Causes of Death in Patients with Rheumatoid Arthritis: Comparison with Siblings and Matched Osteoarthritis Controls

NAMITA KUMAR, NICOLA J. MARSHALL, DONNA M. HAMMAL, MARK S. PEARCE, LOUISE PARKER, STEPHEN S. FURNISS, PHILIP N. PLATT, and DAVID J. WALKER

ABSTRACT. ***Objective.*** Survival of patients with rheumatoid arthritis (RA) is reduced when compared to the general population. We assessed differences in causes and age of death between patients with RA and their siblings. Comparisons were also made with a control group of subjects with lower limb osteoarthritis (OA).

Methods. A population of 257 patients with RA studied in 1991 was compared to 371 of their same-sex siblings and 485 patients with hip and knee OA who were also attending the department at this time. Death certificates were obtained and compared.

Results. Among patients with RA, 54% (139/257) were deceased, compared to 28% (105/371) of the siblings and 32% (154/485) of OA patients (RA vs siblings or OA, $p < 0.05$). There were more deaths due to ischemic heart disease (IHD) in both the RA and OA groups compared to those expected; ratio observed/expected, 1.66 (95% CI 1.01, 2.79) and 1.96 (95% CI 1.21, 3.25), respectively, but not for siblings: observed/expected = 1.05 (95% CI 0.53, 2.08). There was a significant deficit in cancer related deaths in RA patients, observed/expected = 0.62 (95% CI 0.36, 1.03).

Conclusion. Significantly more patients with RA had died than in either of the comparator populations. RA and OA patients died more frequently of IHD than the siblings. The RA population had a 40% reduced rate of cancer related deaths than expected and compared to their siblings. (First Release July 15 2007; J Rheumatol 2007;34:1695–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS SIBLINGS OSTEOARTHRITIS
CARDIOVASCULAR DISEASE DEATHS

Life expectancy is reduced in rheumatoid arthritis (RA)[1], and this reduction is mainly due to cardiovascular disease[2,3]. Cardiovascular deaths cause almost half of all deaths in RA, and the cardiovascular mortality is greater and occurs earlier in RA than in the general population[4]. Why individuals with RA should be particularly at risk of ischemic heart disease (IHD) remains unclear. There are many risk factors implicated in IHD[5], and many have been studied in RA[6]. Family history, physical deconditioning, and gender are well established risk factors for coronary heart disease, but little is known about the effect these have on IHD in RA. There has also been much debate regarding the potential effects of nonsteroidal antiinflammatory drugs (NSAID) on both malignancy and cardiovascular death. There is concern that the use of these drugs increases cardiovascular morbidity and mortality[7] in all patients. Other than their pain-relieving effects, NSAID may also suppress carcinogenesis via cyclooxygenase 1 and 2[8]. Patients with RA and osteoarthritis (OA) use these drugs as a mainstay of treatment.

Our aim was to compare IHD and malignancy as causes contributing to death among patients with RA, their same-sex siblings, and patients with OA, by the study of death certificates. These comparator populations were chosen because the siblings share half their genes and their early social environment with the RA index cases, whereas the OA population share disability and some treatment modalities, NSAID in particular, with the RA patients. The rate of death in each population would give insights into causative factors and the relevance of genetics, early environment, and disability.

From the Musculoskeletal Unit, Freeman Hospital, Newcastle-upon-Tyne; the Paediatric and Lifecourse Epidemiology Research Group, School of Clinical Medical Sciences, University of Newcastle upon Tyne; Department of Cardiology, Freeman Hospital, Newcastle-upon-Tyne, United Kingdom.

Supported by the Rheumatology Department, Freeman Hospital, Newcastle-upon-Tyne.

N. Kumar, MMed, MRCP, Research Registrar; N. Marshall, RGN, MSc, Research Nurse; P.N. Platt, MD, FRCP, Consultant Rheumatologist; D.J. Walker, MD, FRCP, Consultant Rheumatologist, Musculoskeletal Unit, Freeman Hospital; D.M. Hammal, BSc, MSc, Research Associate; M. Pearce, BSc, MSc, PhD, Lecturer; L. Parker, PhD, Professor, Paediatric and Lifecourse Epidemiology Research Group, School of Clinical Medical Sciences, University of Newcastle; S.S. Furniss, MD, FRCP, Consultant Cardiologist, Department of Cardiology, Freeman Hospital.

Address reprint requests to Dr N. Kumar, Musculoskeletal Unit, Freeman Hospital, High Heaton, Newcastle-upon-Tyne, NE7 7DN, UK. E-mail: namitakumar@doctors.org.uk

Accepted for publication March 20, 2007.

MATERIALS AND METHODS

Study population. Patients were recruited from a cohort of RA patients established in 1992. This population of patients and their same-sex siblings, acting as a control group, were recruited for a family study[9]. The inclusion criteria of the original study were RA patients using the classification of Ropes, *et al*[10], with a same-sex sibling living within a 50-mile radius of Newcastle-upon-Tyne. The second control population consisted of subjects with OA of one or both knees or hips as diagnosed by the clinician and attending for medical management. These subjects were identified from the department database as attending in 1991 and could therefore have been included in a similar family study of OA.

Prior to sending data to the Office of National Statistics (ONS), patient demographic data and diagnoses of RA and OA were checked on the hospital databases. This ensured the primary diagnosis had not changed. This also confirmed that these individuals had these diagnoses, even if this was subsequently omitted from the death certificates. Exclusions were gout, pseudogout, systemic lupus erythematosus (SLE), Sjögren's syndrome, psoriatic arthritis, RA (for OA cases), and ankylosing spondylitis.

Demographic data of the resulting individuals were sent to the ONS, to obtain the causes of death. The ONS identified deceased individuals and returned the date and cause of death in paper format, and these were then analyzed. All terms including myocardial infarction, IHD, angina, coronary artery atheroma, atherosclerosis, or occlusion were regarded as part of the IHD spectrum and recorded as a cause of or contributing to death.

Using the death certificate alone could not exclude hypertensive heart disease as an underlying cause of congestive cardiac failure, left ventricular failure, pulmonary congestion, or edema. Therefore these conditions were not counted unless qualified by one of the first terms. The study received ethical approval from the local research and ethics committee. The ONS also subjected the proposal to ethical review.

Statistical methods. In order to compare numbers of deaths, standardization for the 3 populations was necessary. Because this was a relatively small study, comparing the different ages and sex groups of the population would be too cumbersome, and a single standardized or adjusted rate was calculated. The indirect method of standardization was used, as it was felt that this method would yield more stable risk estimates. The study data were divided into numbers of deaths within the following age groups: 30–59, 60–64, 65–69, 70–74, 75–79, 80–84, and > 85 years. Comparison of observed and expected numbers of those with IHD and again for those with malignancy, in each of the age groups, was carried out to determine the final age-adjusted relative risk.

Chi-square tests were used to compare categorical variables between study groups. Statistical analysis was performed using the statistical package Stata 8.0.

RESULTS

The original cohort identified 267 RA index cases. In 10 RA cases, the disease had evolved into other conditions: 1 seronegative arthritis, 3 degenerative arthritis, 1 SLE, 2 psoriatic arthritis, and 2 polyarthralgia. One female patient had onset of disease as a child and so was now regarded as having juvenile idiopathic arthritis. All these patients and their siblings were therefore excluded; 257 RA subjects remained in the study. Therefore data for 1113 individuals were sent to the ONS: 257 RA subjects, 371 same-sex siblings, and 485 OA cases were identified for study.

There were 398 deaths in total. RA deaths numbered 139, sibling deaths 105, and OA deaths 154. The ONS had no trace of 24 individuals and there were insufficient data on 11 further individuals, giving a completion rate of 96.9%. Table 1 shows the numbers of those who had died. Significantly more patients with RA had died compared to their siblings or the OA group ($p < 0.0001$). This confirmed the greater mortality in the RA population and increased interest in the causes of death.

IHD was reported on 45 RA death certificates but on only 19 of their same-sex siblings, with a resulting statistically significant increase in deaths due to IHD ($p < 0.001$ compared to siblings). Only 57 (41%) of the RA patients also had RA itself cited as contributing to the cause of death. There was no significant difference in mortality due to IHD between the RA and the OA populations.

Data previously published from the Health Survey for England, 2003, using International Classification of Disease coding, showed that 18% of those who had died nationally had died of IHD. Applying this to the age structure of our study groups, Table 2 shows the expected and observed proportion of deaths due to IHD. Significantly more IHD deaths were observed in both the RA and the OA groups compared to those expected [observed/expected ratio 1.66 (95% CI 1.01, 2.79) and 1.96 (95% CI 1.21, 3.25), respectively], but not so for the sibling group [observed/expected = 1.05 (95% CI 0.53, 2.08)]. There was a significant deficit in cancer related deaths in those with RA, with about 40% fewer deaths than expected [observed/expected = 0.62 (95% CI 0.36, 1.03)]. The observed and expected rates of death from cancer were as expected for the sibling and OA groups. Survival curves (Figures 1 and 2) for the 3 groups show a significant difference in cardiovascular deaths ($p = 0.001$), where the RA patients have significantly more cardiovascular death.

DISCUSSION

The aim of our study was to compare the causes of death between the 3 groups as recorded on death certificates. The absence of the term IHD on the death certificate does not preclude the individual from having the disease and vice versa. There is evidence that death certificates are often completed suboptimally, and cardiac causes of death may also be overestimated[11,12]. Therefore, even accepting that there will be some inaccuracy in the completion of the certificates, this does not detract from our findings of the age-adjusted mortality due to IHD, because immediate, underlying, or contributory cause of death was greater than expected in both the RA and OA patients, but not in the sibling group. These death certificates were completed in the same area over a given time period, and the results are comparisons as opposed to absolute estimates.

The mortality due to IHD in the siblings was as for the general population, suggesting that having a sibling with RA is not a risk factor for IHD. Similarly, it implies that the increased risk in RA is not related to what is shared between siblings. There are data to suggest, however, that parental history of death from IHD is an important risk factor for fatal cardiovascular disease in patients with RA[13].

We accept that our study design using families with living relatives introduces bias, as these are families with increased

Table 1. Descriptive data for each subgroup.

	RA, n = 257	Siblings, n = 371	OA, n = 485
N (%) deceased	139 (54)	105 (28)	154 (32)
Female:male	104:35	77:28	102:52
Ratio	3:1	3:1	2:1
Mean age at death, yrs (range)	72.2 (47–90)	73.4 (43–93)	78.0 (43–97)
SD	7.95	10.2	10.81
Standard error	0.68	0.99	0.87
Age-adjusted relative risk of death due to IHD (95% CI)	1.66* (1.01, 2.79)	1.05* (0.53, 2.08)	1.96* (1.21, 3.25)
Age-adjusted relative risk due to malignancy (95% CI)	0.62* (0.36, 1.03)	1.33 (0.81, 2.22)	1.00 (0.62, 1.61)

* $p < 0.0001$. IHD: ischemic heart disease.

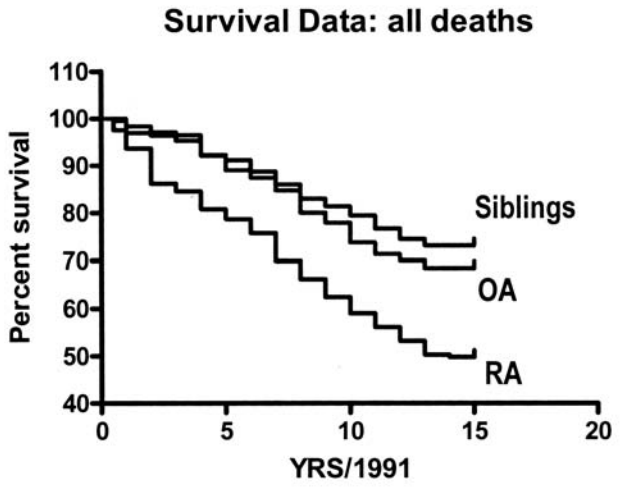

Figure 1. Survival curves of RA patients, siblings, and OA patients due to all deaths. There are significant differences between the survivor functions of the 3 groups ($p = 0.0001$), with significant differences between index versus OA ($p < 0.0001$) and index versus sibling ($p = 0.027$).

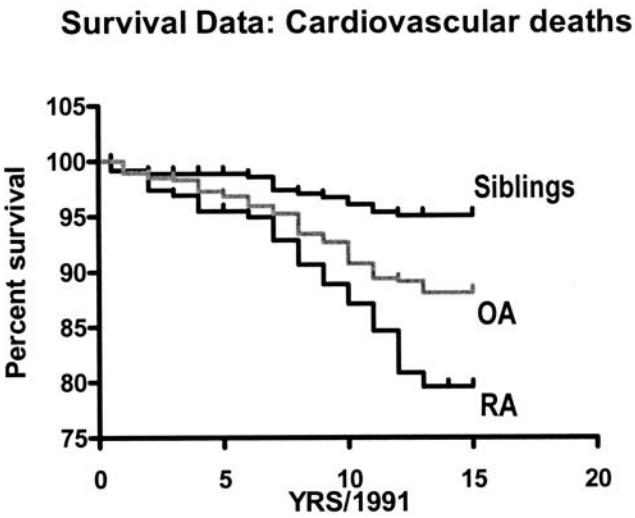

Figure 2. Survival curves of RA patients, siblings, and OA patients due to cardiovascular deaths. More RA patients ($p < 0.0001$) died compared to RA siblings and OA controls.

Table 2. Observed and expected deaths due to ischemic heart disease (IHD).

	Deaths Due to IHD			
	Expected %	Observed %	p	95% CI
OA	17.8	35.7	0.002	1.21, 3.25
RA	19.5	34.5	0.015	1.01, 2.79
Siblings	19.0	21.9	0.652	0.53, 2.08

longevity. However, the RA sibling comparisons have been made within families.

The number of deaths due to IHD in the patients with OA was, however, much greater than in the general population and similar to the risk in patients with RA. This is at variance with previous data[14], where patients with RA have been shown to be 30%–60% more likely to experience a vascular event and 60%–70% more likely to die (over a mean duration of followup of almost 5 years), compared to patients with OA and those with no arthritis. One explanation for this may be that our OA group had disease of the hip and knee and did not include spinal and upper limb OA. OA disease of these joints causes greater ambulatory disability, restricting exercise advised for coronary prevention, and has fewer psychological components. It is also clear that patients with RA have a more inflammatory disease process, reflected by higher inflammatory markers usually found in clinical practice. Another explanation may be that OA patients with lower-limb disease are more likely to be obese and possibly have adverse lipid profiles.

This population with OA was identified from a secondary care rheumatology database, and the disability is likely to have been greater than in those being cared for in the community. Lack of regular exercise is known to be a cardiovascular risk factor[5]. The increased severity of OA disease may also be a surrogate marker for increased use of NSAID, which is also associated with increased IHD[7].

The reduction of deaths in the RA population due to malignancy when compared to the siblings was an unexpected finding. It is known that NSAID protect from certain forms of can-

cer, particularly gastrointestinal, mainly colonic[15], esophageal[16], and gastric[17]. NSAID have also been found to protect against breast, lung, brain[18,19], and bladder malignancy[20]. It is, however, unlikely that NSAID protected the RA group from malignancy, but not the OA population.

The use of antiinflammatories may have increased cardiovascular morbidity in the 2 groups with arthritis. This is supported by the similar ages of death in the 3 groups. We had anticipated the siblings would be older at death, and this is one possible explanation of why this was not the case. The findings can in part be explained with the competing risk of death, that is, if a patient dies of a cardiac event, they cannot then be at risk for death from cancer, and vice versa.

IHD does not appear to have the same magnitude in other inflammatory rheumatological conditions such as ankylosing spondylitis, psoriatic arthritis[21], and scleroderma[22]. This again lends weight to the argument that those coronary risk factors shared with OA may be more pertinent.

IHD in this population proved to be the major cause of death and of similar magnitude in both RA and OA patients. OA affects much of the population. The World Health Organization estimates that 9.6% of men and 18% of women worldwide aged over 60 years have symptomatic OA (www.who.int/chp/topics/rheumatic/en). Further research is required to assess whether there is a consistently increased prevalence of IHD in OA, and which patients are most at risk, particularly as primary prevention strategies in IHD are of proven benefit. The increase in deaths due to malignancy found in the sibling group compared with the RA patients may provide evidence of an anti-cancer effect of NSAID, which requires more careful investigation and further consideration within the entire risk/benefit equation of NSAID.

ACKNOWLEDGMENT

The authors thank Dr. C. Deighton for collecting the original data.

REFERENCES

1. Pincus T, Brooks RH, Callahan LF. Prediction of long term mortality in patients with rheumatoid arthritis. Ann Intern Med 1994;120:26-34.
2. Jacobsson LT, Knowler WC, Pillemer S, et al. Rheumatoid arthritis and mortality. A longitudinal study in Pima Indians. Arthritis Rheum 1993;36:1045-53.
3. Wallberg-Jonsson S, Cederfelt M, Rantapaa Dahlqvist S. Hemostatic factors and cardiovascular disease in active rheumatoid arthritis: an 8 year followup study. J Rheumatol 2000;27:71-5.
4. Kitas G, Banks MJ, Bacon PA. Cardiac involvement in rheumatoid disease. Clin Med 2001;1:18-21.
5. Smith SC, Greenland P, Grundy SM. AHA Conference Proceedings. Prevention Conference V. Beyond secondary prevention: Identifying the high risk patient for primary prevention. Circulation 2000;101:111-6.
6. McEntegart A, Capell HA, Creran D, Rumley A, Woodward M, Lowe GD. Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. Rheumatology Oxford 2001;40:640-4.
7. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal-anti-inflammatory drugs: population based nested case control analysis. BMJ 2005;330:1366-9.
8. Furstenberger G, Krieg P, Muller-Decker K, Habenicht AJ. What are cyclooxygenases and lipoxygenases doing in the driver's seat of carcinogenesis? Int J Cancer 2006;119:2247-54.
9. Deighton CM, Roberts DF, Walker DJ. Effect of disease severity on rheumatoid arthritis concordance in same sexed siblings. Ann Rheum Dis 1992;51:943-5.
10. Ropes MW, Bennett GA, Cobb S, Jacox R, Jessar RA. 1958 Revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958;9:175-6.
11. Lakkireddy DR, Gowda MS, Murray CW, Basarakodu KR, Vacek JL. Death certificate completion: how well are physicians trained and are cardiovascular causes overstated? Am J Med 2004;117:492-8.
12. Messite J, Stellman SD. Accuracy of death certificate completion: the need for formalized physician training. JAMA 1996;275:794-6.
13. Bjornadal L, Brandt L, Klareskog L, Askling J. Impact of parental history on patients' cardiovascular mortality in rheumatoid arthritis. Ann Rheum Dis 2006;65:741-5.
14. Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis or no arthritis in the UK General Practice Research Database. J Rheumatol 2003;30:1196-202.
15. Arber N, DuBois RN. Nonsteroidal anti-inflammatory drugs and prevention of colorectal cancer. Curr Gastroenterol Rep 1999;1:441-8.
16. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterol 2003;124:47-56.
17. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Aspirin protects against gastric cancer: results of a case-control study from Moscow, Russia. Int J Cancer 1999;82:473-6.
18. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994;5:138-46.
19. Ratnasinghe LD, Graubard BI, Kahle L, Tangrea JA, Taylor PR, Hawk E. Aspirin use and mortality from cancer in a prospective cohort study. Anticancer Res 2004;24:3177-84.
20. Castelao JE, Yuan JM, Gago-Dominguez M, Yu MC, Ross RK. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. Br J Cancer 2000;82:1364-9.
21. Farragher TM, Bruce IN. Cardiovascular risk in inflammatory rheumatic diseases: loose ends and common threads. J Rheumatol 2006;33:2105-7.
22. Akram MR, Handler CE, Williams M, et al. Angiographically proven coronary artery disease in scleroderma. Rheumatology Oxford 2006;45:1395-8.