospective cohort study

Fung-Chang Sung [a,b,c], Pei-Chun Chen [d,e], Chih-Hsin Muo [b], Te-Chun Shen [f,g,*], Anthony J. Gerbino [h]

[a] Department of Health Services Administration, College of Public Health, China Medical University, Taichung, 404, Taiwan
[b] Management Office for Health Data, China Medical University Hospital, Taichung, 404, Taiwan
[c] Department of Food Nutrition and Health Biotechnology, Asia University, Taichung, 413, Taiwan
[d] Department of Public Health, College of Public Health, China Medical University, Taichung, 404, Taiwan
[e] National Center for Geriatrics and Welfare Research, National Health Research Institutes, Yunlin, 632, Taiwan
[f] School of Medicine, College of Medicine, China Medical University, Taichung, 404, Taiwan
[g] Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, 404, Taiwan
[h] Division of Pulmonary Medicine, Virginia Mason Medical Center, Seattle, Wa, 98101, USA

A B S T R A C T

Background: This study assessed the risks of developing pulmonary fibrosis and cancer and whether patients are at risk of acquiring subsequent cancer after pulmonary fibrosis development.
Methods: From the claims data of 22 million insured people, we identified 1461 patients with dermatomyositis (DM) and 1058 with polymyositis (PM) diagnosed in 1996–2016 and 50,380 comparison individuals without pulmonary fibrosis and cancer at baseline, matched by sex and age. Incident pulmonary fibrosis and cancer in each cohort were assessed at the end of 2016. We further followed up individuals with and without pulmonary fibrosis to assess the subsequent development of cancer.
Results: The cancer incidence was 2.6-fold higher in the DM/PM groups combined than in comparisons (135.3 vs. 52.1 per 10,000 person-years), with an adjusted hazard ratio (aHR) of 3.11 (95 % confidence interval [CI] = 2.71–3.58). The incidence was lower in patients with PM than in those with DM (81.3 vs. 176 per 10,000 person-years), with an aHR of 0.39 (95 % CI = 0.29–0.54). The likelihood of developing pulmonary fibrosis was 92 times higher in the PM/DM groups combined than in comparisons (37.9 vs. 0.41 per 10,000 person-years; aHR 84.0 (95 % CI = 49.5–143). The incidence was 1.44-fold higher in patients with PM than in those with DM (46.1 vs. 32.0 per 10,000 person-years), but the difference was not significant. Further analysis showed that in 2452 patients with myositis without pulmonary fibrosis, 234 (9.5 %) had cancer, whereas no cancer was identified in 67 patients with pulmonary fibrosis ($p = 0.019$).
Conclusion: Patients with PM and DM are at great risk of developing cancer and pulmonary fibrosis. Patients who develop pulmonary fibrosis might be at low risk of developing cancer. The complexity of cancer risk interplaying between patients with and without pulmonary fibrosis has clinical relevance and deserves further investigation. Patients who are free of pulmonary fibrosis deserve close monitoring to reduce subsequent cancer risk.

1. Introduction

Dermatomyositis (DM) and polymyositis (PM) are rare autoimmune disorders characterized by myositis, with connective tissue inflammation leading to chronic muscle fiber inflammation [1]. The skin also becomes inflamed with a rash appearance in patients with DM. The incidence rates of these two diseases vary among populations, being higher for DM than for PM in general [2–8]. Patients

* Corresponding author. Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, No. 2, Yude Road, Taichung, 404, Taiwan.
E-mail address: chestshen@gmail.com (T.-C. Shen).

https://doi.org/10.1016/j.heliyon.2024.e33883
Received 20 April 2024; Received in revised form 4 June 2024; Accepted 28 June 2024
Available online 2 July 2024
2405-8440/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

are at a higher risk of developing muscular and/or connective tissue damage, involving the heart, lungs, joints, and gastrointestinal tract and thus developing other disorders, including cancers, lung diseases, and cardiovascular diseases.

The increased likelihood of developing cancers and progression of pulmonary fibrosis have been carefully considered in patients with DM and PM [5–8]. The prevalence of cancer varies among populations, in general nearly twofold higher in patients with DM than in those with PM.

Pulmonary complications include extramuscular manifestations in patients with DM and PM. Among the pulmonary involvements, lung cancer and other interstitial lung diseases (ILDs) are common disorders for these patients [9–13]. Pulmonary complications of ILD involve shortness of breath because of lung scarring (fibrosis), with pulmonary fibrosis being the most notable [13–17]. A recent systemic analysis found that approximately 13–40 % of patients with ILDs in Europe and the USA developed a progressive fibrosing phenotype [13].

Lung cancer also has been reported as a common comorbidity of patients with idiopathic pulmonary fibrosis (IPF), with the prevalence ranging from 2.7 % to 48.2 % [18–21]. Lung cancer may develop post-IPF or coexistence with IPF [21,22]. However, the relationship between pulmonary fibrosis and lung cancer for patients with DM and PM remains unclear. An earlier Japanese study found the cumulative incidence of lung cancer in an IPF cohort increased with follow-up years, but the underlying disorder associated with IPF was not specified [23]. Conversely, a Japanese retrospective study using 25-year medical records found that among 134 patients with DM/PM, those with ILD are at a reduced risk of developing cancer [12]. To our knowledge, no other study has ever reported this benefit for patients with ILD or pulmonary fibrosis. Whether patients with DM and PM are at further risk of developing cancers after pulmonary fibrosis remains unclear. We, therefore, used insurance claims data from Taiwan to identify a cohort of patients with DM and a cohort with PM to evaluate the risk of developing pulmonary fibrosis and cancers. The subsequent risk of developing cancers for patients with DM and PM who had developed pulmonary fibrosis was also evaluated.

2. Methods and materials

2.1. Data source and study design

A retrospective cohort study was conducted using the claims data of 22 million individuals covered by the National Health Insurance of Taiwan, which is a mandatory, single-payer social health insurance system [24]. More than 99 % of Taiwan residents have been covered by the system since 1996. Data analyses were conducted at the Health and Welfare Data Science Center designated by the Ministry of Health and Welfare. The database contains medical records of outpatient visits and hospital inpatient stays. Information on demographic status (sex, birth date, residential area, occupation, and income), healthcare provided, and cost was available. Researchers and policymakers can use the data to assess the utilization of healthcare, disparities, and outcomes of disorders. Diseases were coded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) before 2016, and Tenth Revision, Clinical Modification (ICD-10-CM) since 2016. The insurance authority changed all patient identifications into surrogate numbers before releasing the data file to researchers to protect patient privacy. The Ethical Research Committee at China Medical University and Hospital approved the study using the insurance claims data (CRREC-107-021).

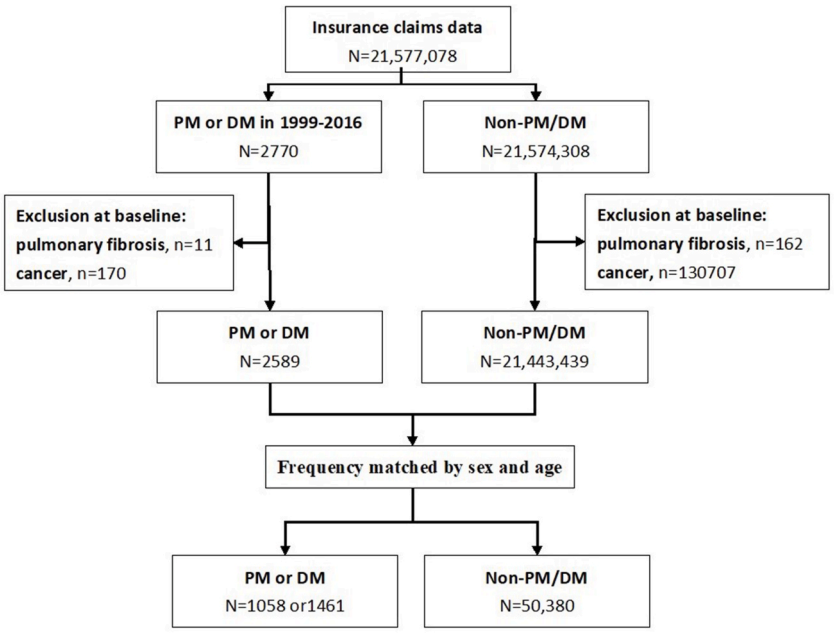

Fig. 1. Flow chart for establishing study cohorts of polymyositis (PM) and dermatomyositis (DM) and comparisons.

2.2. Study population

Using the claims data from 1998 to 2016, a group of patients with DM (ICD-9-CM 710.3; ICD-10 CM M33.0, M33.1, M33.9) and a group of patients with PM (ICD-9-CM 710.4; ICD-10-CM M33.2) aged ≥20 years, newly diagnosed from 1998 to 2016, were identified (Fig. 1). Patients with pulmonary fibrosis (ICD-9-CM 516.3/ICD-10-CM J84.1 or J84.18) or cancer ICD-9-CM 140–208/ICD-10-CM C00–C96) at the baseline were excluded. From the general population without a history of DM, PM, pulmonary fibrosis, and cancer, 20 persons for each patient with DM and PM, with frequency matched by sex and age, were included for comparison. Individuals in these three cohorts were followed up until the diagnosis of pulmonary fibrosis and/or cancer, loss to follow-up, death, or the end of 2016. Person-years of follow-up were calculated for each participant.

2.3. Statistical analysis

Baseline data on sex, age, and income were compared among the three cohorts: patients with DM, patients with PM, and their comparisons. The baseline Charlson comorbidity index (CCI) was also calculated for each person in the study cohorts to substitute individual comorbidities. Descriptive statistics were presented as numbers with percentages for categorical variables. Means (standard deviations) were also used to report continuous measures of age. The Kaplan–Meier method was used to calculate the cumulative incidence of pulmonary fibrosis developed between DM and PM cohorts, and a log-rank test was performed to examine the differences. Incidence rates of pulmonary fibrosis and cancer were then calculated for each cohort by sex. Cox proportional hazards regression analysis was performed to calculate the hazard ratios (HRs) and their related 95 % confidence intervals (CIs) of patients with PM and those with DM who developed pulmonary fibrosis and cancer. Adjusted hazard ratios (aHRs) were calculated after controlling for covariates, including sex, age, income, and CCI. Adjusted sub-distribution hazard ratios (aSHRs) and 95 % CI of pulmonary fibrosis and cancer were also estimated considering death as a competing risk. We then calculated the combined incidence of PM and DM who developed pulmonary fibrosis and cancer and estimated HRs and SRH relative to the comparison group by sex, age, income, and CCI. We further combined patients with DM and PM to identify two subgroups: with and without pulmonary fibrosis. Both subgroups were compared for the incident cancer developed. A case-control analysis was conducted to estimate the risk of developing cancer in patients with myositis with and without pulmonary fibrosis. The fudge skill was used by embedding a "1" case to each cell, replacing the cell with a "0" case, to estimate Fisher's chi-square.

3. Results

Our study cohorts consisted of 1461 patients with DM, 1058 patients with PM, and 50,380 controls without DM and PM, comprising approximately 66 % of women and 49 % aged ≥50 years (Table 1). Income distributions were alike among the three groups. Patients with PM were older, but the prevalence of CCI of >1 in patients with PM was approximately 2.5- and 8-fold greater than that in the DM group and comparisons (72.2, 29.4, and 8.2 %, respectively).

Table 1
Baseline demographic status and Charlson comorbidity index in dermatomyositis and polymyositis patients and comparisons at baseline.

	Comparisons		Dermatomyositis		Polymyositis		
	N = 50380		N = 1461		N = 1058		
	n	%	n	%	n	%	*p*-value
Sex							0.98
Women	33360	66.2	965	66.0	703	66.5	
Men	17020	33.8	496	34.0	355	33.6	
Age							0.001
<50	25840	51.3	800	54.8	492	46.5	
50–59	12180	24.2	337	23.1	272	25.7	
≥60	12360	24.5	324	22.2	294	27.8	
Mean ± SD	47.4	±17.7	45.7	±18.7	49.8	±16.0	<0.0001
Income[a]							0.55
<15000	8942	17.8	281	19.2	182	17.2	
15000–25000	23431	46.5	677	46.3	504	47.6	
≥25000	18007	35.7	503	34.4	372	35.2	
CCI							<0.0001
0	46228	91.8	1031	70.6	294	27.8	
1	2498	4.96	306	20.9	507	47.9	
2	824	1.64	78	5.34	168	15.9	
3	830	1.65	46	3.15	89	8.41	

SD, standard deviation; CCI, Charlson comorbidity index.

[a] NTD, new Taiwan dollar, 1 NTD equals 0.03 USD.

3.1. Incidence of malignancy

The cancer incidence was 2.6-fold greater in the DM and PM cohorts combined than in the control group (135.3 vs. 52.1 per 10,000 person-years), with an aHR of 3.11 (95 % CI = 2.71–3.58) (Table 2). The cancer incidence was higher in men than in women ($p < 0.001$) and increased with age (p for trend <0.001). The additional impact of comorbidities on cancer incidence was minor for patients with myositis compared with controls (7.9 vs. 56.3 per 10,000 person-years, $p < 0.001$).

The malignant incidence was significantly lower in the PM cohort than in the DM cohort (81.3 vs. 176 per 10,000 person-years), with an aHR of 0.39 (95 % CI = 0.29–0.54) and an aSHR of 0.43 (95 % CI = 0.32–0.59) for patients with PM (Table 3). Male patients had a higher rate of developing malignancy than female patients, with the overall incidence 2.2-fold higher in the DM cohort (281 vs. 130 per 10,000 person-years, $p < 0.001$) and 1.4-fold higher in the PM cohort (101 vs. 72.4 per 10,000 person-years, $p < 0.01$). Head and neck cancers were the most common malignancies, followed by lung cancer, and were much higher in men than in women.

3.2. Incidence of pulmonary fibrosis

The Kaplan–Meier method measured the cumulative incidence and showed that approximately 2 % of patients with pulmonary fibrosis developed within 2 years in both DM and PM groups (Fig. 2). The incidence increased to a greater level in patients with PM starting the 3rd year and was 3.6 % higher than that in patients with DM (6.8 vs. 3.2 %) at the end of the 18-year follow-up.

Table 3 shows that the incidence of pulmonary fibrosis was 44 % greater in the PM cohort than in the DM cohort (46.1 vs. 32.0 per 10,000 person-years), a difference that did not reach statistical significance based on measured HRs.

The incidence rate of pulmonary fibrosis in both DM and PM groups combined was 92.4-fold greater than that in the comparison group (37.9 vs. 0.41 per 10,000 person-years), with an aHR of 84.0 (95 % CI = 49.5–143) (Table 4). The incidence was higher in male patients than in female patients, increased with age, and was higher for those with comorbidity. Compared to the study population without comorbidity, the excess incidence in those with CCI of >1 was at a much greater level in patients with DM and PM than in comparisons (23.4 vs. 2.08 per 10,000 person-years) ($p < 0.001$).

3.3. Reduced malignant risk in patients who developed pulmonary fibrosis

Table 5 shows that 234 patients were malignant (9.54 %) among 2452 patients with DM and PM who had been free of pulmonary fibrosis, whereas 67 patients who developed pulmonary fibrosis were malignant-free, with the risk of <1.47 % (1/68), estimated using the fudge skill to embed "1" case to each cell, replacing the cell with "0" case) ($p = 0.019$).

Table 2
Incidences and hazard ratios of cancer compared between cohorts with and without dermatomyositis or polymyositis.

Variable	Dermatomyositis or polymyositis						Hazard ratio (95 % confidence interval)		
	No			Yes					
	Event	PY	Rate[a]	Event	PY	Rate[a]	cHR	aHR[b]	aSHR[c]
All	2401	460862	52.1	234	17294	135.3	2.64 (2.30–3.01) [e]	3.11 (2.71–3.58) [e]	2.31 (1.99–2.68) [e]
Sex									
Women	1397	312381	44.7	127	12034	105.5	2.39 (2.00–2.87) [e]	2.64 (2.19–3.18) [e]	2.10 (1.72–2.56) [e]
Men	1004	148481	67.6	107	5260	203.4	3.05 (2.50–3.73) [e]	3.94 (3.20–4.85) [e]	2.61 (2.08–3.28) [e]
Age									
<50	645	263828	24.4	79	11074	71.3	2.98 (2.36–3.76) [e]	2.75 (2.13–3.55) [e]	2.54 (1.93–3.33) [e]
50–59	670	104296	64.2	80	3697	216.4	3.46 (2.75–4.37) [e]	3.45 (2.69–4.43) [e]	2.86 (2.20–3.73) [e]
≥60	1086	92737	117.0	75	2524	297.1	2.67 (2.11–3.37) [e]	2.56 (2.01–3.25) [e]	1.60 (1.24–2.06) [e]
Income									
<15000	478	77060	62.0	40	3059	130.8	2.14 (1.55–2.95) [e]	2.94 (2.11–4.10) [e]	2.08 (1.46–2.96) [e]
15000–25000	1171	229509	51.0	120	8454	141.9	2.82 (2.34–3.41) [e]	3.29 (2.71–4.00) [e]	2.39 (1.94–2.94) [e]
≥25000	752	1545293	48.7	74	5781	128.0	2.67 (2.10–3.39) [e]	2.92 (2.28–3.74) [e]	2.28 (1.75–2.98) [e]
CCI									
0	2140	436110	49.1	132	10001	132.0	2.72 (2.28–3.24) [e]	3.60 (3.02–4.30) [e]	2.71 (2.24–3.27) [e]
≥1	261	24752	105.4	102	7293	139.9	1.30 (1.03–1.64) [d]	2.27 (1.76–2.91) [e]	1.63 (1.27–2.08) [e]

CCI, Charlson comorbidity index; cHR, crude hazard ratio.
[a] Incidence rate, per 10,000 person-years.
[b] Adjusted hazard ratio, adjusting age, sex, income, and CCI score.
[c] Adjusted subhazard ratio, adjusting age, sex, income, and CCI score by competing Cox model with death as competing factor.
[d] $p < 0.05$.
[e] $p < 0.001$.

Table 3
Incident pulmonary fibrosis and cancer compared between patients with dermatomyositis and polymyositis by sex.

	Dermatomyositis		Polymyositis		Polymyositis to Dermatomyositis		
	N = 1461		N = 1058		Hazard ratio (95 % confidence interval)		
	n (%)	Rate[a]	n (%)	Rate[a]	cHR	aHR[b]	aSHR[c]
Pulmonary fibrosis							
Men	12 (0.08)	37.9	13 (1.23)	57.4	1.47 (0.67–3.22)	1.26 (0.55–2.90)	1.32 (0.59–2.97)
Women	21 (1.44)	29.3	21 (2.00)	41.1	1.36 (0.74–2.50)	1.07 (0.56–2.04)	1.21 (0.62–2.37)
Both	33 (2.26)	32.0	34 (3.21)	46.1	1.40 (0.87–2.26)	1.14 (0.69–1.90)	1.26 (0.75–2.10)
All cancer							
Men	84 (16.9)	281	23 (6.48)	101	0.35 (0.22−0.55) ***	0.31 (0.19−0.49)[f]	0.33 (0.21−0.53) ***
Women	90 (9.33)	130	37 (5.26)	72.4	0.54 (0.37−0.79) **	0.48 (0.32−0.71) ***	0.53 (0.35−0.80)[e]
Both	174 (11.9)	176	60 (5.67)	81.3	0.45 (0.33−0.60) ***	0.39 (0.29−0.54) ***	0.43 (0.32−0.59)[f]
Lung							
Men	15 (3.02)	50.2	4 (1.13)	17.6	0.35 (0.11–1.04)	0.26 (0.08−0.83)[d]	0.29 (0.10−0.78) *
Women	19 (1.97)	27.4	4 (0.57)	7.8	0.27 (0.09−0.79) *	0.24 (0.08−0.74)[d]	0.29 (0.09−0.87) *
Both	34 (2.33)	34.3	8 (0.76)	10.8	0.30 (0.14−0.66) **	0.25 (0.11−0.55) ***	0.28 (0.13−0.60) **
Liver							
Men	9 (1.81)	20.1	4 (1.13)	17.6	0.84 (0.24–2.98)	0.59 (0.15–2.23)	0.66 (0.16–2.76)
Women	NA	8.72	NA	2.05	0.23 (0.03–1.89)	0.20 (0.02–1.85)	0.24 (0.03–2.05)
Both	12 (0.82)	12.1	5 (0.47)	6.83	0.54 (0.19–1.54)	0.40 (0.14–1.20)	0.46 (0.15–1.44)
GI tract							
Men	9 (1.81)	30.1	4 (1.13)	17.6	0.58 (0.18–1.89)	0.54 (0.15–1.89)	0.60 (0.18–1.96)
Women	9 (0.93)	13.0	6 (0.85)	11.7	0.87 (0.31–2.46)	0.69 (0.32–2.05)	0.82 (0.26–2.65)
Both	18 (1.23)	18.2	10 (0.95)	13.6	0.74 (0.34–1.60)	0.61 (0.27–1.39)	0.69 (0.30–1.59)
Head and neck							
Men	38 (7.66)	127	4 (1.13)	17.6	0.13 (0.05−0.37)[f]	0.13 (0.05−0.39)[f]	0.16 (0.05−0.47) ***
Women	6 (0.62)	8.75	NA	5.94	0.63 (0.16–2.51)	0.93 (0.21–4.03)	1.09 (0.31–3.80)
Both	44 (3.01)	44.4	7 (0.66)	9.53	0.20 (0.09−0.45) ***	0.22 (0.09−0.49) ***	0.25 (0.11−0.59) **
Kidney							
Men	NA	6.73	0 (0.00)	0.00	NA	NA	NA
Women	NA	4.33	NA	5.92	1.39 (0.28–6.94)	0.89 (0.17–4.83)	1.02 (0.15–7.18)
Both	5 (0.34)	5.01	NA	4.13	0.80 (0.19–3.33)	0.56 (0.13–2.53)	0.64 (0.13–3.21)
Lymphoma							
Men	6 (1.21)	20.1	NA	8.88	0.42 (0.09–2.09)	0.39 (0.07–2.13)	0.47 (0.10–2.17)
Women	8 (0.83)	11.5	NA	5.93	0.52 (0.14–1.96)	0.50 (0.12–2.05)	0.55 (0.12–2.53)
Both	14 (0.96)	14.1	5 (0.47)	6.84	0.48 (0.17–1.33)	0.44 (0.15–1.31)	0.51 (0.18–1.50)
Other types							
Men	8 (1.61)	26.8	5 (1.41)	22.0	0.81 (0.26–2.46)	0.74 (0.23–2.39)	0.89 (0.32–2.49)
Women	39 (4.04)	56.3	17 (2.42)	33.3	0.57 (0.32–1.01)	0.51 (0.28–0.94)	0.58 (0.32–1.07)
Both	47 (3.22)	47.4	22 (2.08)	29.8	0.61 (0.37–1.01)	0.56 (0.32–0.95)	0.64 (0.38–1.08)

[a] Incidence rate, per 10,000 person-years.
[b] Adjusted hazard ratio, adjusting age, sex, income, and CCI score.
[c] Adjusted subhazard ratio, adjusting age, sex, income, and CCI score by competing Cox model with death as competing factor; cHR, crude hazard ratio; GI, gastrointestinal; NA, the insurance authority prohibits report data with 3 or less cases for privacy protection.
[d] $p < 0.05$.
[e] $p < 0.01$.
[f] $p < 0.001$.

4. Discussion

4.1. Epidemiology of patients with DM and PM

Both DM and PM are rare diseases defined by muscle inflammation with overlapping clinical characteristics of autoimmune myopathies. Previous epidemiologic studies thus often combine these two diseases when reporting findings of developing pulmonary fibrosis and malignancy [2–8]. This population-based longitudinal study used the 18-year claims data on a population of nearly 22 million. We were able to make comparisons between patients with DM and those with PM.

The present study found incident cases of DM were nearly 40 % more than those of PM. DM is likely more prevalent than PM in our study population, a finding consistent with that of previous studies. Patients with PM were older with a baseline comorbidity prevalence of approximately 43 % higher than those with DM.

The incidence in the Taiwan population reported in 2011 was 7.1/106 for DM and 4.4/106 for PM [3], which are approximately similar to the findings in an earlier study in Japan. It merged the data of incident DM/PM of 2004–2010, ranging from 10 to 13 per 1, 000,000 person-years with a prevalence of 13.2 per 100,000 [2]. The combined prevalence of PM and DM was reported as 21.5/100, 000 in the Quebec physician billing and hospitalization database [4]. A recent population-based study found an incidence of 1.1 per 100,000 person-years for DM in Olmsted County, Minnesota from 1995 to 2019 [25]. The number of patients in our study is sufficiently large to compare the subsequent malignant and pulmonary fibrosis risks between patients diagnosed with DM and PM.

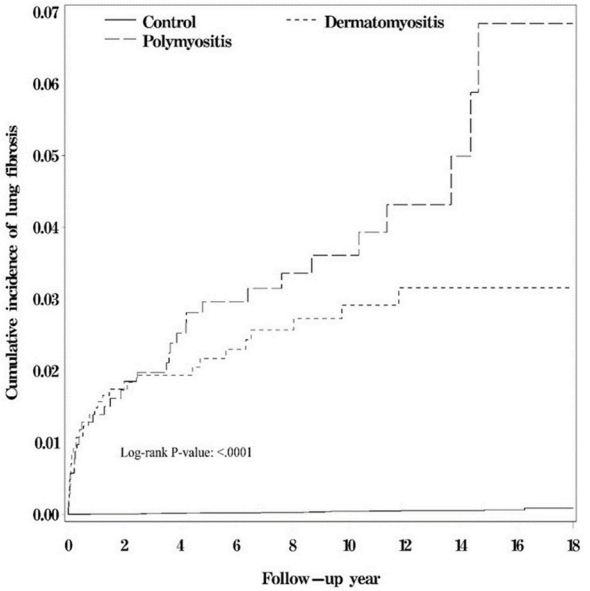

Fig. 2. Cumulative incidence of pulmonary fibrosis in patients with dermatomyositis and polymyositis and comparisons.

Table 4
Incidences and hazard ratios of pulmonary fibrosis compared between cohorts with and without dermatomyositis or polymyositis.

Variable	Dermatomyositis or polymyositis								
	No			Yes			Hazard ratio (95 % confidence interval)		
	Event	PY	Rate[a]	Event	PY	Rate[a]	cHR	aHR[b]	aSHR[c]
All	19	468467	0.41	67	17698	37.9	87.0 (52.2–145) ***	84.0 (49.5–143) ***	67.0 (39.8–113) ***
Sex									
Women	10	317445	0.32	42	12268	34.2	102 (51.0–203) ***	93.8 (46.0–191) ***	78.4 (38.9–158) ***
Men	9	151022	0.60	25	5430	46.0	70.9 (33.0–152) ***	73.5 (33.1–163) ***	55.9 (25.6–122) ***
Age									
<50	4	266255	0.15	26	11234	23.1	150 (52.1–429) ***	113 (38.5–330)[d]	103 (35.0–305) ***
50–59	4	106648	0.37	23	3860	59.6	144 (49.9–419) ***	171 (57.1–512)[d]	145 (46.6–452) ***
≥60	11	95564	1.15	18	2604	69.1	53.1 (24.9–113) ***	43.4 (19.8–95.4) ***	29.3 (14.0–61.4)[d]
Income									
<15000	8	78447	1.02	13	3097	42.0	40.1 (16.6–97.0) ***	50.5 (19.8–129)[d]	32.0 (13.3–76.6)[d]
15000–25000	6	233274	0.26	29	8712	33.3	120 (49.8–289)[d]	110 (44.4–273)[d]	89.5 (36.1–222) ***
≥25000	5	156747	0.32	25	5889	42.4	120 (45.9–314)[d]	114 (42.3–306) ***	100 (38.1–265) ***
CCI									
0	13	443132	0.29	29	10323	28.1	91.9 (47.7–177)[d]	111 (57.5–215) ***	88.1 (46.3–167) ***
≥1	6	25335	2.37	38	7375	51.5	22.6 (9.55–53.6) ***	27.7 (11.3–67.9) ***	22.1 (8.91–54.7) ***

[a] Incidence rate, per 10,000 person-years.
[b] Adjusted hazard ratio, adjusting age, sex, income, and CCI score.
[c] Adjusted subhazard ratio, adjusting age, sex, income, and CCI score by competing Cox model with death as competing factor; CCI, Charlson comorbidity index; cHR, crude hazard ratio.
[d] $p < 0.001$.

4.2. Subsequent cancer in patients with DM and PM

Cancers may be diagnosed concurrently or after the myositis diagnosis. Our study excluded 170 patients with cancer (6.1 %) from patients with myositis diagnosed at baseline. Our study mainly investigated cancers after the myositis diagnosis. Among 1461 patients with DM and 1058 patients with PM, 9 % of patients developed cancer after the myositis diagnosis, which is 2.1-fold higher in the former than in the latter (11.9 % vs. 5.67 %). The overall aHR of cancer was 0.39 (0.29–0.54) for patients with PM compared with those with DM. An earlier Swedish study found that among 392 patients with DM and 396 with PM, 61 and 42 developed cancer with myositis simultaneously, while 59 (15 %) and 37 (9 %) developed cancers after the myositis diagnosis, respectively [5]. A later study using data pooling from Sweden, Denmark, and Finland (SDF data) found that among 618 patients with DM and 914 with PM, 115 (18.6 %) and 85 (9.29 %) developed cancer after the myositis diagnosis, respectively, indicating a 2.3-fold higher incidence in the former than in the latter [6]. A recent study using the 20-year hospital medical records of 1100 patients with DM and 1164 with PM

Table 5
Case-control analysis of subsequent cancer in dermatomyositis or polymyositis patients with and without pulmonary fibrosis by sex.

Sex	Pulmonary fibrosis	Cancer		Fisher's	
	n	Yes, n	No, n	Chi-square	*p*
Men	Yes, 25	(0)+1	25 + 1	2.051	0.238
	No, 826	107 + 1	719 + 1		
Women	Yes, 42	(0) +1	42 + 1	1.880	0.251
	No, 1626	127 + 1	1499 + 1		
Both	Yes, 67	(0) +1	67 + 1	5.228	0.019
	No, 2452	234 + 1	2218 + 1		

For (0) case, we used fudge skill by embedding "1" case to each cell to estimate the Fisher's Chi-square.

cared at a tertiary medical center in Taiwan revealed that cancer occurred in 61 (5.55 %) patients with DM and 38 (3.26 %) patients with PM with a ratio of 1.88. This data demonstrates that the risk of acquiring cancer in patients with DM is approximately twofold higher than in patients with PM.

Types of cancer are different between our study and the SDF data study. The SDF study showed that DM was strongly associated with ovarian cancer and lung cancer, whereas PM was associated with an increased risk of non-Hodgkin lymphoma followed by lung cancer [6].

Our data showed the malignancy risk was greater in men than in women, with a men-to-women incidence ratio of 2.2- and 1.4-fold for patients with DM and those with PM, respectively. It should be noted in our data that head and neck cancer alone contributed 45.2 % and lung cancer contributed another 17.7 % of cancers for men in the DM cohort. Both incidence rates were 14.5- and 1.8-fold greater for men than for women, respectively. These two types of cancer contributed similarly: 17.4 % each to all patients with cancer in men after the PM diagnosis, with incidence rates 3.0- and 2.3-fold greater than women with PM. Higher tobacco and alcohol use in men may contribute to both types of cancer [26,27]. Oncogenic viruses are also considered as predominant risk factors for head and neck cancer in Western populations [27]. However, the extremely high incidence of head and neck cancer in men with DM in our Taiwanese data might also be associated with betel quid chewing [28]. With a male-to-female oral cancer ratio of 9.68 to 1 in Taiwan, the age-adjusted incidence in males has been estimated 5.3 times as high as that in the United Kingdom. It can be suspected a good number of male patients with DM were betel quid users in addition to the link of smoking and drinking.

4.3. High risk of subsequent pulmonary fibrosis

Pulmonary fibrosis is a chronic progressive disorder in the lungs, resulting in respiratory dysfunction. To our knowledge, no previous study has ever investigated and compared the development of this fibrotic disorder between patients with DM and those with PM. Our study revealed a 92.4-fold increased incident pulmonary fibrosis in patients with DM and PM combined, compared with the general population. It is important to note a 2-fold higher incidence of pulmonary fibrosis, but a 54 % decreased incidence rate of cancer, in patients with PM than in those with DM. The incidence of cancer in patients with PM and DM combined was 2.6-fold higher than in the general population. This data reflects that the relative risk of developing fibrosis was much greater than developing cancer for patients with PM/DM than for the general population, while the fibrosis risk might be higher for patients with PM than for those with DM. However, incident cancer cases were higher than incident pulmonary fibrosis and were 5.3-fold (174/33) for patients with DM and 1.8-fold (60/34) for PM patients. The data shows again that the subsequent cancer risk is greater for patients with DM than with PM.

Fibrotic scarring may exert other types of impact on fibrotic survival with subsequent complications or comorbidity such as lung cancer. Studies on pulmonary fibrosis with the coexistence of lung cancer, either after the pulmonary fibrosis diagnosis or simultaneously appearing, might not be based on specific origins.

ILD is a group of devastating chronic fibrotic lung disorders, including IPF, leading to repetitive injuries and progressive lung scarring. Studies have reported an increased risk of developing malignancies in patients with IPF, particularly lung cancer can be fivefold as high or higher as in the controls [21,29,30]. A Greek study evaluated 1016 patients with IPF at eight medical centers and found that among 102 patients with lung cancer comorbidity, 49 were diagnosed post-IPF [21]. A recent study followed up on 25,241 patients diagnosed with IPF in 2009–2014 identified from the Health Insurance Service database in South Korea [30]. The overall cancer incidence was nearly twofold higher in the IPF cohort than in the controls (29.0 vs. 13.9 per 1000 person-years) by the end of 2016 with the incidence of lung cancer being the highest.

No previous studies have ever evaluated the subsequent cancer risk for patients with DM/PM after pulmonary fibrosis diagnosis. With the advantage of large population size, we were able to identify cohorts with large numbers of newly diagnosed patients with DM and PM. Among these patients with myositis, 67 developed pulmonary fibrosis. Further evaluation showed none of the patients developed cancer after the pulmonary fibrosis diagnosis. It is likely patients with IPF are at a higher risk of developing cancers, but might not for patients with DM/PM after the development of pulmonary fibrosis. However, whether these patients with myositis who developed fibrosis are at a minor risk for further development of cancer or it may take a longer follow-up period for the development remains unclear.

4.4. Study limitation

From the population-based 18-year claims data, the numbers of patients with DM and PM identified in the present study were higher than that in most previous studies. However, the main limitation of this study was the number of patients with pulmonary fibrosis was not sufficiently large and "low incidence" of cancer in DM or PM patients with pulmonary fibrosis developed. In addition, the life expectancy of patients with pulmonary fibrosis might not be sufficiently long for further cancer development. The other limitation was the lack of laboratory data to validate the study population at the individual level. Without information on lung function and radiological examinations, we were unable to evaluate the severity of the disorders. Based on the ICD code, the study cohorts of DM and PM and subsequent disorders of pulmonary fibrosis and cancers were likely reliable because all these conditions are categorized as catastrophic disorders, which required validation by at least two physicians. Whether there was misclassification in the control cohort was also unclear.

5. Conclusion

Patients with PM and DM are at greater risk of developing cancer and pulmonary fibrosis. Patients who develop pulmonary fibrosis might be at lower risk of developing cancer. The complexity of cancer risk interplay between patients with and without pulmonary fibrosis has clinical relevance and deserves further investigation. Patients who are free of pulmonary fibrosis deserve close monitoring to reduce subsequent cancer risk.

Data availability

Database used in this work is available on request and analyzed at the Health Data Science Center designated by the Taiwan Ministry of Health and Welfare. All requests to use the data at the center should be reviewed by relevant IRB. Requests to access data should be made to the Ministry.

Funding

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center, Taiwan (MOHW110-TDU-B-212-124004), Ministry of Science and Technology, Taiwan (MOST110-2321-B-039-003), and China Medical University Hospital, Taiwan (DMR-111-228). The funders have no role in the study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

CRediT authorship contribution statement

Fung-Chang Sung: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Pei-Chun Chen:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Chih-Hsin Muo:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Te-Chun Shen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Anthony J. Gerbino:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We are grateful to Health Data Science Center at China Medical University Hospital for providing administrative and technical support for data analyses.

References

[1] M.C. Dalakas, R. Hohlfeld, Polymyositis and dermatomyositis, Lancet 362 (2003) 971–982.
[2] A. Ohta, M. Nagai, M. Nishina, H. Tomimitsu, H. Kohsaka, Prevalence and incidence of polymyositis and dermatomyositis in Japan, Mod. Rheumatol. 24 (2014) 477–480.
[3] C.F. Kuo, L.C. See, K.H. Yu, et al., Incidence, cancer risk and mortality of dermatomyositis and polymyositis in Taiwan: a nationwide population study, Br. J. Dermatol. 165 (2011) 1273–1279.
[4] S. Bernatsky, L. Joseph, C.A. Pineau, , et al.P. Bélisle, J.F. Boivin, D. Banerjee, A.E. Clarke, Estimating the prevalence of polymyositis and dermatomyositis from administrative data: age, sex and regional differences, Ann. Rheum. Dis. 68 (2009) 1192–1196.
[5] B. Sigurgeirsson, B. Lindelöf, O. Edhag, E. Allander, Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study, N. Engl. J. Med. 326 (1992) 363–367.
[6] C.L. Hill, Y. Zhang, B. Sigurgeirsson, et al., Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study, Lancet 357 (2001) 96–100.

[7] J. Wang, G. Guo, G. Chen, et al., Meta-analysis of the association of dermatomyositis and polymyositis with cancer, Br. J. Dermatol. 169 (2013) 838–847.
[8] J.L. Hsu, M.F. Liao, C.C. Chu, et al., Reappraisal of the incidence, various types and risk factors of malignancies in patients with dermatomyositis and polymyositis in Taiwan, Sci. Rep. 11 (2021) 4545.
[9] D. Stockton, V.R. Doherty, D.H. Brewster, Risk of cancer in patients with dermatomyositis or polymyositis, and follow-up implications: a Scottish population-based cohort study, Br. J. Cancer 85 (2001) 41–45.
[10] E.H. Kang, E.B. Lee, K.C. Shin, et al., Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis, Rheumatology 44 (2005) 1282–1286.
[11] R. Vij, M.E. Strek, Diagnosis and treatment of connective tissue disease-associated interstitial lung disease, Chest 143 (2013) 814–824.
[12] K. Motomura, H. Yamashita, S. Yamada, Y. Takahashi, H. Kaneko, Clinical characteristics and prognosis of polymyositis and dermatomyositis associated with malignancy: a 25-year retrospective study, Rheumatol. Int. 39 (2019) 1733–1739.
[13] A. Olson, N. Hartmann, P. Patnaik, et al., Estimation of the prevalence of progressive fibrosing interstitial lung diseases: systematic literature review and data from a physician survey, Adv. Ther. 38 (2021) 854–867.
[14] M. Natsuizaka, H. Chiba, K. Kuronuma, et al., Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences, Am. J. Respir. Crit. Care Med. 190 (2014) 773–779.
[15] E.A. Belloli, F.J. Martinez, K.R. Flaherty, Update in interstitial lung disease 2014, Am. J. Respir. Crit. Care Med. 192 (2015) 538–543.
[16] L. Richeldi, H.R. Collard, M.G. Jones, Idiopathic pulmonary fibrosis, Lancet 389 (2017) 1941–1952.
[17] D.J. Lederer, F.J. Martinez, Idiopathic pulmonary fibrosis, N. Engl. J. Med. 378 (2018) 1811–1823.
[18] B. Ballester, J. Milara, J. Cortijo, Idiopathic pulmonary fibrosis and lung cancer: mechanisms and molecular targets, Int. J. Mol. Sci. 20 (2019) 593.
[19] T. Karampitsakos, V. Tzilas, R. Tringidou, et al., Lung cancer in patients with idiopathic pulmonary fibrosis, Pulm. Pharmacol. Ther. 45 (2017) 1–10.
[20] S. Tomassetti, C. Gurioli, J.H. Ryu, et al., The impact of lung cancer on survival of idiopathic pulmonary fibrosis, Chest 147 (2015) 157–164.
[21] V. Tzilas, E. Manali, I. Tomos, et al., Lung cancer in patients with Idiopathic Pulmonary Fibrosis. A retrospective multicenter study in Greece, Pulm. Pharmacol. Ther. 60 (2020) 101880.
[22] A. Tzouvelekis, P. Spagnolo, F. Bonella, et al., Patients with IPF and lung cancer: diagnosis and management, Lancet Respir. Med. 6 (2018) 86–88.
[23] Y. Ozawa, T. Suda, T. Naito, et al., Cumulative incidence of and predictive factors for lung cancer in IPF, Respirology 14 (2009) 723–728.
[24] T.Y. Wu, A. Majeed, K.N. Kuo, An overview of the healthcare system in Taiwan, London J Prim Care (Abingdon) 3 (2010) 115–119.
[25] V.L. Kronzer, B.A. Kimbrough, C.S. Crowson, JM 3rd Davis, M. Holmqvist, F.C. Ernste, Incidence, prevalence, and mortality of dermatomyositis: a population-based cohort study, Arthritis Care Res. 75 (2023) 348–355.
[26] N. Wang, K. Mengersen, S. Tong, et al., Global, regional, and national burden of lung cancer and its attributable risk factors, 1990 to 2017, Cancer 126 (2020) 4220–4234.
[27] M.D. Mody, J.W. Rocco, S.S. Yom, R.I. Haddad, N.F. Saba, Head and neck cancer, Lancet 398 (2021) 2289–2299.
[28] H.C. Chuang, M.H. Tsai, Y.T. Lin, M.H. Chou, K.L. Yang, C.Y. Chien, Systemic and local effects among patients with betel quid-related oral cancer, Technol. Cancer Res. Treat. 21 (2022) 15330338221146870.
[29] D. Bouros, K. Hatzakis, H. Labrakis, K. Zeibecoglou, Association of malignancy with diseases causing interstitial pulmonary changes, Chest 121 (2002) 1278–1289.
[30] H.Y. Lee, J. Lee, C.H. Lee, K. Han, S.M. Choi, Risk of cancer incidence in patients with idiopathic pulmonary fibrosis: a nationwide cohort study, Respirology 26 (2021) 180–187.