Incidence and predictive factors for malignancies with dermatomyositis: a cohort from southern China

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Abstract

Objective

We aimed to explore the incidence of malignancy in dermatomyositis and assess the potential risk factors of occurrence of malignancy in DM from southern China.

Methods

A retrospective cohort study of patients admitted in the 1st affiliated university hospital between 2003 and 2012 was performed. Demographic information, clinical symptoms, laboratory findings, medications were documented. The endpoint of the study was defined as occurrence of malignancy or death.

Results

For this approximately 10-year retrospective study, 60 out of 246 dermatomyositis patients developed malignancies with the overall incidence of 24.4%. Nasopharyngeal carcinoma (NPC) and ovarian carcinoma were the most common malignant disease, accounting for 35% (21/60) and 15% (9/60) of malignancies, respectively. Lung and colon were followed as the third most common carcinoma (5 out of 60, 8.3%).

Among these 60 patients with malignancies, 39 (65.0%, 39/60) cases occurred within 1 year after DM diagnosis. Subsequently, malignancies were detected in 13 (21.7%, 13/60) patients during the second year and 8 (13.3%, 8/60) during the third year. One patient developed cancer at the 35th month after DM as the latest.

The logistic regression multivariate analysis indicated that male gender [odds ratio (OR) = 3.76, 95% confidence interval (CI) 1.86~7.61, p<0.01], dysphagia (OR= 2.21, 95%CI 1.10~4.48, p=0.03) and elevated erythrocyte sedimentation rate (ESR) (OR= 2.37, 95% CI 1.18~4.75, p=0.02) were risk factors for the occurrence of malignancies, while interstitial lung disease (ILD) acted as a protective factor (OR=0.13, 95%CI 0.06~0.28, p<0.01).

Conclusion

It was necessary to carry out routine malignancy screening for Chinese DM patients due to its high incidence. Nasopharyngeal carcinoma and ovarian cancer were the most common malignant disease. The risk of malignancy was highest in the first year after DM diagnosis and reduced thereafter. Extensive work-ups for malignancy screening should be carried out at the first year. Male gender, dysphagia and elevated ESR were risk factors for occurrence of malignancy. The presence of ILD could diminish the risk of coexisting of malignancy.

Key words

prediction analysis, dermatomyositis, malignancy

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Introduction

Dermatomyositis (DM) is a type of idiopathic inflammatory myositis, which primarily affects proximal skeletal muscle and skin. The pathogenesis remains a mystery. It is a heterogeneous disease, and clinical manifestations vary from a relatively mild disease to that causing significant morbidity and mortality (1). Recent researches report that the 5-year survival in adult-onset DM is 75–90% and malignancy and interstitial lung disease (ILD) are the primary causes leading mortality (1, 2-4). Some epidemiological studies have identified an increased risk of malignancy in patients with DM compared with the general population, with overall standardised incidence ratios (SIR) of 3.8 to 7.7 (5-10). Several studies have suggested that DM in adults should be considered a para-neoplastic syndrome, and about 15–24% of adult-onset DM can coexist with malignancy (1, 8, 11).

The predictive factors for occurrence of malignancy in DM are important for clinicians to identify high-risk patients and make early diagnosis. Many previous studies had described the association between DM and malignancy from Western populations (12-16), and suggested that older age, elevated erythrocyte sedimentation rate (ESR), presence of cutaneous leukocytoclastic vasculitis, and so on, were risk factors for malignancy in DM patients. However, the percentage distribution of malignancy varied with geographic regions and ethnicities. Few studies investigated the incidence and predictive factors for malignancies in patients with DM from southern China. Recently, a review article demonstrated that there was no information about southern China in studies on the association between inflammatory myopathies and malignancy from Asian populations (17).

In this study, clinical and laboratory features were reviewed to discover the incidence of malignancy in DM, and assess the potential risk factors of occurrence of malignancy in DM from southern China, thus helping to provide appropriate medical intervention for malignancy screening and improve prognosis for those patients affected.

Patients and methods

Patients

A retrospective cohort study was performed to gather follow-up data between January 2003 and December 2012 at the First Affiliated Hospital of Sun Yat-Sen University. The diagnostic criteria devised by Bohan and Peter for DM was employed in this study (18, 19). Only those with diagnosis of definite or portable DM were enrolled as eligible patients. Given that the juvenile dermatomyositis (onset age under 17-year old (20)) had not been clearly associated with malignancy and routine malignancy screening was not generally performed in these patients, this disease entry did not include in this study (1, 21). Pathologic examination or genetic inspection was applied to distinct some cases suggestive of inclusion-body myositis (IBM), hereditary or other myopathies in this study. Patients with a preceding malignancy and those who had been in remission for more than 3 years at the time of DM diagnosis were excluded (22).

Study variables

Clinical and demographic information were collected from admission and outpatient clinic records, including gender, age of DM diagnosis, the date of diagnosis of malignancies, types of the concomitant malignancies, abnormalities in laboratory tests, clinical symptoms at the time of diagnosis of DM, therapeutic drugs, and interstitial lung disease. Biochemical abnormalities included elevated serum levels of myogenic enzymes and erythrocyte sedimentation rate (ESR). Myogenic enzyme consisted of creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Biochemical abnormalities were defined as more than the upper limit of normal for these biochemical indexes such as CPK>160 U/L, LDH>240U/L, AST>35U/L, ALT>40U/L and ESR>20mm/h. Immunology abnormalities were composed of positive antinuclear antibody (ANA) and anti-Jo-1 (histidyl t-RNA synthetase) antibody.

Clinical symptoms included dermatomyositis rash, weakness of limb-girdle

muscles and dysphagia. Specific dermatomyositis rash consisted of Gottron's papules, Gottron's sign (macular rash with the same distribution as Gottron's papules without papules), the heliotrope rash of eyelids, photosensitive rashes (the so-called V sign) and mechanic's hands.

Corticosteroids and additional immunosuppressive agents administrated for DM at intensification and maintenance therapy stage were also documented. Immunosuppressive agents included cyclophosphamide (CYC), methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF) and hydroxychloroquine (HCQ).

Interstitial lung disease was diagnosed if pulmonary function test indicated restricted pulmonary ventilation disorder and diffusive dysfunction, and high-resolution computed tomography (HRCT) of the lungs verified.

Several tests were performed to identify the presence of malignancy such as chest radiograph, chest and abdominal CT, nasal endoscopy, abdominal echography, upper gastrointestinal endoscopy, colonoscopy in patients with a positive fecal occult blood test, breast ultrasonography and transvaginal ultrasonography for female patients, prostate-specific antigen for male patients and a thyroid echo in the case of struma.

After the initial diagnosis of DM at our institute, patients were subsequent followed-up and the endpoints of follow-up were considered as death or occurrence of malignancy.

Statistical analysis

SPSS (Statistical Package for Social Sciences) 16.0 statistic software was employed for the analysis. Mean ± SD were presented for normally distributed continuous variables. Categorical variables were presented as the absolute count and percentage. Categorical variables were compared by χ^2 test or Fisher's exact test. Continuous variables were evaluated by *t*-test or Mann-Whitney U-test.

Univariate and multivariate logistic regression analyses were used to predict the malignancy of DM. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated. Variables associated with the outcome at $p<0.20$ were included in a multivariate logistic model with the forward step-wise option. $p<0.05$ was considered to be statistically significant.

Table I. Information on the various cancer types diagnosed among patients with DM.

Type	Total (n=60)	Male (n=41)	Female (n=19)
Nasopharyngeal carcinoma	21	19	2
Ovarian cancer	9	0	9
Lung cancer	5	4	1
Colon carcinoma	5	4	1
Thyroid carcinoma	4	4	0
Lymphoma	4	4	0
Breast carcinoma	3	0	3
Esophageal carcinoma	2	2	0
Gastric carcinoma	2	1	1
Endometrial cancer	1	0	1
Hepatic cell carcinoma	1	1	0
Laryngocarcinoma	1	1	0
Prostatic carcinoma	1	1	0
Pleural mesothelium carcinoma	1	0	1

Results

Demographic characteristics of the dermatomyositis (DM) patients

253 patients fulfilled the inclusion criteria were enrolled in this study. Of the 253 patients, 246 (246/253, 97.2%) had completed follow-up data and 7 were lost because of moving without contact information. The diagnosis of 246 eligible patients were 158 (64.2%) definite DM and 88 (35.7%) probable DM. 246 cases were followed-up for a median of 68.5 months (range: 2–115 months). 60 cases (60/246, 24.4%) occurred malignancies at a median of 9 months (range: 1–35 month) after DM diagnosis.

Of the 60 coexistence of DM and malignancies patients, 41 (41/60, 68.3%) were found in male and 19 (19/60, 31.7%) were found in female, which implied that the incidence of malignancies was higher in male patients compared with female patients. Nasopharyngeal carcinoma (NPC) was the commonest malignant disease and accounted for 35.0% (21/60) of malignancies. It was followed by ovarian cancer (9 out of 60, 15.0%), lung cancer (5 out of 60, 8.3%) and colon carcinoma (5 out of 60, 8.3%). Other malignant diseases included 4 thyroid carcinoma, 4 lymphoma, 3 breast carcinoma, 2 esophageal carcinoma, 2 gastric carcinoma, 1 endometrial cancer, 1 hepatic cell carcinoma (HCC), 1 laryngocarcinoma, 1 pleural mesothelium carcinoma and 1 prostatic carcinoma. There was a difference in predilection site of malignant diseases between male and female patients. Male patients were at increased risk for occurrence of NPC, while female patents were ovarian cancer. Detailed data are listed in Table I.

The onset time of malignancy after DM diagnosis

Sixty patients with malignancies followed the diagnosis of DM, at a mean±SD of 11.4±9.4 months. Thirty-nine (65.0%, 39/60) cases occurred within 1 year after DM diagnosis implied that the risk of malignancy was high during the first year after diagnosis, and the risk of malignancy was highest in the fourth month. For the years afterward, malignancies were detected in 13 (21.7%, 13/60) patients during the second year and 8 (13.3%, 8/60) during the third year. One patient developed cancer at the 35th month after DM as the latest. Figure 1 shows the time of diagnosis of concomitant malignancy after DM. After DM diagnosis, the risk of malignancy was highest in the fourth month and reduced thereafter.

Comparison of demographic and laboratory data between DM with malignancy and without malignancy

The mean age at diagnosis of DM was 49.2±12.7 years (range: 18–85 years). This study presented with a female predominance, and the female: male ratio was about 1.3: 1 (139/107). Anti-

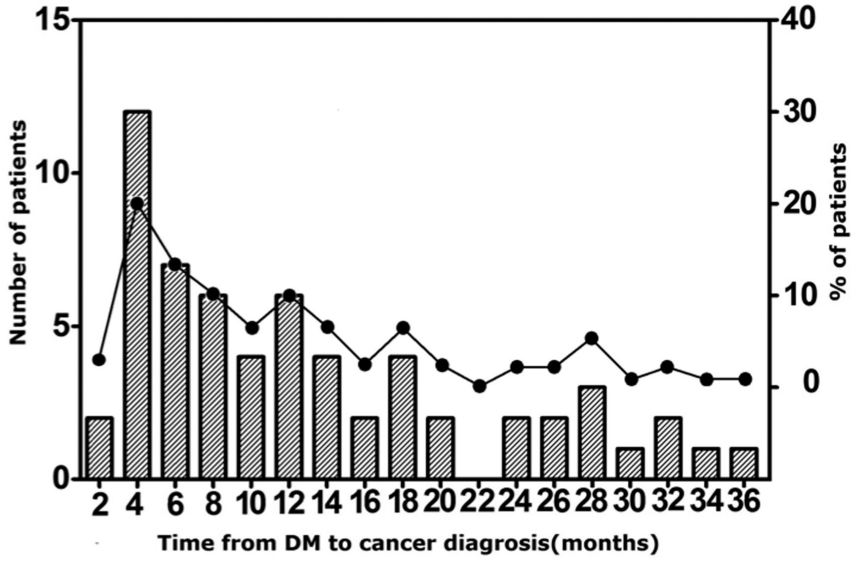

Fig. 1. The time of diagnosis of concomitant malignancy after DM. Expressed as number (dark bars) and percentage (black circles) of patients in every two months of interval from DM to malignancy diagnosis. The number of patients detected malignancies were the most in the fourth month after DM diagnosis, and reduced thereafter.

Table II. Demographic and laboratory data in DM patients.

	With malignancy (n=60)	Without malignancy (n=186)	*p*-value
Age at ADM diagnosis, yrs, mean±SD	49.2±12.7	44.6±12.1	0.01
Male, n (%)	41 (68.3%)	66 (35.5%)	<0.01
Elevated serum CPK, n (%)	45 (75.0%)	105 (56.5%)	0.01
Elevated serum LDH, n (%)	49 (81.7%)	155 (83.3%)	0.84
Elevated serum AST, n (%)	46 (76.7%)	155 (83.3%)	0.25
Elevated serum ALT, n (%)	35 (58.3%)	105 (56.5%)	0.88
Positive anti-Jo-1 , n (%)	5 (8.3%)	10 (5.4%)	0.37
Positive ANA , n (%)	11 (18.3%)	35 (18.8%)	1.00
Elevated serum ESR, n (%)	36 (60.0%)	77 (41.4%)	0.02

ESR: erythrocyte sedimentation rate; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase. The levels of these elevated indexes were defined as CPK>160 U/L, LDH>240U/L, AST>35U/L, ALT>40U/L and ESR>20 mm/h.

nuclear antibody (ANA) was found in about 18.7% (46/246) of our patients and anti-Jo-1 antibody was positive in approximately 6.1% (15/246) of our patients.

Patients with malignancy were significantly older and more frequently male compared with those without malignancy. In addition, the occurrence of malignancy in DM patients was associated with elevated ESR and elevated serum creatine phosphokinase (CPK). There was no significant difference in other myogenic enzymes except CPK between patients with and without malignancy. No difference was found in the percentage of autoantibody profiles, including anti-Jo-1 antibody. Anti-Jo-1 antibody was one of myositis-specific antibodies and might indicate underlying DM, but the results showed that anti-Jo-1 antibody did not have predictive value of malignancy (Table II).

Comparison of clinical symptoms, interstitial lung disease (ILD) and treatment medications between DM with and without malignancy

Gottron's sign and Gottron's papules, heliotrope rashes and photosensitive rashes were of similar occurrence, which found in approximately a half of the patients. Mechanic's hands occurred in 6.1% (15/246) was less common in these specific dermatomyositis rashes. 129 (52.4%, 129/246) patients of this cohort developed interstitial lung disease. Dysphagia, as a result of oropharyngeal and upper oesophageal striated muscles involvement, was noted in 33.7% (83/246) of this patients, which was comparable with 10~54% reported in previous researches (23). Compared with patients without malignancy, patients with malignancy showed a significantly higher incidence of dysphagia (46.7% *vs*. 29.6%, p=0.019) and a lower incidence of interstitial lung disease than those without malignancy (16.7% *vs*. 64.0%, p<0.001). No significant difference was found among other clinical signs and symptoms, including weakness of limb-girdle muscles and skin manifestations (Table III).

Table IV shows the therapeutic drugs administered for DM during follow-up. Oral corticosteroid therapy was taken in 92.7% (228/246) of these patients as the mainstay therapy. Among the additional immunosuppressive agents, hydroxychloroquine (61.4%, 151/246) was used the most frequently. Methotrexate and cyclophosphamide were utilised in 37.8% (93/246) and 29.7% (73/246) of this patients, respectively. Comparison between the patients with and without malignancy, the results showed that corticosteroids and additional immunosuppressive agents were not associated with increased malignancy in DM.

Factors associated with occurrence of malignancy of DM patients

All the demographic and clinical parameters were included in the univariate logistic regression model to assess which variables were significantly related to occurrence of malignancy of DM patients. Logistical regression univariate analysis indicated that age, male gender, dysphagia, elevated ESR, elevated serum CPK and interstitial lung disease were associated with occurrence of malignancy. Variables with p-values <0.2 in the univariate logistic regression were entered to the multiple regression analysis.

After adjusted by multiple logistic regression models, removing the effect of confounding and interaction among variables, only male gender, weakness

Table III. Clinical manifestations and interstitial lung disease in DM patients.

	With malignancy (n=60)	Without malignancy (n=186)	*p*-value
Weakness of limb-girdle muscles, n (%)	51 (85.0%)	164 (88.2%)	0.45
Dysphagia, n (%)	28 (46.7%)	55 (29.6%)	0.02
Gottron's sign and Gottron's papules, n (%)	28 (47.7%)	97 (52.2%)	0.55
Heliotrope rashes, n (%)	30 (50.0%)	84 (45.2%)	0.55
Mechanic's hands, n (%)	3 (5%)	12 (6.5%)	1.00
Photosensitive rashes, n (%)	34 (56.7%)	89 (47.8%)	0.30
Interstitial lung disease, n (%)	10 (16.7%)	119 (64.0%)	<0.01

Table IV. Treatment medications for patients with DM.

	With malignancy (n=60)	Without malignancy (n=186)	*p*-value
Corticosteroid therapy, n (%)	58 (96.7%)	170 (91.4%)	0.17
Cyclophosphamide therapy, n (%)	19 (31.7%)	54 (29.0%)	0.70
Mycophenolate mofetil therapy, n (%)	5 (8.3%)	15 (8.1%)	0.95
Methotrexate therapy, n (%)	24 (40.0%)	69 (37.1%)	0.69
Azathioprine therapy, n (%)	10 (16.7%)	35 (18.8%)	0.71
Hydroxychloroquine therapy, n (%)	41 (68.3%)	110 (59.1%)	0.20

Table V. Significant variables associated with occurrence of malignancy on univariate logistic regression.

	Crude OR	95% CI	*p*-value
Age at ADM diagnosis	1.03	1.01-1.06	0.01
Male gender	3.92	2.11-7.30	<0.01
Dysphagia	2.08	1.15-3.79	0.02
Interstitial lung disease	0.11	0.05-0.24	<0.01
Elevated serum CPK	2.31	1.21-4.44	0.01
Elevated serum ESR	2.12	1.17-3.84	0.01

Table VI. Significant variables associated with occurrence of malignancy on multivariate logistic regression.

	Adjusted OR	95% CI	*p*-value
Male gender	3.76	1.86-7.61	<0.01
Dysphagia	2.21	1.10-4.48	0.03
Interstitial lung disease	0.13	0.06-0.28	<0.01
Elevated ESR	2.37	1.18-4.75	0.02

of limb-girdle muscles, interstitial lung disease and elevated ESR remained being significantly associated with occurrence of malignancy. Gender (male), dysphagia, and elevated serum ESR were all poor predictors, and interstitial lung disease was a protective factor for occurrence of malignancy. The crude and adjusted odds ratios (OR)and corresponding 95% confidence interval (CI) for factors associated with occurrence of malignancy of DM were shown in Table V and Table VI.

Discussion

Dermatomyositis (DM) belongs to the group of inflammatory myopathies which is manifested by symmetrical, proximal muscle weakness and typical cutaneous lesions. DM is a relatively rare disease and the annual incidence is 5.0-8.9 per million persons in adult DM (24, 25). The association between DM and malignancy has been well established in the previous medical literatures and meta-analyses. A systemic review noted that the incidence of malignancy in DM patients was 12.3±8.5% (range: 0%–56%) in the Asian population (17), which was comparable with data from the Caucasian population (5, 7, 15, 16). In the current study, the incidence of DM concomitant with malignancy is 24.4%, which is in accordance with reports above. Since the high likelihood of coexistence of malignancy in DM, it's necessary to take more precautions to DM in tumour screening of Chinese patients.

There was some difference in the frequency of types of associated malignancy among the researches from different geographic regions and ethnicities. A epidemiological study based on population of Europe (Denmark, Finland, Sweden) indicated that lung, trachea and bronchus, and ovarian were the most frequent cancer after DM diagnosis, followed by breast and colorectal cancer (26). A study from America found that the DM patients had the highest risk of developing lung, breast and colon cancer (27). A study from Japan demonstrated that gastric, colon and ovarian cancer were the top three most common malignant diseases (22). In the current study, the dominant malignancies observed were nasopharynx and ovary, followed by lung and colon. Nasopharyngeal carcinoma (NPC) was the commonest malignancy, which was consistent with those reports from other Asian countries, including India, Singapore and Taiwan (10, 28, 29). The immune response to Epstein-Barr virus contributes to the coexistence NPC of DM (10). The incidence rate of nasopharyngeal carcinoma seemed to be higher in most Orientals with DM specifically. Ovarian carcinoma (15%, 9/60) was the second most common cancer in this cohort. The incidence rate was much higher than 0-2.8% of DM patients (publications from most Asian countries such as Korea, Singapore, India, Malaysia, and so on) (17), but was accordance with percentage of Japanese (13.0%, 3/23) and Caucasian (22, 26, 27). It was noteworthy that there was a difference in the location of tumour between female and male patients. The predominantly associated tumour in female patients was ovarian carcinoma, while was nasopharyngeal carcinoma in male. Thyroid carcinoma and lymphoma as the forth most common malignancies were only found in male patients. The current study suggested nasopharyngeal examination should be mandatory for Chinese DM patients addition to routine work-ups

for malignancy screening. Contrary to most Asian female patients, Chinese female patients had a higher risk of developing ovarian carcinoma. It therefore became appropriately to take a more careful look at ovary in Chinese female patients.

In the current study, two thirds of patients occurred malignancies within one year after DM diagnosis, and the fourth month was at its peak of risk. The risk of malignancy was highest in the first year was accordance with most previous studies (10, 26, 30). The confluence of DM and malignancy being established within one year of each other supports the presence of a para-neoplastic syndrome (31). For this, around the 9-year follow-up, there was no patient detected malignancy after three years of DM diagnosis, which was inconsistent with previous literatures (10, 26, 30). They found that a large proportion of patients supervening malignancies were within 5 years of myositis diagnosis, but there were still some patients in whom malignancies occurred beyond 5 years, or exceeding 10 years (10, 26, 30). The reasons for this difference might be that the follow-up time not being long enough and case selection bias. Therefore, this study suggested that the work-ups for malignancy screening should be extensively carried out at the first year and clinicians needed to pay close attention to the latent malignancy during the long-term follow-up.

In order to access the predictive factors for the associated malignancy, clinical variables were analysed by logistic regressions. Male gender, weakness of limb-girdle muscles, interstitial lung disease and elevated ESR were found to be significantly associated with occurrence of malignancy of DM patients. Consistent with previous studies (12, 32), male gender was a independent predictive factor for development of malignancies in DM. Compared to females, the incidence of malignancies in male patients was significantly higher. In an association study with 32 adult-DM patients, Amerio *et al*. (14) reported that ESR appeared as potential markers of associated malignancy. This study also showed that elevated ESR was another important predictor for the occurrence of malignancies with the odds ratio of 2.37 (95% CI 1.18~4.75, p=0.015), which indicated that patients with higher value of ESR were 2.37 times more likely to occur malignancies compared to normal patients. Dermatomyositis-associated dysphagia could lead to cachexia and aspiration pneumonia indicating a bad prognosis. Moreover, our findings suggested that dysphagia was linked with an increased risk of cancer (OR=2.21, 95% CI 1.10~4.48, p=0.03). Dysphagia was more frequent among cancer-associated patients (13), but the pathogeneses of this phenomenon was unknown. It had been surmised that patients with cancer tended to develop severer muscle weakness leading to swallowing muscle involvement (22, 31). Clinicians should take more precautions to occult malignancy in patients with dysphagia. Interstitial lung disease (ILD) and malignancies both bore poor prognoses of DM (33). The incidence of ILD varied widely from 11% to 74% (127). In this study, 52.4 percentage of patients developed ILD. ILD (OR=0.13, 95% CI 0.06~0.28, p<0.001) was negatively associated with occurrence of malignancy in this cohort. The results suggested that presence of ILD could reduce the opportunity of developing malignancies by about 87%. Some previous reports had also demonstrated this tendency (13, 22, 31, 34). A research considered the reason was that the high mortality of ILD led to some patients might die earlier rather than have the chance to develop malignancies (22).

The relatively rarity of DM created difficulty in collecting large series of cases associated with malignancy (31). Some studies found that older DM patients were more prone to developing malignancy (26, 32, 34). In this study, age was also positively associated with occurrence of malignancy of DM patients in univariate analysis. Chow and Airio *et al*. (5, 6) indicated that an increased risk of malignancy was only evident in patients older than 45~50 years of age. Stockton *et al*. (7) found the increased risk for DM patients between 45 and 75 years of age. The study based on Taiwanese population demonstrated that there was a significantly increased risk in every age group for DM patients, especially the age group of 40~59 years old and older than 80 years old (10). We thought that the age effect on DM patients concomitant malignancies might vary from different age groups. Other important clinical data such as cutaneous lesions, the level of serum myogenic enzymes and autoantibody profiles also failed to show any significant difference in our multivariate analysis. The current study systematically analysed the association between DM and malignancy from China. But as a retrospective study, it had its own disadvantages, such as selection bias, information bias and limited sample size.

In conclusion, it was necessary to carry out routine malignancy screening for Chinese DM patients due to its high incidence. Nasopharyngeal carcinoma and ovarian cancer were the most common malignant disease. Additional nasopharyngeal and ovarian examination should be considered for Chinese DM patients. The risk of malignancy was highest in the first year after DM diagnosis and reduced thereafter. Extensive work-ups for malignancy screening should be carried out at the first year, with a long-term follow-up. Male gender, dysphagia and elevated ESR were risk factors for occurrence of malignancy. Clinicians should take more precautions to occult malignancy for those high-risk patients to make early diagnosis. The presence of ILD could diminish the risk of coexisting of malignancy.

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