Polymyositis/dermatomyositis and Malignancy Risk: A Metaanalysis Study

Zaixing Yang, Feng Lin, Baodong Qin, Yan Liang, and Renqian Zhong

ABSTRACT. ***Objective***. To investigate the association between polymyositis (PM)/dermatomyositis (DM) and risks of malignancy.

Methods. We searched Pubmed for articles dated before August 16, 2013. Studies were included if they met the following criteria: (1) a cohort or observational study; (2) PM or DM as one of the exposures of interest; (3) cancer as an outcome of interest; and (4) the rate ratio (RR) or standardized incidence ratio (SIR) were available with their 95% CI. We used random-effects or fixed-effects models to calculate the pooled RR according to the heterogeneity test.

Results. Twenty publications were included. Compared with the general population, the pooled RR for patients with PM, DM, and PM/DM were 1.62 (95% CI 1.19–2.04), 5.50 (4.31–6.70), and 4.07 (3.02–5.12), respectively. The increased risks were more significant in patients within the first year of myositis diagnosis, male patients, and population-based studies (for DM). A significant association was also found between PM or DM and most site-specific malignancies. However, both PM and DM were not associated with stomach and prostate cancers. Significant heterogeneity was found between studies on association between PM/DM and overall malignancy, but not between PM/DM and the majority of site-specific malignancies, suggesting that that inherent malignancy difference may be a major source of heterogeneity.

Conclusion. The present metaanalysis indicates that PM and DM are significantly associated with increased risks of overall malignancy and most site-specific malignancies. The number of studies on association between PM or DM and some malignancies is too small to draw a firm conclusion. Accordingly, more research is needed for these malignancies. (First Release Dec 1 2014; J Rheumatol 2015;42:282–91; doi:10.3899/jrheum.140566)

Key Indexing Terms:
POLYMYOSITIS DERMATOMYOSITIS MALIGNANCY RISK METAANALYSIS

Polymyositis (PM) and dermatomyositis (DM), with female predominance, are types of idiopathic inflammatory myositis, mainly affecting proximal skeletal muscle and skin. They may involve various organs such as the lungs, heart, stomach, intestine, etc. Despite being rare diseases, PM/DM are the most common of the various types of idiopathic inflammatory myopathies. Further, the incidence has been increasing from the 1940s up to now, although it varies in different countries or regions, ranging from about 1.2 to 17 patients per million population[1,2,3,4,5,6,7,8,9]. Since the association between PM or DM and malignant disease was first reported in 1916, it has been studied extensively. In 1994, the first metaanalysis was performed to preliminarily confirm the association with malignancy[10]. However, that metaanalysis involved only 4 studies, including both case-control and cohort ones, and investigated the association between PM or DM and overall cancer. Since then, a large number of studies has been published. Some of them explored the association of PM and DM with specific malignancies. Identification of an association with specific malignancy types would help in choosing the appropriate diagnostic procedure for malignancy screening in affected patients. However, several results remained inconclusive owing to too few cases. A metaanalysis can increase the effective sample size by pooling data from individual studies, thus enhancing the statistical power of analysis. Recently, a metaanalysis was conducted to evaluate such risk factors as age, sex, cutaneous necrosis, dysphagia, etc., for development of malignancies in DM and PM, but not to confirm an association between DM or PM themselves and malignancy risk[11]. Therefore, our present metaanalysis was carried out to assess this association.

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MATERIALS AND METHODS

A literature search of the Pubmed and Embase databases (updated to August 16, 2013) was conducted using combinations of the following terms: "dermatomyositis or polymyositis," "malignancy or cancer or carcinoma or neoplasia or tumor or neoplasm," "relative risk or RR," "odds ratio or OR," "hazard ratio or HR," "standardized incidence ratio or SIR." We considered only publications in English. All eligible articles were retrieved and their references were reviewed to identify additional relevant studies.

Studies were included in the metaanalysis if they fulfilled the following inclusion criteria: (1) a cohort or observational study; (2) PM or DM as one of the exposures of interest; (3) cancer as 1 outcome of interest; and (4) rate ratio (RR) or standardized incidence ratio (SIR) was available with their 95% CI (or with data to calculate them). Studies were excluded if the effect size could not be calculated according to information in the studies.

The Newcastle-Ottawa Scale (NOS) was conducted for quality assessment[12]. Eight items were categorized into 3 dimensions including selection, comparability, and outcome (cohort studies) or exposure (case-control studies). A maximum of 1 star was given for each numbered item in the selection and exposure categories, while a maximum of 2 stars could be given for comparability. Because there are established standard criteria, we considered a study awarded 0 to 3 as low quality, 4 to 6 as moderate quality, and 7 to 9 stars as high quality.

All articles were retrieved and assessed independently by 2 reviewers (Z. Yang and Y. Liang). Any disagreement was resolved by consensus.

Data extraction and statistical analysis. Publications that reported RR or SIR with corresponding 95% CI or data with which RR or SIR could be calculated were selected for inclusion in the metaanalysis. The detailed method for calculating SIR has been described[13]. The corresponding 95% CI were estimated using the PAMCOMP program[14].

Between-study heterogeneity was assessed using the chi-squared test and quantified by I^2, which represented the percentage of total variation across studies that was attributable to heterogeneity rather than chance[15]. The pooled RR was estimated by a fixed-effect model when there was no heterogeneity. Otherwise, it was by a random-effect model. Subgroup analyses were carried out according to duration of followup, sex, region, and study design. Sensitivity analysis was performed to evaluate stability by sequential omission of individual studies. Publication bias was tested by Egger's linear regression test for funnel plot asymmetry and the Begg-Mazumdar test[16]. All analyses were performed with STATA 11.0 software.

RESULTS

Characteristics of included studies. A total of 274 publications were identified in the initial search and 228 records were excluded based on screening of titles or abstracts (Figure 1). Full-text articles were retrieved for 46 publications and assessed for eligibility. Of these 46 publications, 26 were excluded: 3 duplicate publications, 5 reviews, 1 pooled analysis, 5 reporting repeated populations, 1 in which PM/DM was not an exposure factor, 8 in which SIR and 95% CI could not be calculated, and 3 that were not cohort or observational studies. Overall, we identified and included 20 publications meeting the inclusion criteria[17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36]. Notably, of these included studies, 5 were conducted to examine associations between PM/DM and different malignancies including prostate, kidney, bladder, myeloma, breast, cervical, endometrial, ovarian, other female genital, and lung and anal squamous cell; but not to examine for associations of PM or DM separately with various malignancies[17,18,20,21,33]. Accordingly, these 5 studies were not included in the metaanalysis, because our metaanalysis was carried out only to evaluate PM or DM and risks of site-specific malignancies separately.

Study characteristics, demographic information, and adjustment or restriction variables for the included studies are listed in Table 1. The number of studies for associations of PM and DM with malignancy risk are listed in Table 2.

All the studies included were cohort studies, and were deemed of high quality (9 with score of 9, 3 with score of 8, and 8 with score of 7), according to the NOS for cohort studies (Supplementary Table 1, available online at jrheum.org).

PM/DM, PM, DM, and risks of overall malignancy. Because of significant heterogeneity, the random-effect model was used. As shown in Table 2, PM and DM were significantly associated with increased risk for overall malignancy. The pooled RR for patients with PM, DM, and PM/DM were 1.62 (95% CI 1.19–2.04), 5.50 (4.31–6.70), and 4.07 (3.02–5.12), respectively. Further, we conducted subgroup metaanalyses by followup, sex, region, and study design. The overall RR for malignancy were 5.02 (95% CI 2.04–8.01) and 19.41 (95% CI 14.09–24.73), respectively, among patients with PM and DM within the first year of myositis diagnosis, significantly higher than those after the first year (overall RR, 95% CI, 1.27, 1.04–1.50 and 1.98, 1.60–2.36, respectively, for PM and DM). In addition, male patients with DM and PM showed much higher risk for overall malignancy than did female patients. Moreover, the risk became insignificant in female patients with PM (overall RR 1.70, 95% CI 0.89-2.50). Because the US and Australian populations in the included studies were also of European descent and the number of studies was too small in those populations, they were combined with the European population as the Western group. In this way, the subgroup analyses were conducted in Asian and Western populations, respectively. The results indicated that the pooled risks for overall malignancy remained significant in both Asian and Western populations with PM/DM. However, there might be no significant difference between Asian and Western populations. Additionally, for DM but not for PM, the pooled RR was a bit larger in hospital-based studies (pooled RR 9.77, 95% CI 5.28–14.25) but smaller in population-based studies (pooled RR 4.81, 95% CI 3.47–6.15) than was overall RR. The heterogeneity did not significantly change in the majority of subgroup analyses (Table 2).

PM, DM, and risks of site-specific malignancies. For PM, there were 4 studies reporting RR or giving data with which SIR could be calculated for lung, kidney, breast, and ovarian cancer risks; 3 for prostate, bladder, endometrial, cervical, stomach, colorectal, and pancreatic cancers, and lymphoma and myeloma risks; and 2 for esophageal, colon, thyroid, and brain cancer risks. Because of no significant hetero-

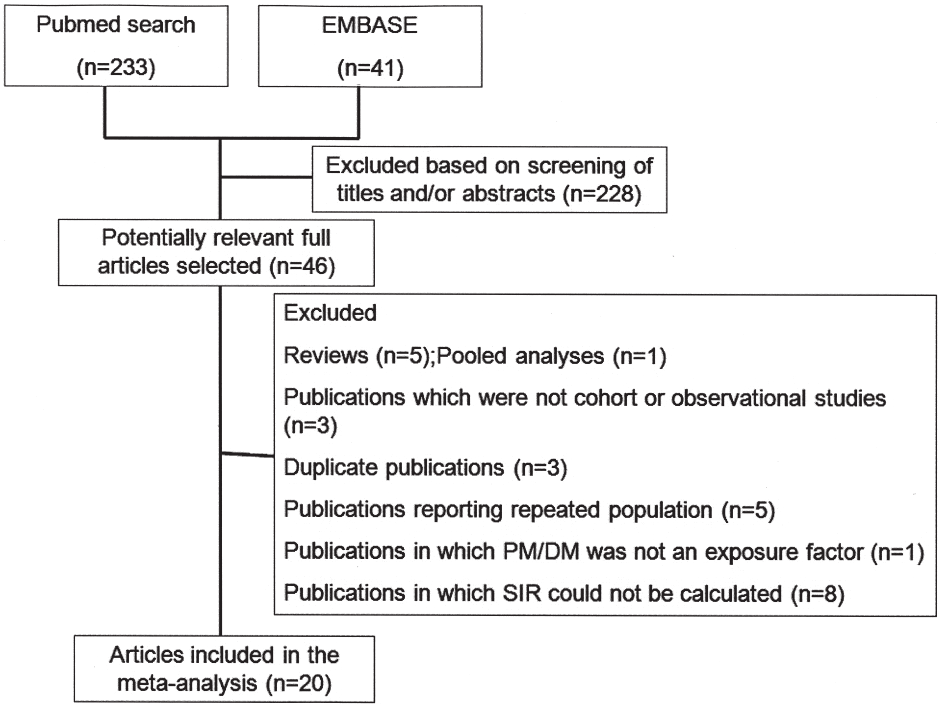

Figure 1. Flowchart of study selection. PM: polymyositis; DM: dermatomyositis; SIR: standardized incidence ratio.

geneity, fixed-effect models were conducted to evaluate associations between PM or DM and various malignancy risks, with the exception of lung, colorectal, and pancreatic cancers in patients with PM; and lung, stomach, melanoma, and kidney cancers in patients with DM. The metaanalyses indicated that PM was significantly associated with increased risks of most organ and system malignancies, with the exception of ovarian cancer, prostate cancer, myeloma, and cancers of the digestive system (stomach, esophageal, colorectal, and pancreatic; Table 2).

For DM, there were 7 studies reporting RR or giving data with which SIR could be calculated for ovarian cancer risk; 5 for breast, lung, and stomach cancer risks; 4 for prostate, bladder, colorectal, and cervical cancer risks; 3 for esophageal and pancreatic cancers and melanoma risks; and 2 for nasopharyngeal, colon, kidney, and endometrial cancers, Hodgkin disease, and unspecified malignancy risks. Because there was no significant heterogeneity, fixed-effect models were conducted to evaluate the association between PM/DM and various malignancy risks, with the exceptions of lung, stomach, and kidney cancers, and melanoma. The metaanalyses indicated that DM was significantly associated with increased risks of the majority of malignancies, with the exceptions of stomach, prostate, and endometrial cancers, lymphoma, Hodgkin disease, and melanoma.

Sensitivity analysis and publication bias. No significant change of pooled RR was found by sequential omission of individual study, indicating that our results were stable and reliable.

In accordance with a previous publication[37], funnel plot and Egger's test were used only to assess the publication bias of metaanalyses pooling 5 or more individual studies. Funnel plot is a scatterplot designed to check for the existence of publication bias. In the absence of publication bias, the plot should resemble a funnel shape, because larger studies are plotted near the average, and smaller studies are spread evenly on both sides of the average. In the presence of publication bias, some smaller studies reporting negative results will be missing, resulting in an asymmetrical funnel plot. Our funnel plot shapes showed no obvious evidence of asymmetry, and all the p values of Egger's tests were over 0.05. These results suggested that publication bias was not evident in various metaanalyses. Details of these results are presented in Supplements 2-9, available online at jrheum.org.

DISCUSSION

We describe a systematic review and metaanalysis with 20 publications of high quality to assess PM or DM and subsequent cancer risks. Our results demonstrated that both PM and DM can increase the risk of overall malignancy and the majority of site-specific malignancies, but that the risks are far greater for DM. The risks of overall malignancies in patients with DM and PM are, respectively, 4.5-fold and 62% higher than those in non-PM/DM individuals.

Table 1. Characteristics of cohort studies on PM/DM and malignancy risks.

Study	Region	Study Period	No. Pts.	Sex	Mean Age at Study Entry, yrs	Malignancies (n)	Mean Yrs Followup	RR Estimate	Adjustment for Covariates
Liu X, *et al* 2013[17]	Sweden	1964–2008	2465	F/M	NA	Prostate (29), kidney (11), bladder (18)	9.75	SIR	Age, sex, region, and socioeconomic status, hospitalization for obesity
Hemminki K, *et al* 2012[18]	Sweden	1964–2008	2465	F/M	NA	Myeloma (4)	9.75	SIR	Age, region and socioeconomic status, hospitalization for obesity
Limaye V, *et al* 2013[19]	Australia	1980–2009	240	F/M	NA	Overall (27)	Median: 9 (PM), 8 (DM)	SIR	NA
Hemminki K, *et al* 2012[20]	Sweden	1964–2008	1246	F	NA	Breast (27), cervical (3), endometrial (4), ovarian (14), other female genital (2)	19	SIR	Age, region and socioeconomic status, hospitalization for obesity
Hemminki K, *et al* 2012[21]	Sweden	1964–2008	2465	F/M	NA	Lung (52)	9.75	SIR	Age, sex, region and socioeconomic status, hospitalization for obesity
Kuo CF, *et al* 2011[22]	Taiwan, China	2003–2007	1303	F/M	44 (DM), 49.2 (PM)	All (142), nasopharyngeal (32), breast (19), lung (15), cervical (9), colon (11), liver and bile duct (7), kidney (7), thyroid (4), other (38)	Median: 3	SIR	Sex, age
So MW, *et al* 2011[23]	South Korea	1989–2010	151	F/M	49.5	All (25), lung (8), stomach (5), breast (4), biliary (2), nasopharyngeal (2), thyroid (2), colon, pancreatic (1), ovarian (1), non-Hodgkin's lymphoma (1)	4.1	SIR	Sex, age
Liu WC, *et al* 2010[24]	Singapore	1996–2006	69 (DM)	F/M	50	All (15), nasopharyngeal (7), colorectal (3), liver (1), breast (2), uterine (1), ovarian (1)	2.1	SIR	Sex, age
Azuma K, *et al* 2011[25]	Japan	1984–2002	121	F/M	51 (DM), 59 (PM)	All (20), stomach (8), colon (3), ovarian (3), breast (2), pancreas (2), thymic (1), invasive thymoma (1), non-Hodgkin's lymphoma (1)	6.4	SIR	Sex, age
Chen YJ, *et al* 2010[26]	Taiwan, China	1997–2007	1655	F/M	41.79 (DM), 48.38 (PM)	All (128), nasopharynx (32), lung (27), breast (12), uterus (1), uterine cervix (4), ovarian (2), lymphoma/leukemia (5), oropharynx and larynx (1), esophagus (1), liver/gall bladder (9), colorectum (10), stomach (1), pancreas (2), kidney (4), urinary bladder (4), melanoma (3), bone/joint (3), brain (2), thyroid (3), metastatic cancers (2)	5.09 (DM), 5.05 (PM)	SIR	Sex, age
Antiochos BB, *et al* 2009[27]	USA	1985–2008	124	F/M	56.7 (DM), 55.7 (PM)	All (27), breast (6), bladder (1), cervix (1), colon (3), endometrium (1), larynx (1), lung (5), ovarian (2), pancreas (3), parotid (1), prostate (1), unknown (1)	NA	SIR	NA
Fardet L, *et al* 2009[28]	France	1995–2007	121	F/M	52 (median)	All (29), ovarian (7), lung (5), breast (5), head and neck (6), non-Hodgkin's lymphoma (2), bladder (1), prostate (1), seminoma (1), neuroendocrine tumor (1)	3	SIR	Sex, age

Table 1. Continued.

Study	Region	Study Period	No. Pts.	Sex	Mean Age at Study Entry, yrs	Malignancies (n) Followup	Mean Yrs Estimate	RR Covariates	Adjustment for
Brown LM, *et al* 2008[29]	UK	1969-1996	NA	M	NA	MM (6), MGUS (5)	NA	RR	Age, calendar year of diagnosis, no. hospital visits, latency between study entry and study exit
Stockton D, *et al* 2001[30]	Scotland	1980–1996	705	F/M	NA	All (29), esophagus (0), stomach (0), colon (2), rectum (2), liver (0), gall bladder (1), malignant melanoma of skin (1), lung (11), breast (8), cervix uteri (2), corpus uteri (1), kidney (0), brain (0), thyroid (0), ovary (3), prostate (3), bladder (0), Hodgkin's disease (3), non-Hodgkin's lymphoma (2), multiple myeloma (1), lip (1), tongue (1), gum (1), secondary and unspecified malignancy (6)	NA	SIR	Age, sex
Buchbinder R, *et al* 2001[31]	Australia	1981–1995	406	F/M	51.7 (DM), 57.1 (PM)	All (55), lung (11), head and neck (5), breast (7), chronic lymphocytic leukemia (4), prostate (3), melanoma (2), non-Hodgkin's lymphoma (3), bladder (2), kidney (1), stomach (2), mesothelioma (1), cervix (3), colorectal (4), ovarian (4), uterus (3), pancreas (1), esophagus (1), myeloma (1), ependymoma (1)	Median: 5.3	SIR	Sex, age, calendar year of diagnosis
Hill CL, *et al* 2001[32]	Sweden, Denmark, Finland	1964–1989	1532	F/M	55.6 male, 55.4 female for DM; 56.2 male, 57.5 female for PM	All (210), esophagus (2), stomach (8), colorectal (22), pancreas (6), lung, trachea, and bronchus (39), breast (24), cervix (2), ovary (15), prostate (9), kidney (6), bladder (12), non-Hodgkin's lymphoma (9), Hodgkin's lymphoma (1), myeloma (3), leukemia (4)	NA	SIR	Sex, age, calendar year of diagnosis
Maoz CR, *et al* 1998[33]	Israel	1983–1994	35	F/M	53	All (13), metastatic cancer (1), ovary (1), esophageal (1), breast (2), Hodgkin's lymphoma (1), myelodysplastic syndrome (1), adeno cancer (1), lung (1), melanoma (1), bladder (1), leukemia (2)	NA	SIR	Sex, age
Mok CC, *et al* 2012[34]	Hong Kong, China	2000–2010	200	F/M	51.5	All (50), nasopharyngeal (21), gastrointestinal (10), lung (10), breast (4), cervical (3)	4.7	SIR	Sex, age
Chang SH, *et al* 2012[35]	South Korea	2000–2012	39	F/M	NA	All (NA), lung (7), colon (5), gastric (4), breast (3)	NA	SIR	Sex, age
Sunesen KG, *et al* 2010[36]	Denmark	1978–2006	1401	F/M	NA	Anal squamous cell carcinoma	9.4	SIR	Sex, age, calendar year of diagnosis

NA: not available; SIR: standardized incidence rate; RR: relative risk; PM: polymyositis; DM: dermatomyositis; MM: multiple melanoma; MGUS: malignant gastric ulcers.

Our present metaanalysis showed persistently increased risks of overall malignant disease both in PM and in DM patients, although the risks were highest during the first year of DM or PM diagnosis. This finding may be partly due to heightened screening for cancers after DM or PM diagnosis. On the other hand, this result might also suggest that a true link with cancer does exist in patients with PM or DM. In some included studies[19,22,24,30,31,32], the clustering of malignancy cases before or at the same time as diagnosis of PM/DM further suggests that the association is not merely due to heightened malignancy surveillance after PM/DM diagnosis. However, a subgroup metaanalysis cannot be conducted because these studies did not give the detailed SIR for malignancy or the number of patients with malignancy occurring before or at the same time as the diagnosis of PM/DM. Of course, the link of cancer with PM/DM may

Table 2. Pooled relative risks of overall and site-specific malignancies.

Malignancies	No. Studies	Refs	Pooled RR or SIR (95% CI)	Heterogeneity	
				I^2 (%)	p
Overall malignancy					
PM/DM	11	19, 22, 23, 25, 26, 27, 30, 31, 32, 33, 34, 35	4.07 (3.02–5.12)	90.3	0
PM	9	19, 22, 25, 26, 27, 30, 31, 32, 34	1.62 (1.19–2.04)	84.0	0
DM	12	19, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 34	5.50 (4.31–6.70)	89.7	0
Subgroup followup					
PM (0–1 yr followup)	4	22, 26, 31, 32	5.02 (2.04–8.01)	93.9	0
PM (> 1 yr followup)	4	22, 26, 31, 32	1.27 (1.04–1.50)	40.3	0.17
DM (0–1 yr followup)	4	22, 26, 31, 32	19.41 (14.09–24.73)	84.0	0
DM (> 1 yr followup)	4	22, 26, 31, 32	1.98 (1.60–2.36)	36.3	0.194
Sex					
PM (female)	6	22, 25, 26, 27, 30, 32	1.70 (0.89–2.50)	91.4	0
PM (male)	6	22, 25, 26, 27, 30, 32	1.80 (1.70–1.90)	24.5	0.25
DM (female)	7	22, 23, 25, 26, 27, 30, 32	5.07 (3.60–6.55)	87.8	0
DM (male)	7	22, 23, 25, 26, 27, 30, 32	5.74 (4.01–7.47)	82.1	0
Region					
PM					
Asia	4	22, 25, 26, 34	2.14 (2.07–2.21)	38.2	0.183
The West	5	19, 27, 30, 31, 32	1.49 (1.07–1.90)	59.6	0.042
DM					
Asia	6	22, 23, 24, 25, 26, 34	5.11 (5.00–5.21)	81.2	0
The West	6	19, 27, 28, 30, 31, 32	5.48 (3.29–7.68)	86.4	0
Study design					
PM (population-based)	6	19, 22, 26, 30, 31, 32	1.76 (1.32–2.20)	86.8	0
PM (hospital-based)	3	25, 27, 34	0.93 (0.23–1.62)	0	0.464
DM (population-based)	7	19, 22, 24, 26, 30, 31, 32	4.81 (3.47–6.15)	92.2	0
DM (hospital-based)	5	23, 25, 27, 28, 34	9.77 (5.28–14.25)	86.6	0
Site-specific malignancy					
PM					
Lung cancer	4	26, 30, 31, 32	3.65 (1.58–5.73)	90.1	0
Kidney cancer	4	26, 30, 31, 32	2.18 (1.75–2.60)	0	0.859
Breast cancer	4	26, 30, 31, 32	1.67 (1.48–1.86)	0	0.675
Ovary cancer	4	25, 30, 31, 32	1.34 (–0.50 to 3.19)	0	0.693
Prostate cancer	3	30, 31, 32	0.72 (0.03–1.40)	28.0	0.249
Lymphoma	3	30, 31, 32	3.96 (1.10–6.82)	0	0.944
Myeloma	3	30, 31, 32	2.70 (–1.06 to 6.47)	0	0.664
Colorectum cancer	3	26, 31, 32	2.32 (–0.54 to 5.17)	97.6	0
Pancreatic cancer	3	26, 31, 32	2.09 (–0.70 to 4.88)	87.8	0
Bladder cancer	3	26, 31, 32	4.32 (3.72–4.91)	64.3	0.061
Endometrial cancer	3	26, 30, 31	6.96 (5.56–8.37)	0	0.623
Cervical cancer	3	26, 31, 32	1.39 (1.10–1.67)	47.7	0.148
Stomach cancer	3	25, 31, 32	0.35 (–0.58 to 1.27)	0	0.650
Esophagus cancer	2	31, 32	1.61 (–2.89 to 6.08)	0	0.581
Colon cancer	2	25, 30	0.63 (–1.07 to 2.33)	0	0.502
Thyroid cancer	2	26, 30	3.12 (2.49–3.75)	0	0.574
Brain tumor	2	26, 30	17.76 (15.24–20.28)	71.5	0.061
DM					
Ovary cancer	7	24, 25, 26, 28, 30, 31, 32	5.43 (4.69–6.17)	42.7	0.106
Breast cancer	5	25, 26, 28, 30, 32	3.49 (3.26–3.72)	28.7	0.230
Lung cancer	5	24, 28, 30, 31, 32	15.01 (5.35–24.67)	96.0	0
Stomach cancer	5	25, 26, 30, 31, 32	3.04 (–0.53 to 6.60)	61.7	0.034
Lymphoma	5	25, 28, 30, 31, 32	4.39 (–0.38 to 9.16)	0	0.682
Prostate cancer	4	28, 30, 31, 32	1.89 (0.11–3.66)	0	0.806
Colorectal cancer	4	24, 26, 31-32	4.03 (3.68-4.39)	35.2	0.201
Cervical cancer	4	28, 30, 31, 32	3.28 (2.91–3.65)	0	0.625
Bladder cancer	4	26, 28, 30, 32	3.94 (3.38–4.49)	11.2	0.337
Hodgkin disease	2	30, 32	7.35 (–12.58 to 27.27)	0	0.587
Nasopharyngeal cancer	2	24, 26	139.95 (134.82–145.09)	0	0.885

Table 2. Continued.

Malignancies	No. Studies	Refs	Pooled RR or SIR (95% CI)	Heterogeneity	
				I^2 (%)	p
Esophagus cancer	3	26, 30, 32	3.06 (2.45–3.67)	0	0.937
Pancreatic cancer	3	25, 26, 32	3.06 (2.46–3.66)	0	0.511
Melanoma	3	26, 30, 31	5.92 (0.08–11.76)	80.6	0.006
Colon cancer	2	25, 30	13.48 (3.18–23.78)	0	0.594
Kidney cancer	2	26, 32	5.74 (5.08–6.40)	84.9	0.01
Endometrial cancer	2	24, 31	16.22 (–16.02 to 48.45)	0	0.870
Unspecified malignancy	2	26, 30	3.58 (3.08–4.09)	67.0	0.082

RR: rate ratio; SIR: standardized incidence ratio; PM: polymyositis; DM: dermatomyositis.

also be that the presenting characteristics of PM/DM are paraneoplastic features of malignancy. In fact, several isolated case reports reviewed by Zahr and Baer[38] as well as some epidemiologic studies[19,22,24,30,31,32] included in the present metaanalysis found the parallel course between PM/DM and malignancy. Further, some studies demonstrated that PM/DM will either improve when the malignancy is treated successfully, or will worsen. These findings indicate that PM/DM may be a paraneoplastic phenomenon. However, the fact that the risks of malignancy were still increased by 27% and 98%, respectively, for PM and DM in our metaanalysis demonstrated that PM/DM themselves may indeed be risk factors for malignancy development. For a patient with PM or DM, longterm use of immunosuppressive drugs may be needed, a treatment that also contributes to raised risk of malignancy. However, as described by Chen, *et al*[26], the malignancy risk in patients with myositis decreases with time, suggesting that the nature of inflammation, rather than immunosuppressive drugs, plays a pivotal role in the development of malignancy diseases. Additionally, the immunosuppressive agents in patients with PM/DM may lead to the reactivation of viral infection, which has been found to be associated with certain types of malignancies, such as Epstein-Barr virus, lymphoma, and others[39]. Accordingly, the role of virus in malignancy development in patients with PM/DM cannot be excluded. In any case, lifelong monitoring for malignancy is important for a patient with PM or DM.

PM and DM predominantly affect women[9]. However, our stratified metaanalysis indicated that male patients with PM or DM showed much higher risk for malignant disease than female patients. The increased risk is not significant in female patients with PM. This difference of malignancy risk between the sexes in patients with PM and DM is consistent with that in the general population[40], suggesting that more surveillance for malignancy is needed for a male patient with DM or PM. Although the detailed mechanisms remain unclear, the explanations for the difference may be that, on one hand, men may be more likely than women to smoke (which is known as a pivotal risk factor for cancers such as those of the lung, larynx, bladder, and others[41,42]), and that estrogen might be a protective factor from development of most cancers, a finding confirmed by several studies[43,44,45].

Of note, age should be considered in the present analysis, although subgroup analysis for age could not be conducted, because there were only 2 studies exploring the association between DM/PM and cancer risk in a series of age ranges[22,26]. Both of those studies found that the risk for malignancy is significantly increased in patients with PM/DM who are ≥ 20 years old (especially in those 40–79 years old), compared with those < 20 years old. There are another 4 included studies specifically focusing on whether age (as a risk factor) was associated with cancer development in patients with DM/PM[23,25,27,28], each of which demonstrated that increased age is closely associated with cancer risk. These results are consistent with those in the previous metaanalysis[11], suggesting that the older the age, the more heightened the malignancy monitoring should be in patients with PM/DM. Although not analyzed in our study, 2 metaanalyses had shown an association of anti-p155/p140 antibody with increased risk of malignancy in patients with DM[46,47]. A number of studies showed that the anti-NXP2 antibody might also be associated with myositis with malignancy; however, further studies are required to confirm these findings[48,49,50]. In contrast, there is no evidence to suggest that other myositis-specific and myositis-associated autoantibodies including anti-aminoacyl-tRNA synthetase, anti-signal recognition particle, anti-Mi2, anti-PM/Scl, anti-U1-RNP, anti-Ku, anti-MDA5, and anti-TIF1-α or TIF1-β antibodies are associated with malignancy development in PM/DM[51,52,53,54].

For DM, increased risk of overall malignancy can be confirmed in both population-based and hospital-based studies. The relative risk from hospital-based studies is far higher than that from population-based studies. The reason may be that hospitalized patients with DM have more severe cases. This also suggests that the more severe DM is, the more likely it will develop into malignancy. However, this conclusion cannot be drawn in patients with PM. The subgroup metaanalysis showed significant association between PM and malignancy risk for population-based studies but not for hospital-based ones. Admittedly, the

number of hospital-based studies (3) was too small to draw a firm conclusion.

Subgroup analysis by region showed that the risk for overall malignancy still remains significant in both Asian and Western populations with PM or DM, although the difference for the risk between them appears to be insignificant. However, the number of studies is small in Western populations, especially in the United States (1) and Australia (2). Therefore, more studies are needed to investigate the association in various regions other than Asia. Significant associations between some rheumatic diseases and malignancy risks have been confirmed frequently, such as systemic lupus erythematosus and decreased risks of breast, ovarian, and endometrial malignancies[55], rheumatoid arthritis and increased risks of lymphoma and decreased risks of colorectal and breast cancers[56], and primary Sjögren syndrome and increased risks of non-Hodgkin lymphoma and thyroid cancer[57]. Compared with other rheumatic diseases, PM and DM (especially DM) may be significantly associated with the risks of a larger number of malignancies, including lung, kidney, breast, bladder, endometrial, cervical and thyroid cancers, lymphoma, myeloma, and brain tumor for PM, and lung, ovarian, breast, colorectal, cervical, bladder, nasopharyngeal, esophageal, pancreatic, colon, and kidney cancers for DM. These results imply that PM and DM are similar but different diseases regarding the types of associated malignancies. In accordance with our results, intensive vigilance for cancers of the lung, breast, cervix, and urinary system, but not for cancers of the stomach and prostate, is needed for patients with PM and DM. In addition, in patients with PM, investigation should also be targeted toward lymphoma and endometrial cancer, while in DM it should be targeted toward ovarian cancer and cancers of the digestive system. Of note, there was no significant heterogeneity among most of the studies on various site-specific malignancies, suggesting that inherent malignancy difference may be a major source of heterogeneity.

Some limitations of our study should be addressed. First, a number of studies that failed to provide data to calculate SIR were not included in the metaanalysis, which may reduce the power of our analysis. However, the exclusion of such studies should be unlikely to bias our results. Second, some variables such as smoking, alcohol consumption, etc., could not be excluded because of an inherent flaw in those included studies, which might bias the results. Third, although no significant publication bias was found in our study, potential publication bias cannot be completely excluded. The reason is that small studies with null results tend not to be published[58]. In addition, some included studies referred to periods in the late 1960s, 1970s, and 1980s, when investigative techniques were less rigorous and thus some malignancies may have been missed relative to more recent studies; this may influence but not bias our results. Finally, data regarding PM/DM and risks of some site-specific malignancies were extremely sparse, limiting our ability to draw firm conclusions.

Our present metaanalysis demonstrates that DM and PM (especially DM) are significantly associated with increased risk of overall malignancy. DM is associated with increased risk of lung, ovarian, breast, colorectal, cervical, bladder, nasopharyngeal, esophageal, pancreatic, colon, and kidney cancers. PM is associated with increased risk of lung, kidney, breast, bladder, endometrial, cervical, and thyroid cancers, and lymphoma, myeloma, and brain tumors. However, because of significant heterogeneity or too few studies for some malignancies, the conclusion should be drawn cautiously. Further, more studies focusing on the association between PM/DM and various site-specific malignancies are needed in the future.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

REFERENCES

1. Benbassat J, Geffel D, Zlotnick A. Epidemiology of polymyositis-dermatomyositis in Israel, 1960–76. Isr J Med Sci 1980;16:197-200.
2. Medsger TA Jr, Dawson WN Jr, Masi AT. The epidemiology of polymyositis. Am J Med 1970;48:715–23.
3. Oddis CV, Conte CG, Steen VD, Medsger TA Jr. Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA 1963–1982. J Rheumatol 1990;17:1329–34.
4. Wilson FC, Ytterberg SR, St Sauver JL, Reed AM. Epidemiology of sporadic inclusion body myositis and polymyositis in Olmsted County, Minnesota. J Rheumatol 2008;35:445–7.
5. Kusumi M, Nakashima K, Nakayama H, Takahashi K. Epidemiology of inflammatory neurological and inflammatory neuromuscular diseases in Tottori Prefecture, Japan. Psychiatry Clin Neurosci 1995;49:169–74.
6. Briani C, Doria A, Sarzi-Puttini P, Dalakas MC. Update on idiopathic inflammatory myopathies. Autoimmunity 2006;39:161-70.
7. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet 2003;362:971-82.
8. Smoyer-Tomic KE, Amato AA, Fernandes AW. Incidence and prevalence of idiopathic inflammatory myopathies among commercially insured, medicare supplemental insured, and medicaid enrolled populations: administrative claims analysis. BMC Musculoskelet Disord 2012;13:103.
9. Mastaglia FL, Phillips BA. Idiopathic inflammatory myopathies: epidemiology, classification, and diagnostic criteria. Rheum Dis Clin North Am 2002;28:723-41.
10. Zantos D, Zhang Y, Felson D. The overall and temporal association of cancer with polymyositis and dermatomyositis. J Rheumatol 1994;21:1855-9.
11. Wang J, Guo G, Chen G, Wu B, Lu L, Bao L. Meta-analysis of the association of dermatomyositis and polymyositis with cancer. Br J Dermatol 2013;169:838-47.
12. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Internet. Accessed October 29, 2014.] Available from: www.ohri.ca/programs/clinical_epidemiology/oxford.htm
13. Liang Y, Yang Z, Zhong R. Primary biliary cirrhosis and cancer

risk: a systematic review and meta-analysis. Hepatology 2012;56:1409-17.
14. Taeger D, Sun Y, Keil U, Straif K. A stand-alone windows applications for computing extract person-years, standardized mortality ratios and confidence intervals in epidemiological studies. Epidemiology 2000;11:607-8.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:589–624.
16. Egger M, Davey SG, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. BMJ 1997;315:629–34.
17. Liu X, Ji J, Forsti A, Sundquist K, Sundquist J, Hemminki K. Autoimmune disease and subsequent urological cancer. J Urol 2013;189:2262-8.
18. Hemminki K, Liu X, Försti A, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on incidence and survival in subsequent multiple myeloma. J Hematol Oncol 2012;5:59.
19. Limaye V, Luke C, Tucker G, Hill C, Lester S, Blumbergs P, et al. The incidence and associations of malignancy in a large cohort of patients with biopsy-determined idiopathic inflammatory myositis. Rheumatol Int 2013;33:965-71.
20. Hemminki K, Liu X, Ji J, Försti A, Sundquist J, Sundquist K. Effect of autoimmune diseases on risk and survival in female cancers. Gynecol Oncol 2012;127:180-5.
21. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on risk and survival in histology-specific lung cancer. Eur Respir J 2012;40:1489-95.
22. Kuo CF, See LC, Yu KH, Chou IJ, Chang HC, Chiou MJ, et al. Incidence, cancer risk and mortality of dermatomyositis and polymyositis in Taiwan: a nationwide population study. Br J Dermatol 2011;165:1273-9.
23. So MW, Koo BS, Kim YG, Lee CK, Yoo B. Idiopathic inflammatory myopathy associated with malignancy: a retrospective cohort of 151 Korean patients with dermatomyositis and polymyositis. J Rheumatol 2011;38:2432-5.
24. Liu WC, Ho M, Koh WP, Tan AW, Ng PP, Chua SH, et al. An 11-year review of dermatomyositis in Asian patients. Ann Acad Med Singapore 2010;39:843-7.
25. Azuma K, Yamada H, Ohkubo M, Yamasaki Y, Yamasaki M, Mizushima M, et al. Incidence and predictive factors for malignancies in 136 Japanese patients with dermatomyositis, polymyositis and clinically amyopathic dermatomyositis. Mod Rheumatol 2011;21:178-83.
26. Chen YJ, Wu CY, Huang YL, Wang CB, Shen JL, Chang YT. Cancer risks of dermatomyositis and polymyositis: a nationwide cohort study in Taiwan. Arthritis Res Ther 2010;12:R70.
27. Antiochos BB, Brown LA, Li Z, Tosteson TD, Wortmann RL, Rigby WF. Malignancy is associated with dermatomyositis but not polymyositis in Northern New England, USA. J Rheumatol 2009;36:2704-10.
28. Fardet L, Dupuy A, Gain M, Kettaneh A, Chérin P, Bachelez H, et al. Factors associated with underlying malignancy in a retrospective cohort of 121 patients with dermatomyositis. Medicine 2009; 88:91-7.
29. Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. Blood 2008;111:3388-94.
30. Stockton D, Doherty VR, Brewster DH. Risk of cancer in patients with dermatomyositis or polymyositis, and follow-up implications: a Scottish population-based cohort study. Br J Cancer 2001; 85:41-5.
31. Buchbinder R, Forbes A, Hall S, Dennett X, Giles G. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. Ann Intern Med 2001;134:1087-95.
32. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellemkjaer L, Airio A, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 2001;357:96-100.
33. Maoz CR, Langevitz P, Livneh A, Blumstein Z, Sadeh M, Bank I, et al. High incidence of malignancies in patients with dermatomyositis and polymyositis: an 11-year analysis. Semin Arthritis Rheum 1998;27:319-24.
34. Mok CC, To CH, Yip ML, Ying KY. Standardized incidence ratios and predictors of malignancies in 215 Southern Chinese patients with inflammatory myopathies [abstract]. Arthritis Rheum 2012;64 Suppl 10:S96.
35. Chang SH, Park JK, Lee EB. Cancer incidence and type of malignancy in rheumatologic diseases in Korea: head-to-head comparison [abstract]. Arthritis Rheum 2012;64 Suppl 10:S44.
36. Sunesen KG, Nørgaard M, Thorlacius-Ussing O, Laurberg S. Immunosuppressive disorders and risk of anal squamous cell carcinoma: a nationwide cohort study in Denmark, 1978-2005. Int J Cancer 2010;127:675-84.
37. Sterne J, Becker B, Egger M. The funnel plot. In: Rothstein HR, Sutton AJ, Borenstein M, eds. Publication bias in meta-analysis: prevention, assessment and adjustments. Chichester: Wiley; 2005.
38. Zahr ZA, Baer AN. Malignancy in myositis. Curr Rheumatol Rep 2011;13:208-15.
39. Selva-O'Callaghan A, Palacios A, Solans-Laque R, Labirua A, Salcedo-Allende T, Vilardell-Tarrés M. Epstein-Barr virus-associated lymphoma in patients with dermatomyositis. Be aware of double immunosuppression. Rheumatology 2009; 48:1462-3.
40. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30.
41. Vineis P, Wild CP. Global cancer patterns: causes and prevention. Lancet 2014;383:549–57.
42. Thun MJ, Henley SJ, Calle EE. Tobacco use and cancer: an epidemiologic perspective for geneticists. Oncogene 2002; 21:7307-25.
43. Kennelly R, Kavanagh DO, Hogan AM, Winter DC. Oestrogen and the colon: potential mechanisms for cancer prevention. Lancet Oncol 2008;9:385–91.
44. Villa E. Role of estrogen in liver cancer. Womens Health 2008;4:41-50.
45. Chandanos E, Lagergren J. The mystery of male dominance in oesophageal cancer and the potential protective role of oestrogen. Eur J Cancer 2009;45:3149-55.
46. Lu X, Yang H, Shu X, Chen F, Zhang Y, Zhang S, et al. Factors predicting malignancy in patients with polymyositis and dermatomyostis: a systematic review and meta-analysis. PLoS One 2014;9:e94128.
47. Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O'Callaghan A, Martínez-Gómez X, Bosch X, Labrador-Horrillo M, et al. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic review and meta-analysis. Arthritis Rheum 2012;64:523-32.
48. Ichimura Y, Matsushita T, Hamaguchi Y, Kaji K, Hasegawa M, Tanino Y, et al. Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: possible association with malignancy. Ann Rheum Dis 2012;71:710-3.
49. Fiorentino DF, Chung LS, Christopher-Stine L, Zaba L, Li S, Mammen AL, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1γ. Arthritis Rheum 2013;65:2954-62.
50. Ceribelli A, Fredi M, Taraborelli M, Cavazzana I, Franceschini F, Quinzanini M, et al. Anti-MJ/NXP-2 autoantibody specificity in a cohort of adult Italian patients with polymyositis/dermatomyositis.

Arthritis Res Ther 2012;14:R97.
51. Lega JC, Fabien N, Reynaud Q, Durieu I, Durupt S, Dutertre M, et al. The clinical phenotype associated with myositis-specific and associated autoantibodies: A meta-analysis revisiting the so-called antisynthetase syndrome. Autoimmun Rev 2014;13:883-91.
52. Hoshino K, Muro Y, Sugiura K, Tomita Y, Nakashima R, Mimori T. Anti-MDA5 and anti-TIF1-gamma antibodies have clinical significance for patients with dermatomyositis. Rheumatology 2010;49:1726-33.
53. Muro Y, Ishikawa A, Sugiura K, Akiyama M. Clinical features of anti-TIF1-α antibody-positive dermatomyositis patients are closely associated with coexistent dermatomyositis-specific autoantibodies and anti-TIF1-γ or anti-Mi-2 autoantibodies. Rheumatology 2012;51:1508-13.
54. Satoh M, Chan JY, Ross SJ, Li Y, Yamasaki Y, Yamada H, et al. Autoantibodies to transcription intermediary factor TIF1β associated with dermatomyositis. Arthritis Res Ther 2012;14:R79.
55. Bernatsky S, Ramsey-Goldman R, Foulkes WD, Gordon C, Clarke AE. Breast, ovarian, and endometrial malignancies in systemic lupus erythematosus: a meta-analysis. Br J Cancer 2011; 104:1478-81.
56. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther 2008;10:R45.
57. Liang Y, Yang Z, Qin B, Zhong R. Primary Sjögren's syndrome and malignancy risk: a systematic review and meta-analysis. Ann Rheum Dis 2014;73:1151-6.
58. Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. J Clin Oncol 2011;29:3775-82.