Are Young Women and Men with Rheumatoid Arthritis at Risk for Fragility Fractures? A Population-based Study

Shreyasee Amin, Sherine E. Gabriel, Sara J. Achenbach, Elizabeth J. Atkinson, and L. Joseph Melton III

ABSTRACT ***Objective.*** Older women and men with rheumatoid arthritis (RA) are at increased risk for fractures, but limited information is available on fracture risk in younger individuals with RA and whether such risk occurs early in the disease onset or only when older. We determined the risk for fractures in both young and older women and men following RA diagnosis.

Methods. We studied a population-based inception cohort with RA from Olmsted County, Minnesota, USA. We identified 822 women and 349 men diagnosed with RA between 1955 and 2007 (308 women and 110 men diagnosed before age 50) and an equal number of paired non-RA subjects, matched by sex and birth year. Incident fractures were collected through review of complete (inpatient and outpatient) medical records available through the linkage system of the Rochester Epidemiology Project.

Results. The hazard ratio (HR; 95% CI) for a non-pathologic fracture occurring from no more than moderate trauma was 1.63 (1.36–1.96) for women and 1.40 (1.02–1.93) for men with RA. Findings were consistent for women and men diagnosed with RA at age ≥ 50 years [HR, 1.43 (1.16–1.77) and 1.34 (0.92–1.94), respectively], or at age < 50 years [HR, 2.34 (1.61–3.42) and 1.74 (0.91–3.30), respectively]. However, young women, but not young men, with RA were at increased fracture risk even before age 50 years (HR, 1.95 [1.08–3.51] and 0.82 [0.28–2.45], respectively).

Conclusion. Young men with RA are at increased risk for fractures only when older, whereas young women with RA have an elevated fracture risk even while still young. (First Release Aug 15 2013; J Rheumatol 2013;40:1669–76; doi:10.3899/jrheum.121493)

Key Indexing Terms:
RHEUMATOID ARTHRITIS BONE FRACTURES OSTEOPOROSIS EPIDEMIOLOGY

Increasingly, bone health is recognized to be adversely affected in rheumatoid arthritis (RA)[1,2]. RA is the only disease specifically included in the World Health Organization fracture prediction algorithm, FRAX® (http://shef.ac.uk/FRAX/)[3]. However, the risk for fractures in younger individuals with RA is not directly estimated by FRAX®, nor is the risk for fractures at sites other than the hip, spine, wrist, and shoulder, considered major osteoporotic fractures. In fact, most studies investigating fracture risk in RA have examined older women[4,5,6,7,8,9,10,11,12,13], and few included older men[7,12]. Further, most studies have focused on fractures of the vertebrae or other major osteoporotic sites even though, collectively, fractures at other skeletal sites account for significantly increased morbidity and healthcare costs[14].

Despite the fact that the mean age at diagnosis for adult-onset RA is ~55 years[15] and that low bone density has been reported in young women and men with RA[16,17,18], there are very few studies on the likelihood of fractures in younger individuals with RA[19,20,21]. The only study that included men examined the risk for fractures only at the hip, shoulder, pelvis, and wrist, and longterm followup was limited[19].

It is clinically important to know the risk for fractures at any site, in addition to fractures at traditional major osteoporotic sites, for those who develop RA at either a younger or older age. It would also be pertinent to determine whether the risk for fractures occurs early in the course of the disease, or instead, primarily manifests later in life,

From the Department of Medicine, Divisions of Rheumatology and Endocrinology, Diabetes, Metabolism and Nutrition; and Department of Health Sciences Research, Divisions of Epidemiology and Biomedical Statistics and Informatics, College of Medicine, Mayo Clinic, Rochester, MN, USA.

Supported by research grants PO1 AG04875-24 and R01 AR46849 and made possible by the Rochester Epidemiology Project (R01 AG034676 from the National Institute on Aging) from the National Institutes of Health, U.S. Public Health Service. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

S. Amin, MD, CM, MPH, Divisions of Rheumatology and Epidemiology; S.E. Gabriel, MD, MSc, Division of Epidemiology; S.J. Achenbach, MS; E.J. Atkinson, MS; Biomedical Statistics and Informatics; and L.J. Melton III, MD, MPH, Endocrinology, Diabetes, Metabolism and Nutrition, and Division of Epidemiology, College of Medicine, Mayo Clinic.

Address correspondence to Dr. Shreyasee Amin, Associate Professor of Medicine, Division of Rheumatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. E-mail: amin.shreyasee@mayo.edu

Accepted for publication June 11, 2013.

irrespective of disease duration. Therefore, we sought to determine the relative and absolute risk for future fractures in both younger and older individuals with RA, using a population-based inception cohort of women and men with an incident diagnosis of RA for whom longterm followup was available.

MATERIALS AND METHODS

Study subjects. Population-based epidemiologic research is possible in Olmsted County, Minnesota, because comprehensive (inpatient, as well as outpatient) medical records for all residents at any local provider are available through a unique medical records linkage system, the Rochester Epidemiology Project (REP)[22,23]. After approval by the Institutional Review Boards (IRB) of Mayo Clinic and Olmsted Medical Center, REP resources were used to identify all residents of Rochester (the central city of Olmsted County) who were ≥ 18 years of age when they fulfilled American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria for RA[24] between January 1, 1955, and December 31, 1994[25,26]. The cohort was subsequently expanded, using the same methodology, to include all Olmsted County residents fulfilling ACR criteria for RA from January 1, 1980 to December 31, 2007[27]. Potential RA subjects were identified by searching the computerized diagnostic index for any diagnosis of arthritis (excluding degenerative arthritis or osteoarthritis) made for residents during these time frames. The complete medical record for each potential RA subject was then reviewed by trained nurse abstractors using a pretested data collection form to confirm or reject the diagnosis, with RA incidence defined as the date of first fulfillment of 4 of the 7 ACR classification criteria[25]. For each subject identified with incident RA, an individual without RA from the same population was randomly selected, matched for sex, birth year (± 3 yrs), and residency. Subjects in the non-RA cohort were assigned an index date corresponding to the RA incidence date of their matched pair.

Fracture ascertainment over followup. After additional approval by the respective IRB, these subjects were followed until death or last clinical contact through their linked medical records in the community (historical cohort study), and their records were searched by trained nurse abstractors for the occurrence of any fracture. Ascertainment of all clinically evident fractures is believed to be complete[28]. Records at Mayo Clinic, for example, contain the details of every hospitalization and outpatient visit, all emergency room and nursing home care, as well as all radiographic and pathology reports, including autopsies, and all correspondence with each patient[22]. By convention, fractures occurring during daily activities and falls from standing height or less were considered to have resulted from no more than moderate trauma, whereas fractures resulting from motor vehicle accidents and falls from a greater height were deemed from severe trauma. In addition, we are able to distinguish fractures that were due to a specific bone lesion (pathologic fractures), as well as fractures only discovered because of radiographic tests performed in the clinical setting for unrelated causes (incidental fractures). From all fractures identified, we defined a subset of fragility fractures (i.e., all non-pathologic fractures occurring as a result of no more than moderate trauma or identified incidentally), as well as a subset of traditional major osteoporotic fractures [i.e., fragility fractures of the proximal femur (hip), thoracic or lumbar vertebrae (spine), distal forearm (wrist), or proximal humerus (shoulder)].

Statistical analysis. Each member of the RA and non-RA matched pair was followed from the index date to the earlier of either of the pair's last followup. Fractures that resulted from severe trauma, or that were considered pathological fractures, were excluded from analyses in order to focus on the risk for fractures most likely related to bone fragility. The cumulative incidence rates for fragility fractures were estimated following the RA diagnosis, or index date for the non-RA subjects, using the Kaplan-Meier method[29] and accounting for the competing risk for death[30,31]. In separate models for women and men, unadjusted Cox proportional hazards models were used to assess the impact of RA on first subsequent fragility fracture and first subsequent major osteoporotic fracture. Analyses were then performed by different age-groups at RA diagnosis/index date (age: ≥ 50 yrs or < 50 yrs). For those < 50 years of age, we performed additional analyses where followup ended either at the earlier date of last known followup for a pair or at 50 years of age, whichever occurred first. Finally, given changes in RA and osteoporosis management over the time span of our study, we performed exploratory analyses to examine whether calendar year of RA diagnosis influenced fracture risk estimates. Person-years after RA diagnosis (or index date for non-RA subjects) and fracture events were divided into bins for each calendar year. Generalized additive models were used to model the influence of age and calendar year on fracture rates, using smoothing splines to allow for nonlinear associations and assuming fractures follow a Poisson distribution. Models were fit separately for RA and non-RA subjects, and by sex. Predicted fracture rates for calendar year were age-adjusted, and the 4 model results were compared graphically. Analyses were done using SAS version 9 and R 2.14 (R Foundation for Statistical Computing).

RESULTS

We identified 1171 Olmsted County residents (822 women and 349 men; 85% from Rochester; 96% white) who had an incident diagnosis of RA between January 1, 1955 and December 31, 2007. Their mean age ± SD at diagnosis was 56 ± 16 years (range 19-94 yrs) for RA women and 58 ± 14 years (range 19-89 yrs) for RA men. Relevant RA-related characteristics for these women and men are noted in Table 1. By design, the 1171 matched non-RA subjects were similar in age at their index date (56 ± 16 yrs for women and 58 ± 14 yrs for men). However, survival was worse in RA than non-RA subjects (at 30 yrs, 31% vs 43%, respectively; $p < 0.001$), and consequently total followup was lower among those with RA. When censored at the earliest followup date of either member of an RA and non-RA pair, there was a total of 12,781 person-years of followup for each group. The median followup for each pair of women was 9 years (range 4 days to 52 yrs) and, similarly, for each pair of men was 9 years (range 16 days to 44 yrs).

Tables 2 and 3 list the sites of all fractures and Table 4 lists their proximate causes for both RA and non-RA subjects, stratified by sex and by age. When compared with their non-RA counterparts, women with RA had more fractures at almost all sites (Table 2), while men with RA tended to have more fractures at major osteoporotic sites, as well as at the ribs and pelvis (Table 3). Younger non-RA women and men were more likely to have fractures attributed to severe trauma (Table 4).

Fracture risk for all women and men with RA. In 9148 person-years of followup for each of the 822 RA and non-RA women, the RA women had a significantly increased risk for a fragility fracture over followup compared with their matched non-RA pair (HR = 1.63, 95% CI 1.36–1.96; Table 5). Similarly, in 3633 person-years of followup for each of the 349 RA and non-RA men, RA men were also at increased risk for a fragility fracture (HR = 1.40, 95% CI 1.02-1.93; Table 5). The cumulative incidence

Table 1. Characteristics and age of all women and men with incident rheumatoid arthritis diagnosed between 1955 and 2007, in Olmsted County, Minnesota.

	Women			Men		
	All	≥ 50 yrs	< 50 yrs	All	≥ 50 yrs	< 50 yrs
n	822	514	308	349	239	110
Mean age at diagnosis, mean yrs ± SD	56 ± 16	66 ± 10	40 ± 8	58 ± 14	65 ± 9	41 ± 7
Rheumatoid factor positive, ever, n (%)	523 (64)	325 (63)	198 (64)	235 (67)	148 (62)	87 (79)
Rheumatoid nodules, ever, n (%)	261 (32)	157 (31)	104 (34)	130 (37)	75 (31)	55 (50)
Erosions/destructive disease, ever, n (%)	447 (54)	290 (56)	157 (51)	176 (50)	112 (47)	64 (58)
Oral glucocorticoids, ever, n (%)	542 (66)	317 (62)	225 (73)	252 (72)	167 (70)	85 (77)

Table 2. Distribution of all fractures and fragility fractures among 822 women following their initial diagnosis of rheumatoid arthritis (RA), by fracture site and proximate cause, compared with an equal number of age-matched non-RA women, from Olmsted County, Minnesota.

Fracture Site	All Women				Women ≥ 50 Yrs				Women < 50 Yrs			
	All Fractures, n (%)		Fragility Fractures*, n (%)		All Fractures, n (%)		Fragility Fractures*, n (%)		All Fractures, n (%)		Fragility Fractures*, n (%)	
	RA	Non-RA	RA	Non-RA	RA	Non-RA	RA	Non-RA	RA	Non-RA	RA	Non-RA
Skull/face	11 (1)	8 (2)	8 (1)	6 (2)	10 (2)	5 (1)	8 (2)	4 (1)	1 (0)	3 (3)	0 (0)	2 (3)
Hands/fingers	25 (3)	21 (5)	14 (2)	9 (3)	13 (2)	12 (3)	8 (2)	6 (2)	12 (4)	9 (8)	6 (3)	3 (5)
Distal forearm	46 (6)	43 (9)	39 (6)	31 (9)	36 (7)	34 (10)	31 (7)	26 (9)	10 (4)	9 (8)	8 (4)	5 (8)
Proximal humerus	31 (4)	17 (4)	23 (4)	13 (4)	23 (4)	15 (4)	17 (4)	12 (4)	8 (3)	2 (2)	6 (3)	1 (2)
Other arm	24 (3)	10 (2)	15 (2)	6 (2)	14 (3)	6 (2)	8 (2)	4 (1)	10 (4)	4 (4)	7 (3)	2 (3)
Clavicle/scapula/sternum	16 (2)	7 (2)	10 (2)	4 (1)	14 (3)	5 (1)	8 (2)	3 (1)	2 (1)	2 (2)	2 (1)	1 (2)
Ribs	86 (11)	49 (11)	60 (9)	30 (9)	50 (9)	37 (10)	36 (8)	26 (9)	36 (13)	12 (11)	24 (11)	4 (7)
Thoracic/lumbar vertebrae	279 (34)	158 (34)	261 (40)	142 (42)	185 (35)	135 (38)	171 (40)	123 (44)	94 (33)	23 (21)	90 (41)	19 (32)
Cervical vertebrae	14 (2)	4 (1)	11 (2)	1 (0)	8 (1)	2 (1)	6 (1)	0 (0)	6 (2)	2 (2)	5 (2)	1 (2)
Pelvis	50 (6)	23 (5)	36 (6)	19 (6)	35 (7)	15 (4)	26 (6)	14 (5)	15 (5)	8 (7)	10 (5)	5 (8)
Proximal femur	68 (8)	36 (8)	59 (9)	31 (9)	57 (11)	35 (10)	49 (11)	31 (11)	11 (4)	1 (1)	10 (5)	0 (0)
Other leg	81 (10)	43 (9)	55 (8)	26 (8)	47 (9)	25 (7)	31 (7)	18 (6)	34 (12)	18 (17)	24 (11)	8 (13)
Feet/toes	84 (10)	44 (10)	58 (9)	24 (7)	42 (8)	29 (8)	31 (7)	15 (5)	42 (15)	15 (14)	27 (12)	9 (15)
All sites	815	463	649	342	534	355	430	282	281	108	219	60

* Excludes severe trauma and pathologic fracture.

Table 3. Distribution of all fractures and fragility fractures among 349 men following their initial diagnosis of rheumatoid arthritis (RA), by fracture site and proximate cause, compared with an equal number of age-matched non-RA men, from Olmsted County, Minnesota.

Fracture Site	All Men				Men ≥ 50 Yrs				Men < 50 Yrs			
	All Fractures, n (%)		Fragility Fractures*, n (%)		All Fractures, n (%)		Fragility Fractures*, n (%)		All Fractures, n (%)		Fragility Fractures*, n (%)	
	RA	Non-RA	RA	Non-RA	RA	Non-RA	RA	Non-RA	RA	Non-RA	RA	Non-RA
Skull/face	4 (2)	2 (1)	1 (1)	0 (0)	2 (1)	0 (0)	1 (1)	0 (0)	2 (3)	2 (4)	0 (0)	0 (0)
Hands/fingers	9 (4)	16 (11)	2 (1)	4 (4)	5 (3)	10 (11)	2 (1)	4 (5)	4 (7)	6 (11)	0 (0)	0 (0)
Distal forearm	7 (3)	10 (7)	2 (1)	5 (5)	6 (3)	4 (4)	2 (1)	4 (5)	1 (2)	6 (11)	0 (0)	1 (4)
Proximal humerus	9 (4)	2 (1)	7 (4)	2 (2)	9 (5)	2 (2)	7 (5)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Other arm	5 (2)	1 (1)	3 (2)	1 (1)	5 (3)	1 (1)	3 (2)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Clavicle/scapula/sternum	8 (3)	7 (5)	1 (1)	2 (2)	4 (2)	3 (3)	0 (0)	2 (3)	4 (7)	4 (7)	1 (2)	0 (0)
Ribs	51 (21)	28 (19)	38 (21)	18 (19)	40 (21)	21 (23)	29 (21)	15 (20)	11 (18)	7 (12)	9 (20)	3 (13)
Thoracic/lumbar vertebrae	98 (40)	51 (34)	91 (50)	45 (46)	72 (39)	32 (34)	67 (49)	30 (41)	26 (43)	19 (34)	24 (53)	15 (65)
Cervical vertebrae	5 (2)	2 (1)	2 (1)	1 (1)	4 (2)	2 (2)	1 (1)	1 (1)	1 (2)	0 (0)	1 (2)	0 (0)
Pelvis	8 (3)	2 (1)	5 (3)	1 (1)	6 (3)	1 (1)	4 (3)	1 (1)	2 (3)	1 (2)	1 (2)	0 (0)
Proximal femur	15 (6)	5 (3)	14 (8)	4 (4)	12 (6)	4 (4)	11 (8)	4 (5)	3 (5)	1 (2)	3 (7)	0 (0)
Other leg	20 (8)	14 (9)	12 (7)	10 (10)	14 (7)	8 (9)	7 (5)	7 (9)	6 (10)	6 (11)	5 (11)	3 (13)
Feet/toes	9 (4)	9 (6)	4 (2)	4 (4)	8 (4)	5 (5)	3 (2)	3 (4)	1 (2)	4 (7)	1 (2)	1 (4)
All sites	248	149	182	97	187	93	137	74	61	56	45	23

* Excludes severe trauma and pathologic fracture.

Table 4. Distribution of all fractures by cause among women and men following their new diagnosis of RA made between 1955 and 2007, in Olmsted County, Minnesota, and/or equivalent index date for matched non-RA subjects, stratified by age at RA diagnosis/index date. Only fractures occurring over their followup, which ended at the earlier followup of the matched pair, are considered.

Sex and Age Groups	Subjects	n	Fracture Cause					
			Severe Trauma n (%)*	Falls from Standing n (%)*	Spontaneous n (%)*	Pathological n (%)*	Uncertain n (%)*	All Causes n
Women ≥ 50 yrs	RA	514	83 (16)	191 (36)	190 (36)	21 (4)	49 (9)	534
	Non-RA	514	60 (17)	132 (37)	127 (36)	13 (4)	23 (6)	355
Women < 50 yrs	RA	308	62 (22)	67 (24)	124 (44)	0 (0)	28 (10)	281
	Non-RA	308	47 (44)	29 (27)	23 (21)	1 (1)	8 (7)	108
Women < 50 yrs**	RA	308	20 (25)	11 (14)	33 (42)	0 (0)	15 (19)	79
	Non-RA	308	21 (51)	12 (29)	4 (10)	0 (0)	4 (10)	41
Men ≥ 50 yrs	RA	239	45 (24)	55 (29)	68 (36)	5 (3)	14 (7)	187
	Non-RA	239	14 (15)	29 (31)	31 (33)	5 (5)	14 (15)	93
Men < 50 yrs	RA	110	15 (25)	12 (20)	30 (49)	1 (2)	3 (5)	61
	Non-RA	110	32 (57)	4 (7)	16 (29)	1 (2)	3 (5)	56
Men < 50 yrs**	RA	110	8 (50)	2 (12)	5 (31)	1 (6)	0 (0)	16
	Non-RA	110	20 (71)	3 (11)	4 (14)	0 (0)	1 (4)	28

* Percentage (%) of each type of fracture. ** Followup ended at age ≤ 50 yrs.

Table 5. Fracture risk [hazard ratio (HR)] for any first fragility fracture or first major osteoporotic fracture (fragility fracture at proximal femur, thoracic/lumbar vertebrae, distal radius, or proximal humerus) among women and men with RA from Olmsted County, Minnesota; stratified by age at diagnosis and relative to their matched non-RA pair.

Sex and Age Groups	Subjects	Total n	Fragility Fractures			Major Osteoporotic Fractures		
			n	Per 1000 P-Y	HR (95% CI)	n	Per 1000 P-Y	HR (95% CI)
All Women	RA	822	282	30.8	1.63 (1.36–1.96)	212	23.2	1.78 (1.43–2.21)
	Non-RA	822	193	21.1	—	129	14.1	—
Age ≥ 50	RA	514	201	40.0	1.43 (1.16–1.77)	158	31.5	1.46 (1.15–1.86)
	Non-RA	514	151	30.1	—	113	22.5	—
Age < 50	RA	308	81	19.6	2.34 (1.61–3.42)	54	13.1	4.05 (2.31–7.10)
	Non-RA	308	42	10.2	—	16	3.9	—
Age < 50*	RA	308	32	16.3	1.95 (1.08–3.51)	14	7.1	4.80 (1.38–16.73)
	Non-RA	308	17	8.7	—	3	1.5	—
All Men	RA	349	88	24.2	1.40 (1.02–1.93)	68	18.7	1.65 (1.13–2.42)
	Non-RA	349	65	17.9	—	43	11.8	—
Age ≥ 50	RA	239	63	30.9	1.34 (0.92–1.94)	51	25.0	1.77 (1.13–2.77)
	Non-RA	239	50	24.5	—	31	15.2	—
Age < 50	RA	110	25	15.7	1.74 (0.91–3.30)	17	10.7	1.49 (0.71–3.12)
	Non-RA	110	15	9.4	—	12	7.5	—
Age < 50*	RA	110	6	8.1	0.82 (0.28–2.45)	3	4.0	0.75 (0.17–3.35)
	Non-RA	110	7	9.4	—	4	5.4	—

* Followup ended at age ≤ 50 yrs. Note that the number of fractures observed may differ from those reported in Table 2 or 3 because only the first fracture of each type per subject was counted. P-Y: person years.

curves for fragility fractures in RA and non-RA women and men, taking into account the competing risk for death, are illustrated in Figure 1. Calendar year of RA diagnosis did not influence our estimates of fracture risk (data not shown). The risk for a first major osteoporotic fracture was also increased for both women and men with RA (HR = 1.78, 95% CI 1.43-2.21 and 1.65, 95% CI 1.13-2.42; respectively; Table 5).

Fracture risk for women and men diagnosed with RA at ≥ 50 years of age. Altogether, 514 (63%) of the 822 RA women were diagnosed with the condition at 50 years of age or later, as were 239 (68%) of the 349 men with RA. Among these 514 RA women and their matched non-RA pair (mean age at diagnosis/index date, 66 ± 10 yrs), median followup was 8 years (range 4 days-35 yrs) and total followup was 5021 person-years for each group. Over followup, there was a significant 1.4-fold increased risk of any fragility fracture and a 1.5-fold increase in major osteoporotic fractures among the older RA women (Table 5). Among the 239 RA men and their matched pair (mean age at diagnosis/index

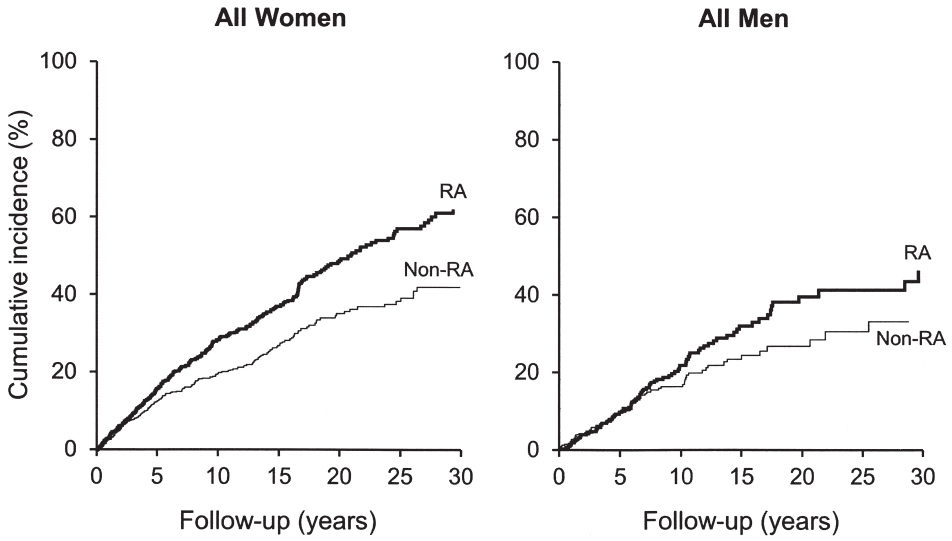

Figure 1. Kaplan-Meier curves for the cumulative incidence of fragility fractures, accounting for the competing risk of death, in all women with RA and their matched non-RA pair and in all men with RA and their matched non-RA pair, following either RA diagnosis or equivalent index date for non-RA subjects. Cumulative incidence of fragility fractures at 20 years is estimated at 49% versus 35%, respectively, for RA and non-RA women and 40% versus 27%, respectively, for RA and non-RA men.

date, 65 ± 9 yrs; median followup 8 years, range 16 days-35 yrs; and total followup, 2042 person-years, for each group) only the 1.8-fold increase in major osteoporotic fractures in RA men was statistically significant, not the 1.3-fold increase in any fragility fractures (Table 5). The cumulative incidence curves for fragility fractures and absolute risk estimates for these older women and men are presented in Figure 2.

Fracture risk for women and men diagnosed with RA at < 50 years of age. Among the 308 younger RA women and their matched pair (mean age at diagnosis/index date, 40 ± 8 yrs; median followup, 11 yrs, range 12 days-52 yrs; and total followup, 4127 person-years, for each group), there was a significant 2.3-fold increase in fragility fractures, as well as a 4.0-fold increase in the risk of a major osteoporotic fracture, for RA women (Table 5). In the 110 younger RA men and their matched pair (mean age at diagnosis/index date, 41 ± 7 yrs; median followup, 12 yrs, range 6 months-44 yrs; and total followup, 1591 person-years for each group), there was a 1.7-fold increase in fragility fractures and 1.5-fold increase in major osteoporotic fractures for RA men, but neither was statistically significant (Table 5). The cumulative incidence curves and absolute risk estimates for fragility fractures for these younger women and men are also illustrated in Figure 2.

Fracture risk before 50 years of age for women and men with RA. Examining the risk for fractures occurring prior to 50 years of age, the median followup for each pair of women in this subanalysis was 5 years (maximum followup, 27 yrs). Over the 1963 person-years of followup for each group, RA women had a 2.0-fold increase in fragility fractures and a 4.8-fold increase in major osteoporotic fractures, prior to age 50 years, both of which were statistically significant (Table 5). The cumulative incidence of fragility fractures at 10 years was 17.5% versus 6.7% for RA versus non-RA women. By contrast, few fractures occurred before age 50 years among men (median followup for each pair, 5 yrs; maximum followup, 31 yrs). Over the 743 person-years of followup in each group, fracture risk was not elevated among the men with RA, because only 6 RA men compared with 7 non-RA men had an incident of fragility fracture before age 50 years (Table 5).

DISCUSSION

After 50 years of age, both women and men are at risk for fragility fractures[32], and the extent to which this risk is affected by a diagnosis of RA is clinically relevant. We were also interested in whether women and men diagnosed with RA at younger ages are at risk for fracture early in the course of their disease, or only when they get older. In our population-based cohort of women and men with confirmed new onset RA, where ascertainment of all clinically-evident fractures was complete and longterm followup was available, we found that both women and men are at increased risk for fragility fractures, generally, as well as fractures at skeletal sites typically considered osteoporotic. However, men with RA appeared to be at increased risk for fracture only later in the course of their disease, and not before the age of 50 years. In contrast, the increased fracture risk was observed in both younger and older women with

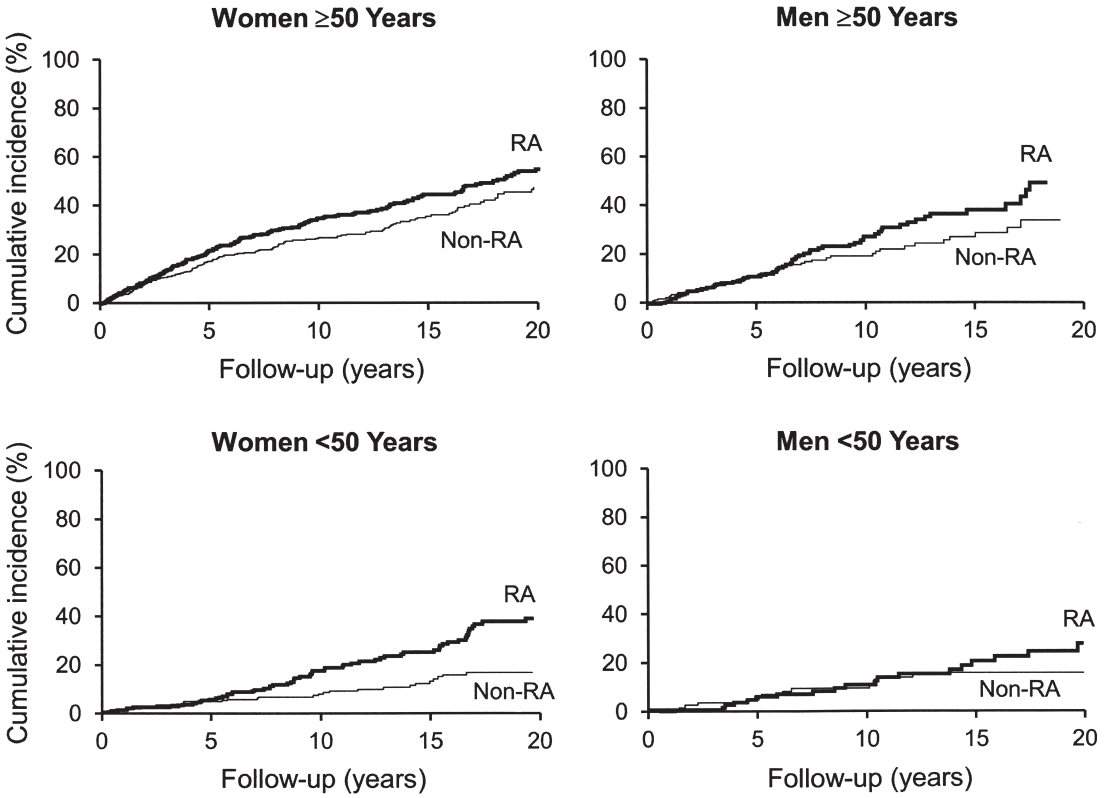

Figure 2. Kaplan-Meier curves for the cumulative incidence of fragility fractures, accounting for the competing risk of death, following either RA diagnosis or equivalent index date for non-RA subjects, each for women and men of different age groups (age ≥ 50 yrs and age < 50 yrs at RA diagnosis/index date). Cumulative incidence for fragility fractures at 20 years was: 56% versus 48% for women age ≥ 50 years; 38% versus 17% for women age < 50 years; 50% versus 35% for men age ≥ 50 years; and 28% versus 16% in men age < 50 years, in RA and non-RA subjects, respectively.

RA and was seen relatively early in the course of their disease. Further, women diagnosed with RA before they were 50 years old were at an increased risk for fragility fractures, particularly at major osteoporotic sites, even before they reached age 50 years.

Most studies evaluating fracture risk in RA have primarily involved older women[4,5,6,8,9,10,11,13], and few have included younger individuals[19,20,21]. One large prospective study examining fracture risk in both sexes with RA, investigated only subjects over age 40 years[7]. A large study that included both younger women and men with RA examined the risk for fractures only at the hip, shoulder, pelvis, or forearm and reported an increased risk for fractures in women, but not in men, under age 50 years[19]. We were able to identify an increased risk not only for major osteoporotic fractures, but also for overall fragility fractures in young women with RA, and even before they reached the age 50 years. We also had very long followup available, which likely accounts for the differences observed with our study in younger men with RA, where we found their risk for fragility fractures to be elevated only with longer disease duration and not before age 50 years.

Our findings have important clinical implications for younger women diagnosed with RA, who need to be made aware that they are at increased risk for a fragility fracture even while still young. Although their absolute risk is lower than older women with RA, it is still essential to ensure that their modifiable risk factors for fractures are addressed (e.g., smoking cessation, maintaining adequate calcium and vitamin D intake, preventing falls, etc.). The evidence on the efficacy and safety of most osteoporosis drug therapies is limited for younger individuals, especially in women of childbearing potential.

In women with RA, especially if diagnosed when older, their increased fracture risk appears to occur relatively soon after diagnosis. In contrast, the increased risk for fractures in men with RA appears to occur later following the diagnosis, and primarily at older, not younger, ages. Our different findings in young men compared with young women with RA may be due to the fact that men have greater peak bone mass and larger bone size relative to women, which may in turn confer a protective advantage against fractures in younger years[33]. Although the risk estimates for fractures were similar between younger and older men with RA, the

fact that relatively fewer men were studied limited our statistical power for analyses of subgroups. Nevertheless, our results suggest that both young and older men with RA have an increased risk for fracture, primarily as they advance in age, and particularly at major osteoporotic sites.

Fracture risk associated with RA is multifactorial[2]. The use of glucocorticoids, often to control the disease, is considered an important risk for fracture[34,35]. Additional risk factors unique to RA include RA-related inflammation, characterized by high levels of proinflammatory cytokines, as well as immune system dysregulation, which is now increasingly recognized to adversely affect bone metabolism[36,37,38]. Further, decreases in physical activity related to joint pain or damage may not only further aggravate bone loss[2,39,40] but also contribute to an increased risk for falls[41], and thereby fractures. Such risk factors were not explored in the current study, as a different study design would be required, especially since the majority of our RA population was exposed to steroids. The main focus of our present work was to determine whether there was a risk for fragility fractures in younger women and men with RA, which had not been previously established, and whether any risk was observed soon after diagnosis, or only when older. Further exploration is needed to determine the extent to which any risk factors differentially influence the likelihood for fractures, not only between women and men, but also between younger and older people with RA. Work is particularly needed in determining who, among younger women with RA, are at the greatest risk for early fracture so appropriate management may be effectively individualized.

It should be noted that our estimates of fracture risk in RA may not be the same for other races, as our population was largely white and non-Hispanic, reflecting the population demographics of Olmsted County. However, hip fracture rates in Olmsted County are reflective of hip fractures rates in white Americans[42], so our findings on fragility fracture risk are likely generalizable to American whites. Although we were able to study a relatively large number of both women and men with RA, our numbers of men were still small, reflecting the lower incidence of RA in men, which likely limited our statistical power in subgroup analyses. Nevertheless, the risk for fragility fractures and major osteoporotic fractures was significantly increased in all men with RA, and the estimates of fracture risk observed in younger and older men, separately, were consistent with these overall results. A unique advantage of our study is that we were able to access data on our RA subjects from the time of their initial diagnosis, which allowed us to evaluate the risk for fractures in older subjects with new onset RA, not those with a combination of new and longstanding disease. Further, all RA subjects were identified from medical records, not self-report, and were confirmed through comprehensive chart review to meet 1987 ACR classification criteria for RA. Similarly, all fractures in our study were documented in contemporary medical records and confirmed by trained nurse abstractors. Moreover, an ascertainment of trauma fracture etiology was possible. While those with RA may be subject to increased radiographic imaging that could lead to increased detection of asymptomatic fractures, relative to their matched non-RA pair, when we excluded fractures that were identified incidentally, our overall findings remained the same. In our exploratory analyses, calendar year of RA diagnosis did not influence our estimates of fracture risk.

In summary, men with RA are at risk for fragility fractures when they are older, particularly at major osteoporotic sites, while women with RA are at increased risk for fragility fractures at any age after diagnosis. Specifically, we found that young women with RA are at increased risk for fragility fractures occurring even before they reach the age of 50 years. While minimizing known risks for bone loss and fractures is important for all with RA, this is especially important to emphasize in young women with RA who may not appreciate their early risk for fragility fractures.

ACKNOWLEDGMENT

The authors thank Leona Bellrichard, RN, Marcia Erickson, RN, Wendy Gay, RN, Julie Gingras, RN, Joan LaPlante, RN, Constance Neuman, RN, Cynthia Nosek, RN, and Diane Wilke, RN for their work in data abstraction.

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