Mortality and Incidence of Malignancy in Korean Patients with Rheumatoid Arthritis

YUN JUNG KIM, JEE-SEON SHIM, CHAN-BUM CHOI, and SANG-CHEOL BAE

ABSTRACT. ***Objective.*** To determine the standardized mortality ratio (SMR) and standardized incidence ratio (SIR) for malignancy in Korean patients with rheumatoid arthritis (RA).

Methods. We enrolled 1534 patients with RA who fulfilled the American College of Rheumatology criteria, from October 2001 to December 2007. Baseline assessment included sociodemographic variables, laboratory findings including rheumatoid factor, anticitrullinated protein antibody, functional class, radiological stage, medication, and the Korean version of the Health Assessment Questionnaire. We used the national mortality rate from 2001 to 2007 from the Korean National Statistical Office (KNSO) and the incidence rate from the Korean Central Cancer Registry (KCCR) from 2001 to 2007 as comparison data for estimates of SMR and SIR. Confidence intervals were calculated based on the Poisson distribution.

Results. There were 57 deaths in 6683 person-years of followup. The number of expected deaths (derived from the KNSO) was 42.33 and the SMR for patients with RA was 1.35 (95% CI 1.02–1.74). The main causes of death were malignancy, cardiovascular disease, and respiratory disease. In the cause-specific SMR, deaths from respiratory disease, especially from interstitial lung disease (ILD) and pneumonia, were significantly higher than expected: 4.66 (95% CI 2.13–8.85) for all respiratory disease, 18.18 (95% CI 2.20–65.64) for ILD, and 10.26 (95% CI 2.79–26.26) for pneumonia. Thirty malignancies had occurred in 1501 patients. The number of expected malignancies derived from the KCCR was 34.91, yielding a SIR for cancer of 0.86 (95% CI 0.58–1.23).

Conclusion. Our study demonstrates that the SMR was slightly higher in patients with RA, but the incidence rates of malignancies were not significantly different from the general population. But deaths from respiratory diseases were significantly higher. (First Release Dec 15 2011; J Rheumatol 2012;39:226–32; doi:10.3899/jrheum.110704)

Key Indexing Terms:
MORTALITY MALIGNANCY RHEUMATOID ARTHRITIS KOREA

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can lead to disability, lowering the quality of life and life expectancy. Numerous epidemiologic studies have reported a positive association between increased mortality and RA, with reported standardized mortality ratios (SMR) ranging from 1.28 to 2.98[1,2]. The increase in mortality seen in patients with RA, which is apparent within the first few years of the disease and increases with disease duration, is mainly due to cardiovascular disease, malignancy, infection, and respiratory disease[1,3,4,5].

There have been concerns that the incidence of malignancy may be increased in patients with RA. While it is generally understood that overall mortality in RA is higher than that of the general population, the association between malignancy and RA is somewhat controversial. Many studies have shown that patients with RA have an increased risk of lymphoma, but do not have a definitely increased risk of solid tumor[6,7,8,9,10,11,12]. For solid malignancies, an increased risk in lung and skin malignancies and a decreased risk in colorectal malignancy have been reported in patients with RA[6,7,8,9,12]. However, the results are not consistent and there are disagreements among the studies. Most of the studies investigating mortality and malignancy in RA have been performed in North America and Europe; such data from East Asia are scarce[13,14,15,16].

We present mortality rates and the causes of death in Korean patients with RA and compare them with those of the general population by linking the cohort with Korean national statistics. The standardized incidence ratio (SIR) of malignancy in patients with RA was also estimated by identifying the cases in the cohort through the Korean Central Cancer Registry (KCCR).

MATERIALS AND METHODS

Our study included 1534 Korean patients with RA who were consecutively enrolled and followed prospectively in the Bae RA Cohort between October

From the Hanyang University Hospital for Rheumatic Diseases, and the Clinical Research Center for Rheumatoid Arthritis, Hanyang University, Seoul, Republic of Korea.

Supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065), and Wyeth Korea, Abbott Korea, Eisai Korea, Schering-Plough Korea, and MSD Korea.

Y.J. Kim, MD, PhD; C-B. Choi, MD, PhD; S-C. Bae, MD, PhD, MPH, Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases; J-S. Shim, PhD, Clinical Research Center for Rheumatoid Arthritis, Hanyang University.

Address correspondence to Dr. S-C. Bae, Hanyang University Hospital for Rheumatic Diseases, 17 Haengdang-Dong, Seongdong-Gu, Seoul 133-792, Republic of Korea. E-mail: scbae@hanyang.ac.kr

Accepted for publication September 28, 2011.

2001 and December 2007. The Bae RA Cohort is composed of Korean patients with RA who are over the age of 19 years and fulfill the 1987 revised American College of Rheumatology criteria[17], and were treated at Hanyang University Hospital for Rheumatic Diseases, a tertiary referral center. Information collected included age at the time of enrollment, sex, age at disease onset, disease duration, comorbidity, smoking and alcohol habits, and other demographics. Disease-specific variables included rheumatoid factor (RF), anticitrullinated protein antibodies, functional class, and radiological stage according to the radiological criteria of Steinbrocker, *et al*[18] at baseline. A Korean version of the Health Assessment Questionnaire (KHAQ) was also assessed.

Estimation of SMR and cause-specific SMR. The Korean National Statistical Office (KNSO) maintains a civil registry for death containing age at death, causes of death, and date and time of death. In Korea, deaths are reported to local government administrative offices according to the Family Register Law and the Statistics Law. The local government administrative offices send the reported data of death to the KNSO. The transmitted data are reviewed and the cause of death is classified and counted according to the Korean Classification of Disease.

We confirmed the deaths of patients in the cohort by linking their national register number to the national death registry of the KNSO. All-cause death risk and cause-specific death risk in the cohort were compared to the mortality of the general population from 2001 to 2007. The person-years at risk for each patient were calculated by subtracting the later of 2 entry dates (the starting date of the observation period, January 1, 2001, or the date of enrollment in the cohort) from the earlier of 2 exit dates (date of death or the end date of the observation period, December 31, 2007). Expected numbers of deaths were calculated by multiplying person-years at risk by age (in 5-year intervals) and the sex-specific death rate. SMR was calculated as the ratio between the observed number of deaths in the cohort and the expected number of deaths. Confidence intervals were calculated based on the Poisson distribution. Cause of death was coded by the KNSO using the 10th revision version of the International Classification of Diseases. SMR of other main causes of death were also estimated using the same methods.

Estimation of SIR of malignancy. The KCCR reports the annual cancer incidence rates in collaboration with 8 regional population-based registries, site-specific cancer registries, and the National Health Insurance Corporation (NHIC)[19]. To improve the completeness of the nationwide cancer registry data, several sources of data were combined: national death certification data from the KNSO, medical claims data from the NHIC, and additional medical record reviews.

Newly diagnosed (incident) malignancies in the cohort were identified by linkage of patient records to the KCCR data. We used the incidence rates provided by KCCR from 2001 to 2007 as comparison data to calculate the expected number of cancer cases. The person-years for each subject were determined by subtracting the later of 2 entry dates (the starting date of the observation period, January 1, 2001, or the date of enrollment in the cohort) from the earliest of 3 exit dates (date of diagnosis from cancer registry, date of death, or the end date of the observation period, December 31, 2007). Expected numbers of cancers were calculated by multiplying person-years at risk by age (5-year intervals) and the sex-specific cancer incidence rate. Cancer SIR and 95% CI were calculated based on the same methods described for the estimation of SMR. As the incidence rates of specific malignancies in Korea differ from those of North America and Europe, we also calculated malignancy-specific SIR.

RESULTS

The general and clinical characteristics of the study subjects are summarized in Table 1. The mean age of the sample was 51.3 ± 12.3 years (range 19–82) with a disease duration of 10.9 ± 8.6 years and a female to male ratio of 8 (1353/181). The proportion of patients with positive RF was 89.8% and the mean KHAQ score was 1.03 ± 0.72.

During the observation period, 57 deaths occurred (40 women, 17 men). The expected number of deaths derived from the KNSO was 42.33, yielding an overall SMR for patients with RA of 1.35 (95% CI 1.02–1.74; Table 2). The 5-year survival rate was 95.8% in the group, 87.7% in men, and 96.8% in women. The causes of deaths included malignancy (12 cases), cardiovascular disease [10 cases including 5 from ischemic heart disease (IHD) and 5 from cerebrovascular disease], respiratory disease [10 cases including 4 from pneumonia, 2 from interstitial lung disease (ILD), and 4 from other pulmonary diseases), RA itself (5 cases), diabetes mellitus (4 cases), and others (16 cases including suicide, sepsis, urinary tract infection, hypovolemic shock, patent ductus arteriosus, agranulocytosis, Parkinson's disease, intestinal perforation, hypertension, dementia, and accident; Table 3).

Compared to the 12 observed cases of death from malignancy, the number of expected cases of death was 14.30 (SMR 0.84, 95% CI 0.43–1.47). The observed and expected deaths, respectively, were as follows: 5 and 2.39 for IHD (SMR 2.09, 95% CI 0.68–4.88), 5 and 6.86 for cerebrovascular disease (SMR 0.73, 95% CI 0.24–1.70), 10 and 1.93 for respiratory disease (SMR 4.66, 95% CI 2.13–8.85), 4 and 0.39 for pneumonia (SMR 10.26, 95% CI 2.79–26.26), and 2 and 0.11 for ILD (SMR 18.18, 95% CI 2.20–65.64; Table 4).

Among the 1534 patients in the Bae RA Cohort, 33 who were diagnosed with malignancy before enrollment were excluded from our study. Thirty cancers occurred among the 1501 patients during the observation period, with 28 cases in women and 2 in men. This included thyroid cancer in 6 patients, stomach cancer in 5, lung cancer in 3, breast cancer in 2, skin cancer in 2, and hepatocellular carcinoma in 2. There was 1 case each of sigmoid cancer, ovarian cancer, bile duct cancer, vulvar cancer, cervical cancer, rectal cancer, pancreatic cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and cancer of an unknown primary site. The observed and expected numbers of malignancies were 30 and 34.91, respectively, yielding a malignancy SIR of 0.86 (95% CI 0.58–1.23; Table 5). The site-specific SIR in all patients, in men, and in women were not significantly different compared with the general population.

DISCUSSION

While RA is a disease that affects joints, it is also a systemic disease with extraarticular manifestations and has highly variable outcomes. The disease not only directly affects quality of life, but also life expectancy. Since the first report on mortality rates in patients with RA was published in 1953[20], numerous studies have investigated the association between RA and increased mortality, various causes of death, mortality trends, and factors predicting mortality[1,3,45,21,22,23,24].

The prevalence, clinical manifestations, and outcome of RA have been reported to vary geographically and nationally[25,26]. Differences may be attributed to differences in genetic background, environmental factors, treatment strategies,

Table 1. General and disease-specific baseline characteristics of the study patients.

Variables	Total, n = 1534	Variables	Total, n = 1534
Age at enrollment, yrs, median ± SD (range)	51.3 ± 12.3 (19–82)	Alcohol consumption, n (%)	
Sex, n (%)		Never	927 (61.7)
Men	181 (11.8)	Former	140 (9.3)
Women	1353 (88.2)	Current	435 (29.0)
Age at onset, yrs, median ± SD (range)	40.4 ± 12.7 (5–78)	Comorbidity	
Onset age category, yrs (%)		Hypertension	212 (14.0)
5-19	68 (4.4)	Diabetes mellitus	74 (4.9)
20-39	672 (43.8)	Angina pectoris	5 (0.3)
40-59	684 (44.6)	Myocardial infarction	3 (0.2)
≥ 60	110 (7.2)	Hepatitis B	8 (0.5)
Disease duration, yrs, mean ± SD	10.9 ± 8.6	Malignancy	31 (2.1)
Disease duration category, yrs, (%)		RA-specific data	
< 10	773 (50.4)	Rheumatoid factor, n (%)	
10 to < 20	551 (35.9)	Negative	156 (10.2)
≥ 20	210 (13.7)	Positive	1378 (89.8)
Demographic data		ACPA, n (%)	
Marital status, n (%)		Negative	186 (15.0)
Single and others	293 (19.4)	Positive	1049 (85.0)
Married	1214 (80.6)	Medication at enrollment, n (%)	
Income (Korean won), n (%), monthly		Corticosteroid	1109 (72.8)
< 2 million	743 (52.9)	Methotrexate	1200 (78.8)
≥ 2 million	662 (47.1)	DMARD (excluding MTX)	1266 (83.1)
Medical insurance, n (%)		Cytotoxic agents	152 (9.9)
Through employer	753 (52.3)	NSAID	1284 (84.3)
Regional	640 (44.5)	Biological	14 (0.9)
Medicaid	46 (3.2)	Functional disorder, n (%)	
Monthly health expenditures [KRwon, n (%)]		No effects upon daily life, work, or hobbies	344 (22.8)
< 150,000	991 (66.2)	Effects on activities of daily life and work but not hobbies	387 (25.7)
≥ 150,000	507 (33.8)	Unable to work but able to participate in activities of daily life	385 (25.6)
Body mass index, kg/m^{2,} n (%)		Unable to participate in activities of daily life	391 (26.0)
< 18.5	212 (13.8)	Radiographic stage by Steinbrocker stage[18], (%)	
≥ 18.5 to < 25.0	1058 (69.0)	1	307 (20.1)
≥ 25.0	264 (17.2)	2	552 (36.1)
Health assessment		3	446 (29.2)
K-Health Assessment Questionnaire, median ± SD (range)	1.03 ± 0.72 (0–3.00)	4	224 (14.6)
Smoking, n (%)			
Never	1255 (83.4)		
Ex-smoker	137 (9.1)		
Current	113 (7.5)		

RA: rheumatoid arthritis; ACPA: anticitrullinated protein antibodies; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug.

socioeconomic status, organization of national health insurance, and quality of healthcare. Therefore, there is a need for nationally specific and geographically specific data collection for the management of RA. Further, because life expectancy and causes of death differ between Western and East Asian countries, studies for mortality in RA should take geographic and national differences into consideration. There have been only 2 reports on mortality in East Asian patients with RA, both from Japan[13,14]. Although most previous studies have consistently demonstrated excess mortality in patients with RA, the regional restriction of the previous studies makes it imprudent to apply the results to regions outside North America and Europe. In an effort to determine the association between excess mortality and RA in East Asian populations, we evaluated mortality in a cohort of Korean patients with RA. In our study, the estimated all-cause SMR was 1.35 (95% CI 1.02–1.74), indicating a 35% increased risk of death compared with the general population.

Causes of death in RA are diverse, but the most common causes reported in previous studies follow similar patterns, with cardiovascular disease being the most common, followed by malignancy, infection, and respiratory disease[4]. Among the main causes of death in patients with RA, the highest SMR in most studies are for deaths from infection[4]. In our study, the most common cause of death was malignancy, followed by cardiovascular disease (IHD and cerebrovascular disease), respiratory disease, and diabetes mellitus, a pattern that is similar to that of the general Korean population except for

Table 2. Standardized mortality ratios (SMR) stratified by age group and gender.

Group	No. Patients	Person-years	Observed Deaths	Expected Deaths	SMR (95% CI)
Total	1534	6683.0	57	42.33	1.35 (1.02–1.74)
Age group					
15-39		893.2	1	0.58	1.72 (0.04–9.60)
40-59		3424.9	12	8.31	1.44 (0.75–2.52)
≥ 60		2364.9	44	33.44	1.32 (0.96–1.77)
Women	1353	5990.3	40	31.92	1.25 (0.90–1.71)
Age group					
15-39		808.6	0	0.49	0.00 (0.00–7.53)
40-59		3131.4	10	6.51	1.54 (0.74–2.82)
≥ 60		2050.3	30	24.92	1.20 (0.81–1.72)
Men	181	692.7	17	10.41	1.63 (0.95–2.61)
Age group					
15-39		84.6	1	0.09	11.11 (0.28–61.89)
40-59		293.5	2	1.80	1.11 (0.13–4.01)
≥ 60		314.6	14	8.52	1.64 (0.90–2.76)

Table 3. Primary cause of death in Korean patients with rheumatoid arthritis.

Cause of Death	Total, n = 57	Women, n = 40	Men, n = 17
Malignancy	12	9	3
Stomach	2	1	1
Colon	1	1	0
Lung	1	1	0
Breast	1	1	0
Pancreas	1	1	0
Bile duct	2	1	1
Gall bladder	1	1	0
Bladder	1	0	1
Non-Hodgkin's lymphoma	1	1	0
Unknown origin	1	1	0
Respiratory system	10	7	3
Pneumonia	4	2	2
Interstitial lung disease	2	2	0
Lung abscess	2	2	0
Asthma	1	1	0
Pneumoconiosis	1	0	1
Ischemic heart disease	5	3	2
Chronic ischemic heart disease	1	0	1
Acute myocardial infarction	4	3	1
Hypertension	1	0	1
Cerebrovascular system	5	3	2
Cerebral infarction	3	2	1
Cerebral hemorrhage	2	1	1
Diabetes mellitus	4	3	1
Rheumatoid arthritis	5	5	0
Sepsis	1	1	0
Urinary tract infection	1	0	1
Intestinal perforation	1	1	0
Patent ductus arteriosus	1	1	0
Dementia	3	2	1
Parkinson's disease	1	1	0
Agranulocytosis	1	1	0
Accident/suicide	3	1	2
Unknown	3	2	1

increased death due to respiratory disease. Results of cause-specific SMR also showed higher than expected mortality for respiratory disease, especially ILD and pneumonia.

Particular attention has been given to IHD as a major cause of death in patients with RA; it has been thoroughly investigated in recent years. Studies showed increases in the age-adjusted and sex-adjusted mortality rate for IHD in patients with RA compared to the general population in Western countries[3,5,27,28]. But this increase was not reproduced in East Asian patients with RA, at least not in Japanese and Korean patients.

A recent study in Japan showed a significant increase in mortality in RA patients, with overall SMR of 1.46–1.90[13]. The main causes of death were malignancy and respiratory diseases. The investigators had no access to the contents of the death certification and Japan has no national registry system for cancer or cause of death, so it was impossible to obtain cause-specific SMR. Instead, the authors simply compared the percentage for causes of death between patients with RA and the general population and found that respiratory disease, especially ILD, was a more prominent cause of death than cardiovascular disease in patients with RA. In our study, deaths from respiratory disease accounted for 17% of all deaths and the ILD-specific SMR was 18.2.

ILD is a well known extraarticular manifestation in RA, and the estimated prevalence of ILD among patients with RA has ranged between 1% and 58%[29]. The great variation in estimates can be accounted for by diversities in method of detection, definition of disease, and study population. The cumulative incidence of ILD in RA was 6.8% and it was the third most common extraarticular manifestation in a retrospective study[30]. ILD can also occur as an adverse effect of various disease-modifying antirheumatic drugs (DMARD). Gold, D-penicillamine, and methotrexate are representative DMARD that can cause ILD, and the association between

Table 4. Cause-specific standardized mortality ratio (SMR).

Condition	Total SMR (95% CI)	Men SMR (95% CI)	Women SMR (95% CI)
Malignancy	0.84 (0.43–1.47)	0.78 (0.16–2.29)	0.86 (0.39–1.63)
IHD	2.09 (0.68–4.88)	3.51 (0.42–12.67)	1.65 (0.34–4.82)
CVD	0.73 (0.24–1.70)	1.47 (0.18–5.31)	0.55 (0.11–1.59)
Respiratory disease	4.66 (2.13–8.85)	4.55 (0.94–13.29)	4.72 (1.73–10.28)
ILD	18.18 (2.20–65.64)	—	25.00 (3.03–90.25)
Pneumonia	10.26 (2.79–26.26)	18.18 (2.20–65.64)	7.14 (0.86–25.79)
Diabetes mellitus	1.41 (0.39–3.62)	1.89 (0.05–10.51)	1.30 (0.27–3.81)
Sepsis	5.88 (0.15–32.76)	—	7.69 (0.19–42.85)

IHD: ischemic heart disease; CVD: cerebrovascular disease; ILD: interstitial lung disease.

Table 5. Standardized incidence ratios (SIR) of malignancy stratified by age group and sex.

Group	No. Patients	Person-years	Observed Incidence	Expected Incidence	SIR (95% CI)
Total	1501	6492.9	30	34.91	0.86 (0.58–1.23)
Age group					
15–39		884.7	1	1.15	0.87 (0.02–4.84)
40–59		3351.3	10	14.26	0.70 (0.34–1.29)
≥ 60		2256.9	19	19.50	0.97 (0.59–1.52)
Women	1326	5820.8	28	28.42	0.99 (0.65–1.42)
Age group					
15–39		800.1	1	1.1	0.91 (0.02–5.06)
40–59		3057.8	10	12.89	0.78 (0.37–1.43)
≥ 60		1962.9	17	14.43	1.18 (0.69–1.89)
Men	175	672.1	2	6.49	0.31 (0.04–1.11)
Age group					
15–39		84.6	0	0.05	0.00 (0.00–73.80)
40–59		293.5	0	1.37	0.00 (0.00–2.69)
≥ 60		294.0	2	5.07	0.39 (0.05–1.42)

ILD and newer drugs, such as leflunomide and tumor necrosis factor blocker, has been reported[29]. Interestingly, leflunomide-induced ILD occurred more frequently and severely in Japanese patients with RA compared to other ethnic groups[31,32,33]. The prevalence of leflunomide-induced ILD in Korea (1.0%) is also considered to be higher than that of the Western countries[34]. The deleterious effect of ILD on survival of patients with RA has also been demonstrated in studies from Western countries[5,35]. A recent study showed that ILD contributed to a 13% increase in the mortality of patients with RA compared to the general population[35]. It was also accountable for a 3-fold increase in the risk of death among patients with RA[35].

It is important to investigate the predictors of premature mortality. Past studies have reported on various predictors of premature mortality in RA, including older age, male sex, low socioeconomic status, high disease activity, RF, high HAQ score, disease duration, and comorbidities[1,3,4,5,21]. We plan to address the issue of predictors in our next study.

The potential association between autoimmune diseases and malignancy has been suspected for many years. Although the reasons for the increased risk of developing malignancy in autoimmune diseases is not clear, the role of the compromised immune system and the use of immunosuppressive agents in the treatment of autoimmune disease are considered factors. Studies on the incidence of malignancy in RA have received increased attention in recent years with the introduction of biologics.

In numerous studies from Western countries, the overall SIR for malignancy was not significantly increased in RA, but the SIR for certain types of malignancy were significantly different from those of the general population. These include increased risks of lymphoma, leukemia, and lung cancer and decreased risks of colorectal and breast cancer[6,7,8,9,11,12,36,37,38,39]. There is a near-complete absence of data on malignancy in RA from East Asian countries, with the exception of recent studies in Japanese and Taiwanese patients with RA[16,40]. A Japanese study published in 2010 showed results comparable to those done in Western countries, despite fairly different incidence rates of site-specific malignancies between the Japanese and Western general populations. In a Japanese study, the SIR of malignancy was slightly increased and a significant increase in lymphoma and lung cancer and decreased incidence of colorectal cancer were demonstrated[16]. A Taiwan

study published in 2011 showed that the overall risk of malignancy in patients with RA was higher than in the general population, and in addition to being at risk of hematologic cancers, patients with RA had a great risk for the development of various solid tumors[40]. But our study did not show significant association between RA and an increase in malignancy. We confirmed cases of malignancy using the national registry for cancer, instead of relying on medical records, to reduce surveillance or detection bias.

There were some limitations in our study. Our study population was a mixture of inception and prevalent cohorts, and in some of the patients in the prevalent cohort, we were not able to determine whether the malignancy had occurred before or after the onset of RA. They were excluded from the study even though a considerable number of patients are presumed to have developed malignancy after the onset of RA, making the number of observed cases of malignancy small. The observation period also may have not been long enough to accurately estimate the SIR, especially the site-specific SIR. Also, although our study was from the largest RA cohort in Korea, it was a cohort of patients from a single tertiary referral center and it may not fully reflect the whole RA population.

An increased risk of mortality was identified in Korean patients with RA, but there was no significant increase in malignancy. The main cause of death and prominent cause of death were distinctly different from the previous studies done in Western countries. A high risk of death due to respiratory diseases in Korean patients with RA was observed, calling for vigilant surveillance and meticulous treatment of respiratory diseases, with particular attention to ILD.

REFERENCES

1. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 2008;5 Suppl 51:S35-61.
2. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009;11:229.
3. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481-94.
4. Naz SM, Symmons DP. Mortality in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007;21:871-83.
5. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology 2007;46:350-7.
6. Abasolo L, Judez E, Descalzo MA, Gonzalez-Alvaro I, Jover JA, Carmona L. Cancer in rheumatoid arthritis: occurrence, mortality, and associated factors in a South European population. Semin Arthritis Rheum 2008;37:388-97.
7. Bernatsky S, Ramsey-Goldman R, Clarke A. Malignancy and autoimmunity. Curr Opin Rheumatol 2006;18:129-34.
8. Franklin J, Lunt M, Bunn D, Symmons D, Silman A. Influence of inflammatory polyarthritis on cancer incidence and survival: Results from a community-based prospective study. Arthritis Rheum 2007;56:790-8.
9. Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. Int J Cancer 2000;88:497-502.
10. Ekstrom K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekbom A, et al. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum 2003;48:963-70.
11. Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A, et al. Haematopoietic malignancies in rheumatoid arthritis: Lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1414-20.
12. 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.
13. Nakajima A, Inoue E, Tanaka E, Singh G, Sato E, Hoshi D, et al. Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. Scand J Rheumatol 2010;39:360-7.
14. Hakoda M, Oiwa H, Kasagi F, Masunari N, Yamada M, Suzuki G, et al. Mortality of rheumatoid arthritis in Japan: A longitudinal cohort study. Ann Rheum Dis 2005;64:1451-5.
15. Moritomo H, Ueda T, Hiyama T, Hosono N, Mori S, Komatsubara Y. The risk of cancer in rheumatoid patients in Japan. Scand J Rheumatol 1995;24:157-9.
16. Yamada T, Nakajima A, Inoue E, Tanaka E, Taniguchi A, Momohara S, et al. Incidence of malignancy in Japanese patients with rheumatoid arthritis. Rheumatol Int 2010 May 16 [Epub ahead of print].
17. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
18. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc 1949;140:659-62.
19. Won YJ, Sung J, Jung KW, Kong HJ, Park S, Shin HR, et al. Nationwide cancer incidence in Korea, 2003-2005. Cancer Res Treat 2009;41:122-31.
20. Cobb S, Anderson F, Bauer W. Length of life and cause of death in rheumatoid arthritis. N Engl J Med 1953;249:553-6.
21. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum 2003;48:1530-42.
22. Gonzalez A, Maradit Kremers H, Crowson CS, Nicola PJ, Davis JM 3rd, Therneau TM, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007;56:3583-7.
23. Jacobsson LT, Knowler WC, Pillemer S, Hanson RL, Pettitt DJ, Nelson RG, et al. Rheumatoid arthritis and mortality. A longitudinal study in Pima Indians. Arthritis Rheum 1993;36:1045-53.
24. Kroot EJ, van Leeuwen MA, van Rijswijk MH, Prevoo ML, van 't Hof MA, van De Putte LB, et al. No increased mortality in patients with rheumatoid arthritis: Up to 10 years of follow up from disease onset. Ann Rheum Dis 2000;59:954-8.
25. Dadoniene J, Uhlig T, Stropuviene S, Venalis A, Boonen A, Kvien TK. Disease activity and health status in rheumatoid arthritis: A case-control comparison between Norway and Lithuania. Ann Rheum Dis 2003;62:231-5.
26. Albers JM, Paimela L, Kurki P, Eberhardt KB, Emery P, van 't Hof MA, et al. Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60:453-8.
27. Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP. Mortality in early inflammatory polyarthritis: Cardiovascular mortality is increased in seropositive patients. Arthritis Rheum 2002;46:2010-9.
28. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: A

population-based cohort study. Arthritis Rheum 2005;52:402-11.
29. Nannini C, Ryu JH, Matteson EL. Lung disease in rheumatoid arthritis. Curr Opin Rheumatol 2008;20:340-6.
30. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: Incidence trends and risk factors over 46 years. Ann Rheum Dis 2003;62:722-7.
31. Sawada T, Inokuma S, Sato T, Otsuka T, Saeki Y, Takeuchi T, et al. Leflunomide-induced interstitial lung disease: Prevalence and risk factors in Japanese patients with rheumatoid arthritis. Rheumatology 2009;48:1069-72.
32. Shidara K, Hoshi D, Inoue E, Yamada T, Nakajima A, Taniguchi A, et al. Incidence of and risk factors for interstitial pneumonia in patients with rheumatoid arthritis in a large Japanese observational cohort, IORRA. Mod Rheumatol 2010;20:280-6.
33. McCurry J. Japan deaths spark concerns over arthritis drug. Lancet 2004;363:461.
34. Ju JH, Kim SI, Lee JH, Lee SI, Yoo WH, Choe JY, et al. Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. Arthritis Rheum 2007;56:2094-6.
35. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: A population-based study. Arthritis Rheum 2010;62:1583-91.
36. Chakravarty EF, Genovese MC. Associations between rheumatoid arthritis and malignancy. Rheum Dis Clin North Am 2004;30:271-84, vi.
37. Hemminki K, Li X, Sundquist K, Sundquist J. Cancer risk in hospitalized rheumatoid arthritis patients. Rheumatology 2008;47:698-701.
38. Buchbinder R, Barber M, Heuzenroeder L, Wluka AE, Giles G, Hall S, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum 2008;59:794-9.
39. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1421-6.
40. Chen YJ, Chang YT, Wang CB, Wu CY. The risk of cancer in patients with rheumatoid arthritis: a nationwide cohort study in Taiwan. Arthritis Rheum 2011;63:352-8.