

EXTENDED REPORT

Mortality risk associated with rheumatoid arthritis in a prospective cohort of older women: results from the Iowa Women's Health Study

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Objective: To determine whether rheumatoid arthritis (RA) is associated with excess mortality among older women.

Methods: RA associated mortality was examined in a prospective cohort study that was started in 1986, and included 31 336 women aged 55–69 years without a history of RA at baseline. Up to 1997, 158 cases of RA were identified and validated against medical records. The relative risk (RR) and 95% confidence interval (CI) were calculated as measures of association between RA onset and subsequent mortality (overall and cause-specific) using Cox proportional hazards regression.

Results: Compared with non-cases, women developing RA during follow up had a significantly increased mortality risk (RR=1.52; 95% CI 1.05 to 2.20). Mortality was higher among rheumatoid factor (RF) positive cases (RR=1.90; 95% CI 1.24 to 2.92) than among RF negative cases (RR=1.00; 95% CI 0.45 to 1.99). There were trends towards increased proportions of RA related deaths from infection (RR=3.61; 95% CI 0.89–14.69) and circulatory disease (RR=1.46; 95% CI 0.76 to 2.81) but not malignancy (RR=0.97; 95% CI 0.46 to 2.04).

Conclusions: RA was associated with significantly increased mortality in a cohort of older women, and the association appeared to be restricted to those with RF positive disease.

A number of population based studies have shown that rheumatoid arthritis (RA) leads to substantial disability as well as premature mortality.^{1–3} A 1996 review of RA mortality studies from 16 centres in North America and Europe showed an increased mortality attributed to RA in all but one of the investigations.⁴

Although RA is often perceived as a disease of the middle-aged, RA incidence increases at least until the age of 70, particularly among women.^{5–6} Although findings have not been uniform,^{7,8} older onset RA (commonly defined as onset after age 60) has been associated with more rapid functional decline⁹ and more aggressive radiographic disease progression¹⁰ than younger onset RA. Few mortality studies have specifically examined the impact of RA in this demographic group. In a hospital based, retrospective cohort of men and women, age adjusted mortality in patients with older onset seropositive RA was nearly three times that of the general population.¹¹ Given the significant impact of RA in older adults, it is important to determine its contribution to overall mortality. In this report we examine the association of older onset RA with mortality in a large, prospective, population based cohort of older women.

MATERIALS AND METHODS

Study cohort and follow up

The Iowa Women's Health Study (IWHS) is a prospective cohort study established in 1986, initially enrolling 41 836 women aged between 55 and 69 years. Characteristics of this well studied cohort have been described previously.^{12–14} Self reported items on the baseline questionnaire included demographic data (race/ethnicity, education), comorbidity (including heart disease, hypertension, diabetes mellitus, and cancer), anthropometrics, lifestyle factors, and dietary intake. Follow up questionnaires (response rates for living eligible subjects) were mailed in 1987 (91%), 1989 (89%), 1992 (83%), and 1997 (79%).

Identification and validation of patients with RA

The process of identification and validation of cases of RA has been described in detail elsewhere.^{15–17} In brief, respondents were asked on the 1992 follow up questionnaire, "Have you ever been told by a doctor that you have rheumatoid arthritis?" and if yes, to provide their age at the time of diagnosis. On the 1997 IWHS questionnaire, respondents were similarly asked, "Since July 1992, were you diagnosed for the first time by a doctor as having rheumatoid arthritis?" Potential patients (those responding "yes", "not sure", or "yes" but missing age at onset) were then contacted by mail to confirm their responses, to obtain names and addresses of all the doctors that they had consulted about their RA, and to obtain consent for release of their medical records. For deceased subjects, next of kin were contacted. We identified a total of 1227 potential incident cases through this process.

Medical records were requested from the doctors identified to validate RA diagnosis for each remaining potential case. Doctors were asked to complete a brief questionnaire and provide all medical, laboratory, and radiographic records pertinent to the diagnosis. Medical records were obtained from 1186/1227 (96.7%) potential incident cases.

A combination of two trained reviewers from a group including rheumatologists, a rheumatology advanced practice nurse, and a rheumatology physician assistant independently reviewed all medical records to determine RA case status using the "ever" (since cohort baseline) satisfaction of 4/7 American College of Rheumatology (ACR) criteria.^{18,19} A third reviewer adjudicated any disagreement between the two primary reviewers. Concordance between the two primary reviewers for

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; IWHS, Iowa Women's Health Study; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, relative risk; SMR, standardised mortality rate

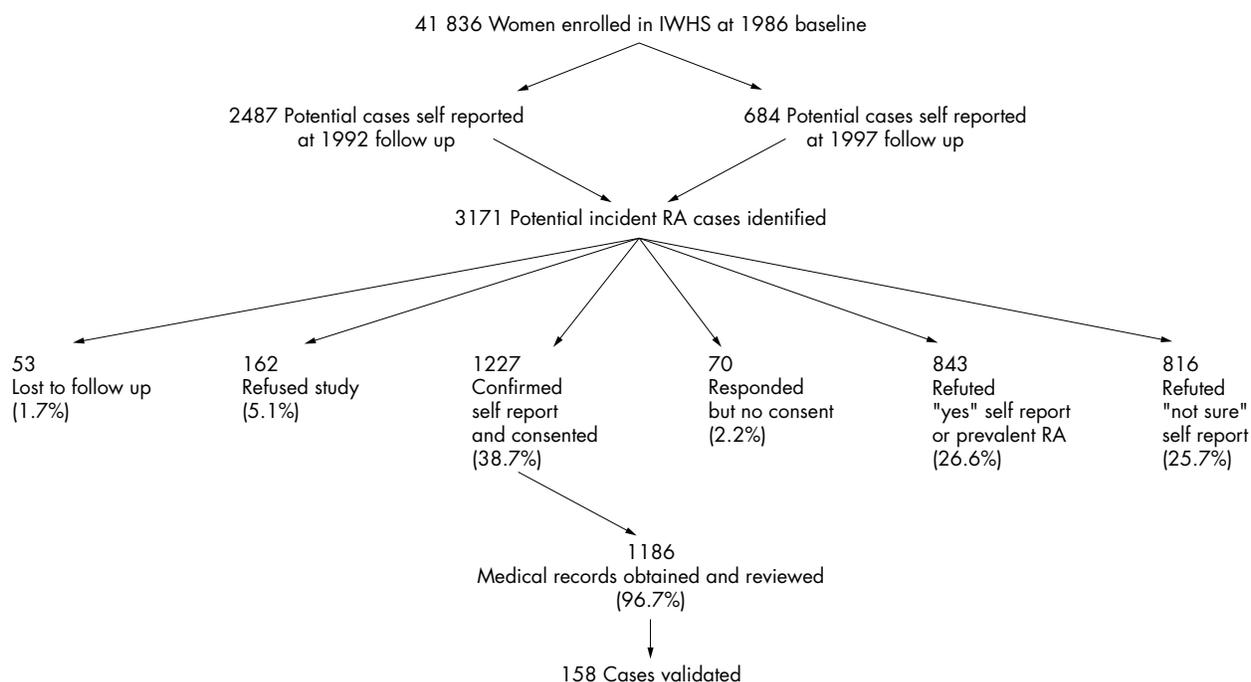


Figure 1 Validation process for potential incident cases of rheumatoid arthritis in the Iowa Women's Health Study, 1986–97.

case validation was 90.6% ($\kappa=0.92$ for interobserver reliability). Any diagnosis of “definite RA” provided by a board certified/eligible rheumatologist was also considered a validated case.

Disease onset was defined as the first date of an RA symptom subsequently leading to the satisfaction of ACR criteria or a rheumatologist's diagnosis of RA. Women with onset of RA symptoms before 1 January 1987 were considered prevalent cases and excluded from the analysis. Women with self limited arthritis (for example, viral arthritis) or who had alternative diagnoses, such as gout, were also excluded. Review of the 1186 sets of records resulted in 158 validated cases of RA. Clinical characteristics of the 158 patients with RA were obtained from medical record reviews and questionnaires completed by the respondents' doctors.

Determination of vital status

Vital status was ascertained by several methods. Firstly, participant identifiers (name, address, social security number, birth date, and maiden name) were linked by computer to death certificates at the State Health Registry of Iowa for 1986–2000. This was supplemented by death reports received in response to the follow up surveys sent in 1987, 1989, 1992, and 1997. The vital status of non-respondents to the follow up surveys was identified by linkage to the National Death Index. It has been previously estimated that this method accurately identifies approximately 99% of all deaths in this cohort.²⁰ Underlying causes of death were coded according to the International Classification of Diseases, ninth and tenth revisions (ICD-9 and ICD-10). For deaths occurring in Iowa, underlying causes of death were assigned by the Iowa Department of Health. For deaths outside Iowa, a trained nosologist assigned causes of deaths. Causes of death were further classified in the following categories of greatest interest based on previous studies of RA mortality^{1–3}: (a) infections (ICD-9 (or ICD-10 equivalent) codes of 001–139, 320–322, 480–487); (b) malignant neoplasms (ICD-9 codes 140–208), and; (c) diseases of the circulatory system (ICD-9 codes 390–459).

Exclusions

Figure 1 summarises the cases validated and excluded. From the original cohort of 41 836 women, we excluded women

who did not complete either the 1992 or 1997 follow up questionnaires because of death or non-response ($n=6201$) and those reporting that they had been diagnosed with RA before 1 January 1987 ($n=2102$). The remaining exclusions ($n=2197$) included women who were lost to follow up ($n=53$), refused further participation ($n=162$), refuted their original “yes” response on the 1992 or 1997 survey subsequent to contact ($n=843$), failed to meet case criteria after a review of the records ($n=1028$), reported incident RA but failed to provide consent for examination of medical records ($n=70$), or for whom records were not provided ($n=41$). This left a final analysis cohort of 31 336 women, including 158 incident cases and 31 178 non-cases.

Statistical methods

Each woman accumulated person-years from the date of receipt of the 1986 baseline questionnaire to the date of death or, if censored, until a common closing date of 15 October 2000 (the last date of death recorded as of March 2001). To describe the association between the development of RA and mortality (overall and cause-specific), we calculated relative risks (RRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression.²¹ We modelled survival as a function of age rather than time-in-study because age is a better predictor of survival than the length of follow up in this type of analysis.²² To account for the fact that RA diagnosis occurred after the study began, the development of RA (a dichotomous predictor variable) was modelled as a time dependent variable.

Multivariable Cox models were constructed to adjust for variables potentially confounding the association between RA and mortality. Covariates chosen a priori included smoking history (never, former <20 pack-years, former ≥ 20 pack-years, current <20 pack-years, current ≥ 20 pack-years), alcohol use (none, <3 g/day, ≥ 3 g/day), education (<high school, high school graduate, vocational/some college, and \geq college graduate), body mass index, and the presence of any of four comorbidities at baseline (hypertension, heart disease, cancer, or diabetes mellitus). We also adjusted for daily decaffeinated coffee consumption (none, ≤ 1 cup/day, ≥ 2 cups/day) because of its association with RA onset in this cohort.¹⁶ In subgroup

Table 1 Demographics at the time of the 1986 baseline survey. Iowa Women's Health Study

	Patients (n=158)	Non-patients* (n=31178)
Age (years), mean (SD)	61.1 (3.9)	61.5 (4.2)
Body mass index (kg/m ²), mean (SD)	26.8 (4.6)	26.8 (4.9)
White subjects (No (%))	157 (99)	30636 (99.4)
Education (%)		
<High school graduate	23 (15)	5351 (17.2)
High school graduate	72 (46)	12997 (41.7)
Vocational education/some college	44 (28)	8475 (27.2)
≥ College graduate	19 (12)	4291 (13.8)
Alcohol (%)		
Never use	87 (55)	17087 (54.8)
<3 g/day	26 (16)	5754 (18.5)
≥3 g/day	45 (28)	8337 (26.7)
Smoking status (%)		
Never smoked	88 (57)	20593 (67.0)
Former smoker	32 (21)	5968 (19.4)
Current smoker	34 (22)	4176 (13.6)
Decaffeinated coffee consumption (%)		
None	59 (37)	13669 (43.8)
≤1 Cup/day	44 (28)	9653 (31.0)
≥2 Cups/day	55 (35)	7856 (25.2)
Comorbidities (%)		
Diabetes mellitus	6 (4)	1559 (5.0)
Hypertension	60 (38)	10750 (34.5)
Heart disease	11 (7)	2374 (7.6)
Cancer	10 (6)	2652 (8.5)

*Denominator as noted with the exception of missing data for race (346 non-patients), education (64 non-patients), and smoking (441 non-patients and four patients).

analyses we examined the association between the development of rheumatoid factor (RF) positive RA and mortality; subjects with unknown RF status (n=12) were assigned to the RF negative group. All analyses were conducted using SAS for Windows, version 8.0 (SAS Inc, Cary, NC).

RESULTS

Between 1 January 1987 and 31 August 1997, 158 women in the cohort with no history of RA in 1986 developed incident RA. RA diagnosis was based on either cumulative satisfaction of ACR RA criteria (n=146, 92% of the total cases) and/or diagnosis by a rheumatologist (n=139; 88% of the total cases). During an average follow up period of 13.4 (SD 1.5) years, 30 patients (19%) and 3646 non-patients (11.7%) had died. Table 1 summarises the demographic and other relevant baseline characteristics for patients and non-patients. With the exception of smoking history and decaffeinated coffee use, there were no striking differences in these characteristics between the two groups.

Table 2 shows the clinical characteristics of the 158 validated cases of patients with RA. The average age of onset was 68 years (range 57–79). A significant proportion of the patients (nearly 90%) were seen by a rheumatologist. About 60% of the patients with incident RA (n=97) had RF positive

disease. The average time between receipt of the baseline survey and RA diagnosis (defined as the date of first symptom onset) was 6.1 (SD 3.0) years.

Table 3 shows the univariate and multivariable adjusted hazard ratios, reflecting the associations of RA and covariates with mortality. After adjusting for multiple potential confounding variables, there was a significant and positive association between RA onset and mortality (RR=1.52; 95% CI 1.05 to 2.20). This effect appeared to be restricted to women with RF positive disease (RR=1.90; 95% CI 1.24 to 2.92 v RR=1.00; 95% CI 0.45 to 1.99 for RF negative RA). These results were unchanged when subjects with either unknown RF status or those without cumulative ACR criteria were eliminated from the analysis (data not shown).

Table 4 shows the proportion of deaths of patients and non-patients from infection, malignant neoplasm, and circulatory disease and the cause-specific hazard ratios. Specific ICD-9 (or alternatively, ICD-10) codes were not available for two (7%) of the 30 patient deaths and 122 (3.3%) of the 3646 non-patient deaths. Non-significant trends towards increased mortality from infection (RR=3.61; 95% CI 0.89 to 14.69) and circulatory disease (RR=1.46; 95% CI 0.76 to 2.81) were seen among women with incident RA compared with non-patients. In contrast, there was no trend towards an RA

Table 2 Clinical characteristics of patients with validated rheumatoid arthritis (RA)

	All patients (n=158)	RF+ (n=97)	RF- or unknown (n=61)*
Age at onset (years), mean (SD)	67.8 (4.9)	67.4 (4.7)	68.4 (5.1)
Average time from onset to diagnosis (months), mean (SD)	13.4 (21.7)	14.4 (23.6)	11.9 (18.4)
Number of ACR criteria satisfied, mean (SD)	4.6 (1.1)	5.0 (0.9)	4.0 (1.2)
Rheumatoid nodules (%)	14.2	16.6	10.2
Radiographic bone erosions (%)	49.7	46.9	54.2
RA diagnosed by a rheumatologist (%)	89.7	87.6	93.2

*Includes 12 patients with unknown rheumatoid factor (RF) status. ACR, American College of Rheumatology.

Table 3 Relative risks (RR) and 95% confidence intervals for the associations of rheumatoid arthritis (RA) and self reported comorbidities with mortality, Iowa Women's Health Study, 1986–2000

	Age adjusted		Multivariable adjusted*	
	RR	95% CI	RR	95% CI
RA (all cases)	1.76	1.23 to 2.53	1.52	1.05 to 2.20
Seropositive RA	2.16	1.42 to 3.29	1.90	1.24 to 2.92
Seronegative RA	1.17	0.59 to 2.34	1.00	0.45 to 1.99
Hypertension	1.40	1.32 to 1.50	1.28	1.19 to 1.37
Diabetes mellitus	2.58	2.34 to 2.85	2.20	1.97 to 2.44
Heart disease	1.84	1.68 to 2.02	1.63	1.48 to 1.80
Cancer	1.69	1.54 to 1.86	1.59	1.44 to 1.74

*Adjusted for all variables in the table in addition to education, alcohol use, smoking history, body mass index, and daily decaffeinated coffee consumption.

Table 4 Cause-specific mortality among subjects with and without rheumatoid arthritis, Iowa Women's Health Study, 1986–2000. Results are shown as No (% of total at risk)

Cause of death*	Patients† (n=156)	Non-patients (n=31056)	Relative risk‡ (95% CI)
Infection	2 (1)	106 (0.3)	3.61 (0.89 to 14.69)
Diseases of the circulatory system	9 (6)	1254 (4.0)	1.46 (0.76 to 2.81)
Malignant neoplasm	8 (5)	1380 (4.4)	0.97 (0.46 to 2.04)
Other	9 (6)	784 (2.5)	–

*Infections include conditions with ICD-9 (or ICD-10 equivalent) codes of 001–139, 320–322, 480–487. Malignant neoplasms include ICD-9 codes 140–208, while diseases of the circulatory system include ICD-9 codes 390–459.

†Subjects were excluded from the analysis if data for ICD-9 code were missing (two patients and 122 non-patients).

‡Calculated using Cox proportional hazards regression (multivariable adjustments for comorbidity, education, smoking history, alcohol use, body mass index, and daily decaffeinated coffee consumption).

related increase in mortality from malignancy (RR 0.97; 95% CI 0.46 to 2.04).

DISCUSSION

In this prospective cohort study of older women, RA was significantly associated with increased mortality. This risk appeared to be restricted to women with RF positive disease. Trends towards increased mortality from underlying infection and circulatory disease, but not malignancy, corroborated findings from previous RA cohorts.^{1–3}

Our results contrast with those from two recent prospective cohort studies^{23, 24} of younger patients that showed no association between RA and mortality. This difference may be due to differences in the study groups. Compared with the IWHs cohort, participants in those studies were younger and about one third of the participants were male. It is noteworthy that in a recent pooled analysis of RA mortality studies, Ward observed a mean standardised mortality rate (SMR) of 1.7,²⁵ an estimate that approximates our results.

In an earlier investigation of mortality associated with older onset RA, Dutch investigators reported an SMR of 2.8 (95% CI 1.6 to 4.1) for older onset RF positive RA and an SMR of 0.5 (95% CI 0.1 to 1.3) for RF negative disease.¹¹ Using proportional hazards regression, we observed a similar age adjusted mortality risk associated with RF positive disease (RR=2.16; 95% CI 1.42 to 3.29) but no comparable protective trend associated with RF negative RA. This difference may be due to statistical variability or to actual differences in natural history and/or treatment between the two RF negative cohort components. In the Dutch study, for example, the older onset RF negative patients had a mean erosion score of 0 at baseline (range 0.0–0.8) and none had subcutaneous nodules, whereas 10% of the IWHs seronegative patients had rheumatoid nodules and approximately one half had radiographic erosions

present at the time of diagnosis. Both erosions and nodules have been associated with earlier mortality in RA.²⁶

In addition to providing age adjusted mortality rates, we also adjusted for several potentially important confounding variables. Both cigarette smoking and body mass index have been linked not only to increased overall mortality but also to RA.^{27–30} In previous analyses of the IWHs cohort, we found that cigarette smoking resulted in a significant twofold increase in the risk of developing RA,¹⁷ whereas body mass index was not associated with RA incidence.¹⁵ To eliminate the potential confounding effect of cigarette smoking, we repeated our analysis after eliminating women with any previous smoking history, and our results remained unchanged (data not shown).

The apparent increase in infection and circulatory related deaths parallels findings from several previous RA cohort studies. Higher infection related mortality has been confirmed in three separate longitudinal studies,^{1–3} with relative risks ranging from 5.3 to 14.9, values well within the 95% confidence interval for our observed estimate. Using the United Kingdom National Health Service Central Register,¹ Symmons *et al* reported an SMR of 2.2 for cardiovascular related mortality in RA among men and women. We found a slightly lower relative risk (RR=1.46; 95% CI 0.76 to 2.81), perhaps because our cohort consisted entirely of women who, in general, have lower rates of cardiovascular disease than men. Reports on malignancy associated RA mortality have been inconsistent,³¹ and our analysis showed no such association.

The mechanism by which RA exerts its negative impact on survival remains undefined. Several baseline disease measures including RF status,^{3, 11, 26} radiographic erosions,²⁶ swollen joint counts,³² nodules,²⁶ functional disability scores,³² grip strength,³² and leucocytosis³³ have all been associated with higher mortality rates. RF status appears to be a particularly

salient prognostic factor among patients with elderly onset RA,^{11,34} and our analysis showed that nearly all the excess mortality was in the RF positive cases. RF may simply serve as a marker for more active disease; or, alternatively, the differential impact of RF positive and RF negative disease may reflect the substantial overlap between RF negative RA and polymyalgia rheumatica,³⁵ a condition that has not been associated with increased mortality.³⁶

The strengths of this study include the prospective cohort design, rigorous case validation, community setting, and the availability of ample data to control for potential confounders of the association of RA with mortality. A potential weakness is that we did not clinically examine each patient with RA. However, our rigorous case validation methods, including the requirement that all cases meet ACR criteria and/or confirmation by a rheumatologist make substantial misclassification unlikely. A high proportion of our cases were confirmed by a rheumatologist, consistent with the use of subspecialist report as the definitive standard in most studies of diagnostic criteria.^{37,38} As shown by several population based studies,^{39–42} the use of ICD-9 (and ICD-10) codes from death certificates might have been a potential source of misclassification in our examination of cause-specific mortality.

Non-patients might have developed RA between the dates of the last follow up and the end of the study (either the date of death or the common closing date). Subjects with milder RA or those not seeking medical attention might have gone unrecognised among the non-patient group. However, the extremely large group of non-patients used as the comparison group makes false negatives a substantially less important concern for this analysis. If RA exerts a negative impact on mortality, differential misclassification of non-patients with a more fatal course would lead to a conservative estimate of the true mortality risk associated with RA in this elderly population of women.

The relatively homogeneous nature of the IWHS cohort—elderly, predominantly white women, from a single well defined geographic region—may limit the generalisability of our findings. This fact, however, should not overshadow the importance of our results. With the population aging and a disease incidence that increases into the eighth decade of life,^{5,6} RA represents a growing public health problem, especially among elderly women. The potential public health impact in this group is emphasised by the observation that the mortality risk associated with RF positive RA equalled or exceeded hazard rates associated with self reported hypertension, heart disease, and cancer—chronic diseases long-recognised to contribute to overall mortality. Our findings provide important insight into the impact of RA on a demographic group commonly affected by the disease.

In summary, RA was an independent predictor of early mortality among older women, particularly in those with seropositive disease. Future research must focus on identifying modifiable risk factors for mortality in this RA population. Coexistent disease plays a major part in determining RA mortality,³¹ and the precise effect of antirheumatic treatment on RA mortality remains incompletely defined. The efficacy of measures targeting disease-specific risk factors and associated comorbid conditions deserves increased attention.

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