Anti-Cyclic Citrullinated Peptide Antibody, Smoking, Alcohol Consumption, and Disease Duration as Risk Factors for Extraarticular Manifestations in Korean Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** We examined the prevalence of extraarticular manifestations (EAM) in Korean patients with rheumatoid arthritis (RA). Risk factors for development of EAM were identified from patients' general characteristics and clinical or laboratory data.

Methods. Using a retrospective medical record review, 405 patients, who fulfilled the American College of Rheumatology 1987 criteria for RA, were consecutively enrolled. EAM such as serositis, vasculitis, neuropathy, ocular lesions, sicca symptoms, pulmonary fibrosis, cervical myelopathy, and rheumatoid nodules were assessed. Statistical analysis was performed using a chi-square test, Fisher's exact test, 2-sample t-test, and multivariate logistic regression analysis.

Results. The overall prevalence of EAM in our patients was estimated to be 21.5% (n = 87). The most common EAM was rheumatoid nodule (8.4%, n = 34). Univariate analysis revealed anti-cyclic citrullinated peptide (anti-CCP) antibody positivity, smoking, alcohol consumption, and disease duration to be the risk factors associated with development of EAM. Multivariate logistic regression analysis also revealed a positive anti-CCP antibody, smoking, alcohol consumption, and disease duration to be closely associated with the development of EAM ($p = 0.003$, OR 5.006, 95% CI 1.729–14.494; $p = 0.002$, OR 5.260, 95% CI 1.876–14.753; $p = 0.001$, OR 0.218, 95% CI 0.086–0.553; $p < 0.001$, OR 1.061, 95% CI 1.032–1.091, respectively).

Conclusion. The prevalence of EAM in Korean RA patients is lower than in European, North American, and Mediterranean populations. Longer disease duration, smoking history, and positive anti-CCP antibody contributed significantly to the occurrence of EAM. Alcohol consumption in patients with RA had a negative association with EAM. (First Release May 1 2008; J Rheumatol 2008;35:995–1001)

Key Indexing Terms:
EXTRAARTICULAR MANIFESTATION
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Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease with an unknown etiology that presents as synovial inflammation[1]. Musculoskeletal manifestations of RA are a symmetric polyarthritis mainly affecting the hands, wrists, and feet, resulting in joint damage with bony erosion and disability. Besides the joint manifestations, the distinct features of RA also include various extraarticular manifestations (EAM), such as rheumatoid nodules, pleuritis, pericarditis, Felty's syndrome, hematological abnormalities, rheumatoid vasculitis, some types of ocular inflammation (e.g., scleritis, episcleritis, or retinal vasculitis), secondary Sjögren syndrome, interstitial lung disease with fibrosis, and polyneuropathy[2-5].

It has been recognized that the number and severity of EAM depends on the duration or severity of the disease[2,3,6]. Further, clinical importance of EAM in patients with RA is associated with increased mortality and a poor prognosis[2,3,6-8]. The variability in the prevalence and incidence of EAM in RA depends on geographic or ethnic differences and the selection of the patients[4-6,9-12]. The clinical or laboratory measures and genetic background are considered potent risk factors for occurrence of EAM. Previous studies reported that EAM are associated with smoking, early disability, high levels of rheumatoid factor (RF), the presence of antinuclear antibody (ANA), and the "shared epitopes" of HLA-DRB1[9,13-18].

The anti-cyclic citrullinated peptide (anti-CCP) antibody has become the focus of attention for diagnosis, with 90%–98% specificity and 60%–80% sensitivity, comparable to the IgM-RF test[19], and indicates a marker of severe dis-

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ease in RA[20]. A recent study reported that anti-CCP antibody is associated with HLA class II RA-related susceptibility alleles and severe disease manifestations[21]. There are no data on the effects of anti-CCP antibody on the development of EAM in RA, although some authors have observed a tendency for positive association between anti-CCP antibody titer and EAM in RA[22,23].

The aims of this study were to assess the prevalence of EAM, and to determine the contributing risk factors among clinical and laboratory measures, particularly the RF and anti-CCP antibody, and the medical comorbidities associated with the development of EAM in Korean RA patients.

MATERIALS AND METHODS

Patients. A total of 405 consecutive patients who fulfilled the American College of Rheumatology (ACR; formerly the American Rheumatism Association) 1987 revised criteria for the classification of RA[24] were enrolled from outpatients of the rheumatism clinic at Daegu Catholic University Medical Center. The study protocol was approved by the Institutional Review Board Committee of Daegu Catholic University Medical Center.

Criteria for EAM. Classification of EAM in patients with RA was based on revised definitions or criteria suggested by Turesson, *et al*[2,3,15] and Cimmino, *et al*[5]. EAM in this study included pericarditis, pleuritis, Felty's syndrome, cutaneous vasculitis, polyneuropathy, ocular involvement (e.g., scleritis, episcleritis, retinal vasculitis), glomerulonephritis, vasculitis involving other organs, amyloidosis, xerostomia, keratoconjunctivitis sicca, secondary Sjögren syndrome, pulmonary fibrosis, cervical myelopathy, and rheumatoid nodules irrespective of the sites involved. Both subcutaneous rheumatoid nodules and rheumatoid nodules in the other organs were integrated in this study. Glomerulitis was defined on the presence of microscopic hematuria and proteinuria in successive urinary analysis and clinical judgment by a nephrologist. Cervical myelopathy was determined by clinical complaints and verification using cervical spine plain radiography or magnetic resonance imaging. The presence of EAM was identified using a detailed review of the patient's medical records and a physical examination. Development of EAM was defined by the presence of one or more of the 15 EAM described above.

The risk factors for the development of EAM were evaluated by examination of demographic and clinical characteristics in the disease or comorbidities, disease duration, age of disease onset, smoking history, alcohol consumption, the presence or absence of comorbidities such as hypertension, diabetes mellitus, renal failure, pulmonary tuberculosis, thyroid disease and heart failure, and family history of RA. Smoking status was classified into 2 groups: smokers (patients with history of cigarette smoking currently or in the past) and nonsmokers (patients without exposure to cigarettes)[25]. The classification of alcohol consumption was similar to that of smoking and also consisted of 2 groups: alcohol consumers (alcohol consumption ≥ 1 drink per week) and nonconsumers (alcohol consumption < 1 drink per week). The data on alcohol consumption and smoking were obtained from individual interview and medical record review at the time of study enrollment.

Laboratory measures including RF, anti-CCP antibody, erythrocyte sediment rate (ESR), and C-reactive protein (CRP) were evaluated at time of enrollment. Positive IgM-RF and anti-CCP antibody were assessed by immunoturbidimetry (Cobas integra RFII; Roche Diagnostics, Mannheim, Germany) and the ELISA method (Diastat™; Axis-Shield Diagnostics, Dundee, UK), respectively. The blood samples were obtained at the time of enrollment. Patients were considered positive if the titer for RF was > 10 IU/ml and titer for anti-CCP antibody was > 5 U/ml, as recommended by each manufacturer. For statistical analysis, patients with RF or anti-CCP antibody were classified into 2 groups: low titer and high titer. High titer of the 2 autoantibodies was ≥ 80 IU/ml for RF and ≥ 60 U/ml for anti-CCP based on the median value of the titers of each antibody.

Statistical analysis. The statistical values for the association between risk factor and individual or overall EAM are described as p value, odds ratio (OR), and 95% confidence intervals (CI). Data were analyzed using SPSS version 12.0 for Windows (SPSS, Chicago, IL, USA). Differences in continuous or incontinuous variables between groups were compared using a 2-sample t-test, chi-square test, or Fisher's exact test. The results from the former analysis were reassessed using multiple logistic regression to exclude confounding effects of risk factors for EAM. A p value < 0.05 was considered significant.

RESULTS

Demographic and clinical features of patients with RA are described in Table 1, including sex, age, disease duration, age of disease onset, alcohol consumption, smoking history, presence of comorbidities, medications, and the RA-related autoantibodies RF and anti-CCP. About 90% (n = 365) of patients studied were female. Among the comorbidities, hypertension was the most common disease combined with RA (n = 77, 19%). The positivity of RF and the anti-CCP antibody was 91.1% and 84.2%, respectively.

The study identified 15 individual EAM in RA patients (Table 2). The overall frequency of EAM was 21.5%, which developed in 87 patients. The most common EAM was rheumatoid nodules (n = 34, 8.4%), followed by sicca syndrome (n = 30, 7.4%). Interestingly, the frequency of patients with neuropathy was higher than expected (n = 26,

Table 1. Demographic and clinical characteristics of patients with rheumatoid arthritis (n = 405). Data are mean ± standard deviation, except number (%).

Characteristics	No. of Patients
Demographics	
Male/female, n (%)	40/365 (9.9/90.1)
Age, yrs	56.0 ± 11.74
Disease duration, yrs	10.8 ± 8.6
Age at onset, yrs	45.2 ± 13.5
Family and social history	
Family history, n (%)	19 (4.7)
Smoking, n (%)	48 (11.9)
Alcohol consumption, n (%)	76 (18.8)
Comorbidities	
Hypertension, n (%)	77 (19.0)
Diabetes mellitus, n (%)	32 (7.9)
Renal failure, n (%)	1 (0.2)
Pulmonary tuberculosis, n (%)	13 (3.2)
Heart failure, n (%)	3 (0.7)
Ischemic heart disease, n (%)	6 (1.5)
Thyroid disease, n (%)	15 (3.7)
Fracture, n (%)	5 (1.2)
CRP, mg/l	27.9 ± 41.4
ESR, mm/h	49.3 ± 29.5
RA-related autoantibodies	
RF-positive, n (%)	369 (91.1)
RF titer, IU/ml	174.2 ± 358.1
Anti-CCP antibody-positive, n (%)	341 (84.2)
Anti-CCP antibody titer, U/ml	59.6 ± 49.9

Table 2. Frequency of extraarticular manifestations (EAM) in patients with rheumatoid arthritis (n = 405).

Extraarticular Manifestations	No. of Patients (%)
Pericarditis	4 (1.0)
Pleuritis	0 (0.0)
Felty's syndrome	0 (0.0)
Vasculitis	3 (0.7)
Neuropathy	26 (6.4)
Scleritis, episcleritis, or renal vasculitis	0 (0.0)
Glomerulonephritis	0 (0.0)
Amyloidosis	3 (0.7)
Sicca syndrome	30 (7.4)
Xerostomia	28 (6.9)
Keratoconjunctivitis sicca	26 (6.4)
Secondary Sjögren's syndrome	8 (2.0)
Pulmonary fibrosis	12 (3.0)
BOOP	0 (0.0)
Cervical myelopathy	6 (1.5)
Rheumatoid nodule	34 (8.4)
Overall EAM	87 (21.5)

BOOP: bronchiolitis obliterans organizing pneumonia.

6.4%). The EAM of pleuritis, Felty's syndrome, ocular features, glomerulonephritis, and BOOP (bronchiolitis obliterans organizing pneumonia) were not found.

In the next step, the risk factors among the demographic variables and family or personal history (Table 1) for development of individual or overall EAM were identified (Table 3). Differences between male and female patients for EAM were not significant (p = 0.329). However, there was a significant difference in the disease duration between patients with and those without EAM (p < 0.001), but not in the age at disease onset (p = 0.201) (Figure 1). Figure 2 shows an increased cumulative incidence of EAM with increasing disease duration. Table 3 shows that smoking was positively related to the development of pericarditis, pulmonary fibrosis, and overall EAM (p < 0.001, OR 1.091, 95% CI 1.002–1.118; p = 0.001, OR 8.357, 95% CI 2.578–27.088; p = 0.012, OR 2.248, 95% CI 1.178–4.292, respectively). In contrast, the occurrence of neuropathy, sicca syndrome, and overall EAM showed a negative association with alcohol consumption (p = 0.007, OR 0.921, 95% CI 0.894–0.951; p = 0.024, OR 0.138, 95% CI 0.018–1.029; p = 0.023, OR 0.432, 95% CI 0.206–0.907). In addition, the acute-phase reactants ESR and CRP in the group with EAM were similar to the non-EAM group at the time of study (51.42 ± 25.48 mm/h vs 48.69 ± 30.51, p = 0.398; 30.38 ± 48.45 mg/l vs 27.16 ± 39.24, p = 0.520, respectively). In addition, we found no association between EAM and comorbidities including diabetes mellitus (p = 0.401), hypertension (p = 0.868), renal failure (p = 1.000), tuberculosis (p = 0.315), heart failure (p = 1.000), ischemic heart disease (p = 1.000), thyroid disease (p = 1.000), and fracture (p = 0.293).

The effects of RA-associated autoantibodies, such as RF and anti-CCP antibody, on the development of EAM were investigated. The presence of RF was not associated with the development of any EAM irrespective of the titer (Table 3). However, the development of EAM in patients with a high RF titer was significantly higher than in those with low RF titer (p = 0.003, OR 2.202, 95% CI 1.304–3.719). The appearance of rheumatoid nodules and overall EAM in patients with anti-CCP antibody was significantly higher than in patients without anti-CCP (p = 0.032, OR 6.750, 95% CI 0.975–50.267; p = 0.001, OR 4.826, 95% CI 1.702–13.679). The frequency of EAM in patients with a high anti-CCP titer was significantly different from those with low anti-CCP titer (p = 0.001, OR 2.450, 95% CI 1.410–4.256).

Multivariate logistic regression analysis was used to adjust for any potential confounding influences of disease duration, smoking, alcohol consumption, and positivity of anti-CCP antibody (Table 4). This revealed that disease duration, smoking, and positivity of anti-CCP were closely

Table 3. Analysis of association between risk factors assessed and extraarticular manifestations (EAM).

Risk Factor	Non-EAM (%)	EAM (%)	p	Odds Ratio (95% CI)
Nonsmoking	287 (70.9)	70 (17.3)		
Smoking	31 (7.7)	17 (4.2)	0.012	2.248 (1.178–4.292)
Non-alcohol consumption	251 (62.0)	78 (19.3)		
Alcohol consumption	67 (16.5)	9 (2.2)	0.023	0.432 (0.206–0.907)
RF-negative	31 (7.7)	5 (1.2)		
RF-positive	287 (70.9)	82 (20.2)	0.245	1.771 (0.668–4.701)*
Low-titer RF†	141 (34.8)	25 (6.2)	0.858	1.099 (0.390–3.097)*
High-titer RF †	146 (36.0)	57 (14.1)	0.073	2.421 (0.897–6.533)*
Anti-CCP antibody-negative	60 (14.8)	4 (1.0)		
Anti-CCP antibody-positive	258 (63.7)	83 (20.5)	< 0.001	4.826 (1.702–13.679)*
Low-titer anti-CCP antibody††	107 (28.9)	21 (5.2)	0.072	2.692 (0.884–8.199)*
High-titer anti-CCP antibody††	141 (34.8)	62 (15.3)	< 0.001	6.596 (2.296–18.948)*

* Calculated using RF-negative or anti-CCP antibody-negative as reference value, respectively. RF: rheumatoid factor, anti-CCP: anti-cyclic citrullinated peptide. † Development of EAM in patients with high-titer RF compared with patients with low-titer RF (p = 0.003). †† Development of EAM in patients with high-titer anti-CCP antibody compared with patients with low-titer anti-CCP antibody (p = 0.001).

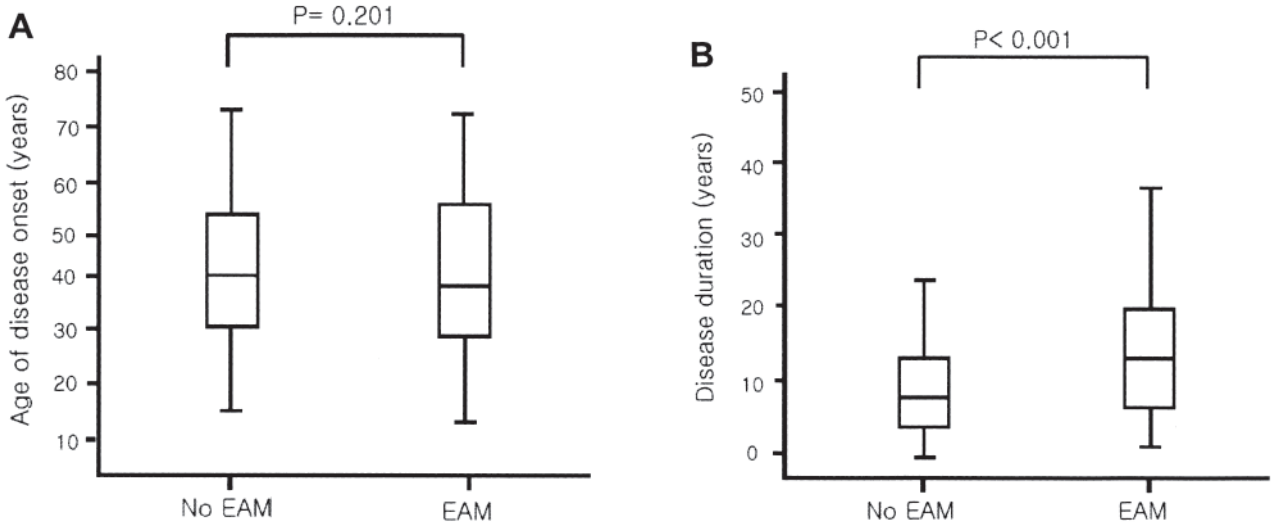

Figure 1. The association between extraarticular manifestations and (A) age of disease onset and (B) disease duration.

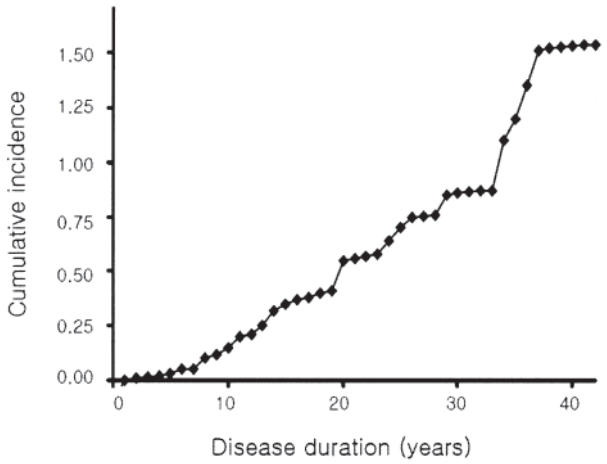

Figure 2. Cumulative incidence of extraarticular manifestations and disease duration.

Table 4. Multivariate logistic regression analysis of risk factors for development of extraarticular manifestations as dependent factor.

	B	p	Odds Ratio (95% CI)
Disease duration	0.059	< 0.001	1.061 (1.032–1.090)
Smoking	1.662	<0.001	5.260 (2.338–11.876)
Alcohol consumption	–1.521	0.001	0.218 (0.088–0.541)
Anti-CCP antibody-positive	1.609	0.003	5.006 (1.728–14.457)

associated with the development of EAM, whereas alcohol consumption carried a lower risk for occurrence of EAM.

DISCUSSION

The development of EAM is considered to be one of the peculiar features of RA characterized by chronic inflammatory diseases mainly involving the musculoskeletal systems. The prevalence of EAM in RA varies widely because of dissimilarities of ethnic groups or geographic areas, or the lack of definite inclusion criteria for EAM used in each study. For example, Caucasian populations in Britain and North America[7,15] showed a high prevalence of EAM compared with East Asian and African populations[13,14], even though the all-British study did not always agree with previous results[9]. The prevalence of overall EAM in Mediterranean populations and nearby nations such as Spain, Italy, and Turkey was found to be intermediate between results from Europe or North America and East Asia or Africa[4,5,12]. Our study identified the prevalence of overall EAM to be 21.5% (n = 87) in a total of 405 patients with RA, which is comparable to the 20.2% (n = 137) in Korean RA patients (total n = 675) reported previously[26], although the inclusion criteria for EAM of these Korean studies were different. This showed a much lower prevalence than that reported in Mediterranean populations. These results suggest a lower occurrence of EAM in Korean patients compared with other ethnic populations. An Italian study suggested the possibility of geographical differences in prevalence of EAM within the same country[5]. In contrast, the overall EAM in our RA patients dwelling in the southern areas of Korea were similar to those in patients dwelling in the northern region in a previous study[26].

A number of studies of EAM have been performed without definite inclusion criteria for EAM or their definition. Recently, Turesson, *et al* suggested well designed inclusion criteria for EAM in RA[2,3,13,15,18]. However, other authors have reported different inclusion criteria for EAM[4,5,12]. Therefore, it is difficult to evaluate the prevalence of EAM in RA patients and directly compare values assessed in each study. Nevertheless, most studies considered the relatively common EAM, rheumatoid nodules, sicca syndrome or secondary Sjögren syndrome, vasculitis, pulmonary abnormal-

ities, neuropathy including carpal tunnel syndrome, renal involvement, and vasculitis. The most common EAM was rheumatoid nodules, which ranged from 18.1% to 53% in European and North American populations[4,7,11,12]; the frequency of sicca syndrome was higher than that of rheumatoid nodules in studies of Malaysian and Chinese populations[10,11]. In particular, Veerapen, *et al* observed rheumatoid nodules as the most common EAM in British patients[11]. In contrast, sicca syndrome was the most common in a Malaysian population, consisting of races including Chinese, Indians, and Malaysians. However, the incidence of rheumatoid nodules in our study was estimated to be 8.4% (n = 34) of the total patients, followed by sicca syndrome (7.4%, n = 30). The prevalence of rheumatoid nodules and sicca syndrome in our Korean population was much lower than in other ethnic groups or geographic regions. The incidence of neuropathy in this study was relatively high (6.4%, n = 26) compared with other EAM, with the exception of rheumatoid nodules and sicca syndrome. Neuropathy including carpal tunnel syndrome in Spanish and North American patients was estimated to be 10%[4,7], whereas the incidence was < 3% in Turkish and Italian populations[5,12]. No other EAM, such as pleuritis, Felty's syndrome, ocular and renal abnormalities, or BOOP (bronchiolitis obliterans organizing pneumonia), were found in this study. Korea is an area endemic for pleurisy secondary to pulmonary tuberculosis, and tuberculosis pleurisy is frequently encountered in clinical practice. Thus, it is difficult to definitely diagnose RA patients with pleuritis after ruling out a *Mycobacterium tuberculosis* infection according to the inclusion criteria suggested by Turesson, *et al*[2,3,15]. Renal or ocular manifestations and Felty's syndrome have also been reported in other studies, albeit infrequently[2,4,5,7,12]. Similarly to our results, another analysis for EAM in Southern Chinese patients did not identify Felty's syndrome and ocular lesions, apart from episcleritis[10].

There has been increasing interest in the occurrence of EAM because they have been closely associated with disease severity, poor prognosis, and increased mortality in patients with RA[2,3,6-8]. The potential predictors of the development of EAM in RA include environmental, clinical, laboratory, and genetic factors. Until now, the risk factors known to be related to EAM included smoking, male sex, early disability, high expression of RF, ANA positivity, and the shared epitope of HLA-DRB1 including HLA-DRB1*04 and HLA-DRB1*01 alleles[13-18]. Our study identified smoking, alcohol consumption, and disease duration as the clinical or environmental factors for EAM, as confirmed by previous studies. In addition, it was found that anti-CCP antibody might play an important role in predicting development of EAM. Data for the predominance of or trend toward development of individual or overall EAM in men have been reported[5,12,18], but some studies showed no male dominance[2,13,15]. In our study, there was no difference in the frequency of EAM between male and female patients. This may be due in part to the relatively smaller male population enrolled for study.

Serum RF level was found to be a useful serologic marker for diagnosis of RA and is one of 7 described in the ACR 1987 revised classification criteria[24]. Conaghan, *et al* reported that the serum RF level was a representative quantitative marker for the prognosis or clinical outcomes of RA including functional disability, radiological progression, and mortality[27]. Because of these predictive roles of RF in clinical practice, RF is considered a powerful candidate for EAM. Some studies report that the frequency of RF in patients with EAM was significantly different from those without EAM[5,12,15]. In particular, Turesson, *et al* demonstrated that RF positivity contributed to the occurrence of EAM through multivariate regression analysis[15]. The frequency of EAM was similar in patients testing positive for RF and those negative for RF. However, there were significant differences in the development of EAM between patients with a low RF titer and those with high RF titer ($p = 0.003$). This suggests that a high RF titer may have more influence on EAM rather than just the presence of RF. In addition, some studies in non-Asian populations demonstrated that positive ANA is an independent risk factor or differential factor in the analysis for EAM[5,13,15]. Thus more information on the role of ANA in determining EAM is required.

Anti-CCP antibody is a useful test for early diagnosis of RA, with high specificity, and might provide prognostic information as a potent marker of disease severity, and in particular the radiographic damage and functional outcomes of RA[28,29]. To date there is no definite association between the presence of anti-CCP antibody and EAM in patients with RA. Some authors observed a tendency of the presence of anti-CCP antibody titer toward the appearance of extraarticular features[22,23]. In our analysis, anti-CCP antibody was found to be a risk or predictive factor for development of EAM; patients with high anti-CCP antibody titer had a higher risk of EAM than patients with low anti-CCP. This suggests either the presence of or a high titer of anti-CCP antibody as an independent risk factor for development of EAM.

It has been recognized that smoking is the most significant potential environmental risk factor for development of RA, particularly seropositive RA[30,31], as well as for severe disease manifestations[32-34], although some studies have reported otherwise[35,36]. The precise mechanism of smoking in the development of RA has not been identified. Recently, studies demonstrated the potent interaction of both smoking and positivity for shared-epitope alleles in development of citrullinated proteins[25,37]. Lee, *et al* described a definite role of smoking in patients with a positive shared epitope for citrullinated protein in a large North American cohort study[38]; the smoking group (current or previous smokers) had a higher incidence of EAM than nonsmoking patients. Because the shared epitope in each patient was not investigated, the

influence of smoking on the presence of citrullinated peptides in patients with the shared epitope was not determined.

Alcohol consumption has been implicated in the pathogenesis of some inflammatory rheumatic diseases; for example, a negative association has been found in systemic lupus erythematosus[39] and a positive association in gouty arthritis[40]. Studies describe the effects of alcohol consumption on development of RA[41,42], but debate on this issue continues. The protective effect of ethanol against development of destructive arthritis in a collagen-induced arthritis model was reported through a decrease in the activity of nuclear factor-κB, a well known signal pathway related to RA[43]. A large epidemiology study in Sweden identified increased alcohol consumption to be associated with a lower risk of developing RA[44]. However, the role of alcohol consumption in the occurrence of EAM in RA patients has not been described. Our results identified alcohol consumption to be inversely associated with the risk of EAM in RA, although the precise relation of alcohol and EAM was not determined.

There are some limitations of the assessment for prevalence and risk factors of the development of EAM in our study. The prevalence of EAM in RA may depend on the definition or inclusion criteria for the EAM assessed, in addition to ethnic or geographic variations. Results for risk factors associated with EAM in our study may be different if other inclusion criteria were applied to the same patients. Definite inclusion criteria for EAM are required. Clinical features or laboratory measures we used as risk factors were limited to identification for the presence of overall EAM, and not for individual EAM.

The prevalence of EAM in Korean patients with RA was lower than in European, North American, and Mediterranean populations. Risk analysis for EAM revealed a longer disease duration, smoking history, and positive anti-CCP antibody were associated with a higher risk of EAM, whereas alcohol consumption decreased the risk of developing EAM. Our results need to be confirmed by a longitudinal study in a larger population.

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