

## EXTENDED REPORT

## Mortality of rheumatoid arthritis in Japan: a longitudinal cohort study

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**Objective:** To determine the mortality risk of Japanese patients with rheumatoid arthritis, taking into account lifestyle and physical factors, including comorbidity.

**Methods:** 91 individuals with rheumatoid arthritis were identified during screening a cohort of 16 119 Japanese atomic bomb survivors in the period 1958 to 1966. These individuals and the remainder of the cohort were followed for mortality until 1999. Mortality risk of the rheumatoid patients was estimated by the Cox proportional hazards model. In addition to age and sex, lifestyle and physical factors such as smoking status, alcohol consumption, blood pressure, and comorbidity were included as adjustment factors for the analysis of total mortality and for analysis of mortality from each cause of death.

**Results:** 83 of the rheumatoid patients (91.2%) and 8527 of the non-rheumatoid controls (52.9%) died during mean follow up periods of 17.8 and 28.0 years, respectively. The age and sex adjusted hazard ratio for mortality in the rheumatoid patients was 1.60 (95% confidence interval, 1.29 to 1.99),  $p < 0.001$ . Multiple adjustments, including for lifestyle and physical factors, resulted in a similar mortality hazard ratio of 1.57 (1.25 to 1.94),  $p < 0.001$ . Although mortality risk tended to be higher in male than in female rheumatoid patients, the difference was not significant. Pneumonia, tuberculosis, and liver disease were significantly increased as causes of death in rheumatoid patients.

**Conclusions:** Rheumatoid arthritis is an independent risk factor for mortality. Infectious events are associated with increased mortality in rheumatoid arthritis.

Since the first such report was published in 1953, numerous studies have investigated mortality in rheumatoid arthritis, and many of these have found an increase in mortality.<sup>1-29</sup> Most of the studies compared the observed number of deaths among rheumatoid patients during the follow up period with the expected number of deaths calculated from census data. Although several lifestyle and physical factors such as smoking status, alcohol use, body mass index, and comorbidity can affect mortality, these factors were never included for control subjects in the analyses because the control data were always obtained from census data.

Mikuls *et al* were the first to take into account such lifestyle and physical factors in the analysis of mortality in rheumatoid arthritis.<sup>25</sup> The researchers used the Iowa women's health study cohort and obtained potential confounding factors including smoking history, alcohol use, education level, body mass index, and comorbidity of four diseases (hypertension, heart disease, cancer, and diabetes). They found a significantly increased mortality risk among individuals with incidentally developed rheumatoid arthritis even after multiple adjustments for such factors. The cohort used in the study, however, comprised only women of older ages. Navarro-Cano *et al* followed 779 rheumatoid patients for 6.3 years and concluded that rheumatoid disease severity was significantly associated with mortality regardless of the presence of comorbid disease.<sup>30</sup>

To investigate whether rheumatoid arthritis is an independent risk factor for mortality, we analysed a Japanese cohort of atomic bomb survivors that has been followed up longitudinally for more than 40 years. We show here that the mortality risk of rheumatoid arthritis is significantly increased in both men and women compared with non-rheumatoid individuals, even after multiple adjustments for lifestyle and physical factors including comorbidity. This is

the first report of mortality risk in Japanese patients with rheumatoid arthritis.

## METHODS

## Study population

The total study population is an atomic bomb survivor cohort, which was established in 1958 to investigate the long term effects of ionising radiation from the atomic bombs.<sup>31</sup> The original cohort consisted of 19 961 individuals, approximately half of whom were exposed to significant doses of ionising radiation from the atomic bombs proximally (<2000 m from the hypocentre). The other half of the cohort either were exposed distally ( $\geq 3000$  m from the hypocentre) or were not in the city at the time of the bombings and thus were not substantially exposed to atomic bomb radiation. The subjects were followed longitudinally by biennial clinical examination at the Radiation Effects Research Foundation in Hiroshima and Nagasaki in Japan. This follow up study is named the adult health study and its detailed study design has been described elsewhere.<sup>31</sup>

Patients with rheumatoid arthritis were identified among this population during 1958-1966 using the American Rheumatism Association (ARA) diagnostic criteria for population studies.<sup>32</sup> In all, 16 119 individuals who came for clinical examination during this period were screened for rheumatoid arthritis, and 91 cases with definite or classical rheumatoid arthritis were identified.<sup>33-34</sup> There was no significant association between the prevalence of rheumatoid arthritis and radiation dose from the atomic bombs.<sup>32-33</sup>

## Baseline data

All of the cohort members were invited to undergo clinical examinations every two years. Physical examinations including measurement of body weight, height, and blood pressure were carried out at each clinic visit. The participants were interviewed by nurses to obtain disease histories and lifestyle

**Table 1** Baseline characteristics of study population

Variable	RA group	Non-RA group	p Value*
No of individuals	91	16 028	
Percent female	80.2	61.5	<0.01
Age (years)	56.8	44.6	<0.01
BMI (kg/m <sup>2</sup> )	21.3	21.2	NS
Current smoking (%)	16.7	36.5	NS
Alcohol use (g/week)	2.5	2.9	NS
Radiation dose (Gy)	0.36	0.37	NS
Comorbid disease (%)			
Hypertension	29.7	27.5	<0.01
Diabetes	6.6	7.3	NS
CHD	2.2	2.8	NS
Stroke	3.3	1.8	NS
Anaemia	34.1	20.3	NS
Kidney disease	4.4	1.2	<0.05
Liver disease	2.2	2.3	NS
COPD	14.3	10.7	NS
Cancer	3.3	2.5	NS

The values for age, BMI, alcohol use, and radiation dose are the mean of each group.

\*For the comparison between rheumatoid arthritis and non-rheumatoid arthritis individuals, adjustments were made for age and sex except for the comparison of female percentage and mean age.

BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive lung disease; RA, rheumatoid arthritis.

information such as smoking status and drinking habits. The baseline for rheumatoid patients in the present study was the time of the clinic visit at which the diagnosis of rheumatoid arthritis was made during the period of screening for the disease (1958–1966). For non-rheumatoid individuals, the baseline was established as the time of the earliest clinic visit during the same period, with the aim of obtaining a conservative estimate of rheumatoid arthritis mortality risk.

### Mortality data

Deaths were identified through checks on the status of all surviving cohort members, using the Japanese family registration system (*koseki*). The death data accumulated until March 1999 were used for the present analysis. No individual was lost during the follow up. Information on the underlying cause of death was obtained from death certificates and coded according to the *International Classification of Diseases* (ICD). Four ICD revisions were used depending on the time of death. Thus, the seventh, eighth, ninth, and 10th revisions (ICD 7, ICD 8, ICD 9, and ICD 10) were used for deaths during 1966–1967, 1968–1978, 1979–1997, and 1998–1999, respectively.

### Statistical analysis

Cox proportional hazards models were used to estimate the mortality risk attributable to rheumatoid arthritis by adjusting for several variables at the baseline that were potential confounders for mortality risk. These variables included age, sex, smoking habits (never, former, current), alcohol use (g/week), body mass index (BMI) (kg/m<sup>2</sup>), systolic blood pressure (mm Hg), total cholesterol level (mg/dl), estimated radiation dose (Gray),<sup>35</sup> and comorbidity (yes/no). Baseline

comorbid diseases taken into account were diabetes, hypertension, coronary heart disease (CHD), stroke, chronic liver disease, kidney disease, chronic obstructive pulmonary disease (COPD), tuberculosis, digestive ulcers, anaemia, and cancers. Similar analysis was undertaken to estimate mortality risk attributable to rheumatoid arthritis for each cause of death.

CHD, coronary heart disease; CI, confidence interval; RA, rheumatoid arthritis.

### RESULTS

Characteristics of the study population at baseline are presented in table 1. The female to male ratio in the rheumatoid patients was 4.1:1.0, while that of non-rheumatoid arthritis individuals was 1.6:1.0. The mean age of rheumatoid patients at baseline was 56.8 years, which was significantly higher than for the non-rheumatoid individuals (44.6 years). The mean duration of rheumatoid arthritis was 8.8 years. Although baseline data for physical activity were not available, rheumatoid factor positivity, x ray findings in the hands and wrists, and erythrocyte sedimentation rate (ESR) were available for 80, 75, and 86 patients, respectively. The proportion of patients with positive rheumatoid factor was 78.8%, and the proportion with radiographic bone erosion was 52.0%. Mean ESR was 40.5 mm/h. BMI was not significantly different between the rheumatoid and non-rheumatoid groups. Although the proportion of current smokers tended to be lower in the rheumatoid than in the non-rheumatoid group, the difference was not statistically significant after adjustment for age and sex. Radiation dose from the atomic bombs did not differ between rheumatoid and non-rheumatoid individuals.

**Table 2** Deaths observed up to March 1999

Variable	RA group			Non-RA group		
	Both sexes	Female	Male	Both sexes	Female	Male
No of individuals	91	73	18	16 028	9 856	6 172
No of death	83	65	18	8 527	4 623	3 904
Person years	1624	1391	233	443 945	292 018	156 927
Mean follow up period	17.8	19.1	12.9	28.0	29.6	25.4
Death rate (/1000 person years)	51.1	46.7	77.4	19.0	15.8	24.9

RA, rheumatoid arthritis.

**Table 3** Mortality risk of rheumatoid arthritis

Adjustment	Hazard ratio	95% CI	p Value
Both sexes			
Age, sex	1.60	1.29 to 1.99	<0.001
+Physical and lifestyle factors*	1.57	1.25 to 1.94	<0.001
Female			
Age	1.63	1.26 to 2.06	<0.001
+Physical and lifestyle factors	1.54	1.19 to 1.95	<0.001
Male			
Age	1.40	0.85 to 2.15	0.157
+Physical and lifestyle factors	1.83	1.14 to 2.82	0.011

\*Smoking habits, alcohol use, body mass index, systolic blood pressure, total cholesterol level, estimated radiation dose, and comorbidity, including diabetes, hypertension, coronary heart disease, stroke, chronic liver disease, kidney disease, chronic obstructive pulmonary disease, tuberculosis, digestive ulcers, anaemia, and cancers. CI, confidence interval.

The prevalence of diseases other than rheumatoid arthritis at baseline is presented in table 1. The proportion of individuals with hypertension appeared to be higher in the rheumatoid than in the non-rheumatoid population. However, after adjustment for age and sex, the proportion with hypertensive became significantly lower among the rheumatoid patients. This is probably because the prevalence of hypertension is age dependent and the mean age of the rheumatoid patients was greater than the mean age of the non-rheumatoid population. The prevalence of other diseases was also compared between the rheumatoid and non-rheumatoid populations after adjusting for age and sex (table 1). Although anaemia tended to be more prevalent among the rheumatoid patients, the difference was not statistically significant. Kidney disease was more prevalent among the rheumatoid patients than among the non-rheumatoid individuals. Significant differences between the rheumatoid and non-rheumatoid populations in prevalence at baseline were not observed for diabetes, coronary heart disease, stroke, cancer, chronic liver disease, or chronic obstructive pulmonary disease.

Up to March 1999, 83 deaths occurred among the 91 rheumatoid patients, whereas 8527 of the 16 028 non-rheumatoid individuals died during the same period (table 2). Mean follow up was 17.8 years for rheumatoid patients and 28.0 years for the non-rheumatoid group. The death rate for the rheumatoid patients was 51.1 per 1000 person years, and for the non-rheumatoid group 19.0 person years.

Age and sex adjusted hazard ratio for mortality was 1.60 (95% confidence interval (CI), 1.29 to 1.99),  $p < 0.001$ , for the rheumatoid patients (table 3). Other adjustments were made for variables including physical and lifestyle factors, as described in Methods, were then further adjusted for the

estimation of mortality risk. After these adjustments, the mortality hazard ratio for rheumatoid arthritis was 1.57 (95% CI, 1.25 to 1.94),  $p < 0.001$  (table 3).

Analysis restricted to the individuals without significant exposure to atomic bomb radiation (those distally exposed to the bombs or who were not in city at the time of the bombings) gave similar results. In all, 45 rheumatoid patients and 7927 non-rheumatoid individuals were included in this category, and the mortality hazard ratio was 1.80 (95% CI, 1.29 to 2.42) after multiple adjustments ( $p < 0.001$ ).

The mortality risk of rheumatoid arthritis was obtained for each sex separately. For women, the age adjusted mortality risk was 1.63 (95% CI, 1.26 to 2.06),  $p < 0.001$ , and the fully adjusted risk was 1.54 (1.19 to 1.95),  $p < 0.001$ , neither of which differed significantly from the values obtained for the group overall. For men, on the other hand, the age adjusted mortality risk was 1.40 (95% CI, 0.85 to 2.15),  $p = 0.157$ , and the fully adjusted mortality risk was 1.83 (95% CI, 1.10 to 2.82),  $p = 0.011$ . Although the fully adjusted mortality risk for the male rheumatoid patients seemed higher than for the female patients, the difference was not statistically significant.

The mortality risk of rheumatoid arthritis was analysed for each cause of death. Fully adjusted mortality risk results are presented in table 4. When the causes of death were classified according to organ system, an increased mortality risk was observed only for respiratory diseases. Although the hazard ratios for death from cardiovascular disease, digestive tract disease, kidney disease, and infectious disease were all greater than 1.0, the increases were not statistically significant. No significant increase in mortality from cancers was observed in the rheumatoid patients. Subsequently, more specific organs and diseases were analysed, and it was found that the mortality risk in rheumatoid patients was

**Table 4** Causes of death in the overall population and in the patients with rheumatoid arthritis

Cause of death	No of deaths (%)		Mortality risk in RA	
	RA	Non-RA	Hazard ratio (95% CI)	p Value
All causes	83	8527	1.57 (1.25 to 1.94)	<0.001
Cardiovascular	29 (34.9)	3206 (37.6)	1.30 (0.88 to 1.84)	0.16
CHD	5 (6.0)	646 (7.6)	1.26 (0.45 to 2.75)	>0.5
Stroke	15 (18.1)	1551 (18.2)	1.34 (0.76 to 2.15)	0.27
Cancer	12 (14.5)	2343 (27.5)	0.98 (0.52 to 1.66)	>0.5
Digestive tract	5 (6.0)	504 (5.9)	1.89 (0.67 to 4.11)	0.16
Liver	4 (4.8)	249 (2.9)	4.53 (1.38 to 10.8)	0.003
Kidney	2 (2.4)	192 (2.3)	1.66 (0.27 to 5.37)	0.49
Respiratory	13 (15.7)	839 (9.8)	2.83 (1.54 to 4.71)	<0.001
Pneumonia	9 (10.8)	533 (6.3)	2.97 (1.41 to 5.44)	0.001
Tuberculosis	4 (4.8)	141 (1.7)	4.32 (1.30 to 10.6)	0.005

**Table 5** Baseline characteristics and mortality risk of rheumatoid arthritis

Baseline factor	No of patients	Hazard ratio	95% CI	p Value
Rheumatoid factor				
Positive	63	1.76	1.33 to 2.26	<0.001
Negative	17	0.85	0.49 to 1.34	>0.5
Radiographic bone erosion				
Present	39	1.67	1.19 to 2.27	0.002
Absent	36	1.38	0.94 to 1.94	0.078
ESR				
≤40 mm/h	48	1.68	1.24 to 2.21	<0.001
>40 mm/h	38	1.30	0.89 to 1.81	0.147

CI, confidence interval; ESR, erythrocyte sedimentation rate.

significantly raised for liver disease, pneumonia, and tuberculosis.

Although baseline data for physical activity were not available for the rheumatoid patients, x ray findings in the hands and wrists, rheumatoid factor positivity, and ESR values were available for 75, 80, and 86 patients, respectively. The effects of these baseline variables on mortality were analysed. As shown in table 5, the presence of bone erosions in the hands and wrists was associated with increased mortality compared with non-rheumatoid individuals. On the other hand, in patients without bone erosions, the increase in mortality was not significant. The presence of rheumatoid factor was associated with increased mortality in rheumatoid patients but mortality of patients without rheumatoid factor was not increased. ESR values of more than 40 mm/h were also associated with higher mortality in rheumatoid patients, whereas lower ESR values were not.

## DISCUSSION

In this study, rheumatoid arthritis mortality risk was measured using death data on both rheumatoid and non-rheumatoid individuals in a Japanese cohort that has been followed up longitudinally. Thus our study directly compared the mortality of patients with rheumatoid arthritis with that of non-rheumatoid individuals. This is in contrast with most previous studies in which control mortality was estimated from census data. In addition to age and sex, we also adjusted for several potentially important confounding factors, including smoking status, alcohol intake, body mass index, blood pressure, and comorbidities. Even after these adjustments, the mortality risk did not change substantially, suggesting that the increased mortality risk of rheumatoid arthritis does not reflect the confounding of other lifestyle and physical factors. Mikuls *et al* also adjusted for several confounding factors and observed a significantly increased mortality risk of rheumatoid arthritis in a prospective cohort of older women.<sup>25</sup> These results confirm that rheumatoid arthritis is an independent risk factor for mortality.

We observed significantly increased mortality from pneumonia in the rheumatoid patients. We also found increased mortality from tuberculosis. In Japan, tuberculosis mortality until the early 1970s was five to 10 times higher than that during the 1990s according to the census data. As all deaths from tuberculosis in the rheumatoid patients in our cohort occurred before 1973, our present finding of increased mortality from tuberculosis may be related to Japan's high background tuberculosis mortality. Although information on drug usage was not available for the present cohort, the use of corticosteroids might have been associated with infectious events in the rheumatoid patients. Liver disease was also increased as a cause of mortality in the rheumatoid patients in our study. As aspirin and indomethacin were available in Japan at the baseline period of this study, such drugs may have played a role in the induction of liver disease in the rheumatoid patients. Methotrexate may be associated with

liver toxicity, but the use of this drug in Japan became popular only in the mid 1990s, and most deaths in our rheumatoid cohort occurred before this. Jacobsson *et al* studied a cohort of Pima Indians and reported that the death rate from liver cirrhosis and other alcohol related diseases was increased in rheumatoid patients.<sup>14</sup> Deaths from cardiovascular disease tended to be increased in rheumatoid patients in our study, but the increase was not statistically significant.

In addition to the availability of data on potentially confounding factors for mortality analysis, one of the strengths of our study is the long follow up period of over 40 years. During this follow up, more than 90% of the rheumatoid patients died. Other strengths include the prospective cohort design, population based setting, and complete coverage of information on health status. Limitations include the small number of rheumatoid patients, the lack of information on the physical activity and treatment of the rheumatoid patients, and the potential misclassification of causes of death obtained from death certificates. It is unlikely that radiation exposure influenced the results as the mean radiation dose in the rheumatoid and non-rheumatoid groups was similar. Furthermore, analysis restricted to the individuals without substantial exposure to atomic bomb radiation gave similar results.

Individuals who did not have rheumatoid arthritis at baseline may have developed it during the follow up period. However, as the non-rheumatoid group at baseline was large, the contribution of this factor is unlikely to have had an important influence on the results. Furthermore, if the individuals who developed rheumatoid arthritis during follow up had an increase in mortality similar to that shown for the group with the disease at baseline, our results may be a conservative estimate of the true mortality risk of rheumatoid arthritis in our cohort.

## Conclusions

We showed that rheumatoid arthritis is an independent risk factor for mortality by adjusting for several potential confounding factors in a population based Japanese cohort. In Japan, no disease modifying antirheumatic drugs were commercially available until 1970, and the use of methotrexate only became popular in the 1990s. As our patients participated in the study between 1958 and 1966, our estimate of the mortality of rheumatoid arthritis may be a reflection of its natural course. Our data provide a basis for the evaluation of treatment strategies for rheumatoid arthritis in terms of improvement in mortality prognosis.

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