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Is The Epidemiology Of Rheumatoid Arthritis Changing? Results From a Population-based Incidence Study, 1985-2014

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Abstract

Objectives: To examine trends in the incidence of rheumatoid arthritis (RA) from 2005–2014 overall and by serologic status as compared to 1995–2004 and 1985–1994.

Methods: We evaluated RA incidence trends in a population-based inception cohort of individuals age ≥18 years who first fulfilled the ACR 1987 criteria for RA between 1/1/1985 and 12/31/2014. Incidence rates were estimated and were age- and sex-adjusted to the white population in the US in 2010. Trends in incidence were examined using Poisson regression methods.

Results: The 2005–2014 incidence cohort comprised 427 patients: mean age 55.4 years, 68% female, 51% rheumatoid factor (RF) positive, 50% cyclic citrullinated peptide antibody (anti-CCP) positive. The overall age- and sex-adjusted annual RA incidence in 2005–2014 was 41/100,000 population (age-adjusted incidence: 53/100,000 in women and 29/100,000 in men). While these estimates were similar to the 1995–2004 decade, there was a decline in the incidence of RF-positive RA in 2005–2014 compared to the previous two decades ($p=0.004$), with a corresponding increase in RF-negative cases ($p<0.001$). Smoking rates declined and obesity rates increased from earlier decades to more recent years.

Conclusions: Significant increase in incidence of RF-negative RA and decrease in RF-positive RA in 2005–2014 compared to previous decades was found using 1987 ACR criteria. The incidence of RA overall during this period remained similar to the previous decade. The changing prevalence of environmental factors, such as smoking, obesity and others, may have contributed to these trends. Whether these trends represent a changing serological profile of RA requires further investigation.

Keywords

Rheumatoid arthritis; incidence; rheumatoid factor

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INTRODUCTION

Rheumatoid arthritis (RA) is a major public health problem, associated with a substantial burden of functional disability. Globally, the overall age-standardized prevalence and incidence rates of RA have been increasing since 1990.[1] In the US, RA affects over 1.3 million adults, representing 0.6–1% of the population.[2,3] The incidence of RA shows temporal and geographic variability, likely influenced by genetic and environmental factors. Despite variable incidence estimates in different populations, declines in RA occurrence have been reported in several populations in the US (including the population of Rochester, MN), Western Europe and Japan during the second half of the 20th century.[4–7] An increase in the incidence of RA in the late 1990s to early 2000s, particularly in females, has been reported in Olmsted County, MN and in Denmark.[3,8] More recent trends in RA occurrence, particularly, recent trends in RA incidence by serologic status, have not been widely studied. A decline in the incidence of rheumatoid factor (RF) positive RA has been reported in Finland in 1980–2000, primarily among patients born after the mid-1940s compared to earlier birth cohorts.[9] A decline in prevalence of RF-positive RA has been reported in the Pima Indian population, also in younger birth cohorts.[10] These findings have been suggested to reflect a potential decline in RA severity in association with advancements in RA treatment over time. However, no changes in the incidence or prevalence of RA by serologic status have been reported thus far in the US population, including the population of Olmsted County, MN, where the proportion of RF-positive and RF-negative RA cases remained largely unchanged since 1955.[3,11]

Understanding the epidemiology of RA by serologic phenotype may provide insights into the pathophysiology of RA with implications for the course of the disease and choice of treatments, as well as healthcare use and planning. We aimed to examine trends in the incidence of RA from 2005 to 2014 as compared to the previous decades, and to separately assess trends in the incidence of RF-positive and RF-negative RA.

METHODS

The population of Olmsted County, Minnesota is uniquely suitable for an investigation of RA epidemiology due to availability of comprehensive medical records for all residents seeking medical care for more than half a century. The population-based data resources of the Rochester Epidemiology Project (REP) medical record linkage system provide essentially complete ascertainment of all individuals in the community regardless of age, sex, race/ethnicity, insurance status, or care delivery setting (inpatient and outpatient).[12] The REP enables complete, decades-long, follow up for each patient across all care providers, including the Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes, and the few private practitioners. This system offers a unique opportunity to study the key epidemiologic characteristics of morbidity, including incidence.[13]

Using the resources of the REP, we have assembled and continue to update the only population-based, longitudinal RA inception cohort in the US. In order to identify all potential incident cases of RA in this population during the 2005–2014 period, the

computerized diagnostic index was searched for any diagnosis of arthritis (excluding degenerative arthritis or osteoarthritis) made between 1/1/2005 and 12/31/2014 among Olmsted County residents who were 18 years of age and older. All persons in the community who qualified during the defined period, regardless of race, ethnicity, or socioeconomic status, were included. The complete inpatient and outpatient medical records for each potential case were reviewed by an experienced nurse abstractor, using a pretested data collection form. All questionable cases were additionally reviewed by co-investigators supervised by the principal investigator. Confirmation or rejection of RA diagnosis was accomplished based on the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria for the classification of RA.[14] The incidence date was defined as the earliest date when the patient fulfilled at least 4 of the 1987 ACR criteria for RA. Subjects were allowed to accumulate the criteria over time until fulfillment of the 4th criterion.[15] This inception cohort of patients in whom RA was diagnosed during the time period from 2005 through 2014 augmented the previously assembled cohort of residents with incident RA from 1985 through 2004.

Information on the following parameters was collected at RA incidence: age, sex, race/ethnicity (White, American Indian /Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, more than one race, or race unknown), smoking status (current, former and never), body mass index (BMI), and obesity (BMI≥30 kg/m^2). Data on positivity for RF and/or anti-cyclic citrullinated peptide antibody (anti-CCP antibody) and joint erosions/destructive changes during the first year after RA incidence were also gathered from the medical records.

Both RF and anti-CCP antibody were considered for criteria fulfillment when available. However, anti-CCP testing was not widely available until the 2000s, thus incidence rates were calculated for RF positive vs negative without inclusion of anti-CCP to allow fair comparison of incidence rates over 3 decades (i.e., 1985–2014).

Descriptive statistics (percentages, means, etc.) were used to summarize patient characteristics in each cohort. Comparison of patient characteristics between cohorts was performed using chi-square and rank sum tests. Age- and sex-specific incidence rates were calculated using the number of incident cases as the numerator and population counts from the REP census as the denominator.[12] Overall incidence rates were age- and/or sex-adjusted to the population of white persons living in the US in 2010. In order to compute 95% confidence intervals (95% CIs) for incidence rates, it was assumed that the number of incident cases followed a Poisson distribution. Trends in incidence rates were examined using Poisson regression models. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). This study was approved by institutional review boards of Mayo Clinic (IRB #17–002593) and Olmsted Medical Center (IRB #017-OMC-17).

RESULTS

The incidence cohort for 2005–2014 consists of 427 patients. The mean age at incidence of RA was 55.4 years, and 291 (68%) of the patients were female. Table 1 shows patients'

characteristics for the 2005–2014 incidence cohort as compared to the 1985–1994 and 1995–2004 cohorts. There were no statistically significant differences in age, sex, or race at RA incidence between the 2005–2014 cohort, 1995–2004, or 1985–1994 cohorts. Smoking rates declined and obesity rates increased substantially from earlier decades to more recent years.

All patients were tested for RF. In the 2005–2014 cohort, 216 patients (51%) were positive for RF compared to 69% of patients with incident RA in the 1985–1994 and 1995–2004 cohorts ($p<0.001$, Table 1).

The proportion of patients positive for anti-CCP antibody was 50% in the 2005–2014 cohort compared to 49% in the 1995–2004 incidence cohort, where only 174 out of 344 patients were tested due to the lack of test availability during most of this time period. Definite radiographic changes (erosions) during the first year after RA incidence were more frequent in patients with RA incident in 2005–2014 (96 patients, 25%) as compared to the 1985–1994 (33 patients, 17%) and 1995–2004 cohorts (65 patients, 21%; $P = 0.048$). The proportion of subjects who underwent radiographic examination in 2005–2014 was similar to the previous decade (89% vs 92%), and both were higher than in the 1985–1994 cohort (83%). When the prevalence of erosive disease was compared by RF status, patients with RF-positive RA in 2005–2014 did not differ from those in the previous decades (Table 1). However, the proportion of erosive disease in RF-negative RA patients has increased in the 2005–2014 cohort compared to the prior decades.

Table 2 shows RA incidence rates per 100,000 population for the 3 most recent decades and by RF status. The overall age- and sex-adjusted annual RA incidence in 2005–2014 was 41/100,000 population with age-adjusted incidence in women 53/100,000 population and 29/100,000 population in men. These estimates were similar to the previous decades ($p=0.26$). There was a significant decline in the incidence of RF-positive RA in 2005–2014 compared to the previous 2 decades ($p=0.004$), with a corresponding increase in RF-negative cases ($p<0.001$, Table 2). This decline affected both sexes and most age groups. Online supplementary Figures S1–S3 show RA incidence rates by age group, sex, time period and RF positivity.

DISCUSSION

The epidemiology of RA is dynamic. Previous studies, including ours, have shown that the incidence of RA varies between geographic areas and over time.[3–8] This retrospective population-based cohort study reports on the recent trends in incidence of RA in Olmsted County, MN in 2005–2014 as compared to the previous decades. The major finding of this study is decreasing incidence of RF-positive RA and increasing incidence of RF-negative RA in 2005–2014 as compared to the previous decades. This decline in incidence of RF-positive and rise in RF-negative RA resulted in a stable incidence of RA overall in 2005–2014 versus 1995–2004. Correspondingly, the proportion of patients in the overall cohort who were RF-positive was only 51%. This is in contrast to our earlier studies showing persistent predominance of RF-positive RA patients exceeding 65% of all cases over past decades (1955–2004).[3,11]

Several recent studies examined trends in RA incidence after 2000 with inconsistent results. A recent nationwide population-based cohort study from the UK showed decline in the annual incidence of RA by 1.6% between 1990 and 2015, using a code-based definition of RA.[16] The estimates were slightly lower that in our study with an estimate for overall RA incidence of 38.1/100,000, consistent with the lower estimates for Europe and the UK versus the US in previous studies.[17,18] A nationwide register-based study from Finland reported a decrease in incidence of seronegative RA cases and stable incidence of seropositive RA from 2000 to 2014 based on the ICD-10 codes.[19] Variability in the incidence of RA based on ICD-9 and ICD-10 codes has been described in a Canadian province during the 2001–2014 period (age- and sex-adjusted incidence rates were highest at 73.1 cases/100,000 in 2013 and lowest at 33.7 cases/100,000 in 2015), but no consistent trend towards decrease or increase in RA incidence was detected.[20] The incidence of RA overall and by sex in 2005–2014 in this study was similar to the estimates from the recent nation-wide, register-based study of RA incidence in Sweden in 2006–2008[21], which may be due to common genetic background, since many Minnesota residents have Northern European ancestry.

What are the potential reasons for the observed increase in incidence of seronegative RA? As incidence estimates vary depending on case definition, the change in classification criteria for RA from 1987 ACR criteria to 2010 ACR/EULAR criteria may have influenced the results of studies using code-based definitions of RA, reflecting differences between coding of inflammatory arthritis diagnoses in practice and classification criteria performance. While 2010 ACR/EULAR criteria were designed to facilitate recognition of early RA, low sensitivity of these criteria to seronegative RA has been reported[22–24] and can account for some variability in identification of seronegative RA cases in population-based studies using different criteria sets.[19]

Changes in environmental exposures may affect the risk of developing RA. RF and/ or anti-CCP-positive and RF and/or anti-CCP-negative RA are increasingly recognized as etiologically distinct subtypes of RA disease, and different risk factors have been shown to be selectively associated with seropositive or seronegative subtype.[25]

Cigarette smoking is an established risk factor for seropositive RA. The link between smoking and anti-CCP is primarily present in patients with RA who have shared epitope (SE) for HLA-DRB1, the major genetic risk factor for RA.[26] Findings from two recent large population-based studies in European and Asian populations suggest that the association of cigarette smoking with anti-CCP may be driven by the presence of the SE, while the association of smoking with RF-positivity may be independent of the presence of the SE.[27,28] Smoking cessation has been associated with decreased risk of anti-CCP and RF positivity.[28–30] A decline in incidence of RA, particularly seropositive RA, has been reported alongside the decline in cigarette smoking in European populations in the past several decades.[9,16] Concordantly, the decline in incidence of RF-positive RA in our study coincided with a significant decrease in current or former smoking and an increase in rates of never smokers in Olmsted County, MN.

Obesity is a significant risk factor for RA, even after adjusting for smoking status.[31] Growing evidence from population-based studies shows an association of increased body

mass index (BMI) and obesity with anti-CCP-negative RA, particularly in women, while an inverse association between BMI and anti-CCP-positive RA has been shown in men.[25,32] Less is known about the association of obesity with the presence of RF. Given the recognized correlation between seropositivity for RF and anti-CCP,[27,33] it could be hypothesized that the growing obesity rates in the population of Olmsted County, MN can be contributing to the observed increase in RF-negative RA. However, more studies are needed to further understand the effects of increased BMI and obesity on the risk of RA by serologic status.

Several other environmental and lifestyle factors have been evaluated for their association with the risk of RA in prior studies, including periodontitis[34], vitamin D deficiency[35] breastfeeding and oral contraceptive use[36,37]. While this study focused on trends in incidence of RA, investigation of time trends in environmental and lifestyle factors and its association with RA incidence is a subject for future research.

Seronegative RA is frequently thought of as a milder disease. However, growing evidence suggests delayed diagnosis, more severe disease at presentation and challenges in remission induction in patients with seronegative RA.[38,39] In our study, erosions in the first year were more frequent in patients with RA in 2005–2014, and this trend was driven by RF-negative RA that was more prevalent in this recent decade than in the previous decades. In fact, radiographic erosions within the first year of RA disease onset in the 2005–2014 cohort were as common in RF-negative as in RF-positive RA patients. Taken together with our findings of a rising incidence of RF-negative RA, these data suggest a need for increased awareness and timely vigilant management of RF-negative RA.

Strengths of our study include its longitudinal population-based design and the use of a systematic and standardized approach to case identification over several decades. RA was defined based on 1987 ACR classification criteria rather than current 2010 ACR/EULAR criteria, ensuring comparability of the estimates with earlier decades and minimizing the possibility of misclassification due to changes in criteria sets. In addition, prior studies have indicated low sensitivity of 2010 criteria in patients with seronegative RA, suggesting that use of this criteria set may not be ideal in population-based studies of RA epidemiology.[22] Incidence rates were calculated for RF positive vs negative without inclusion of anti-CCP-antibody to allow fair comparison of incidence rates over 3 decades (i.e., 1985–2014) when anti-CCP testing was on the rise.

There is a possibility of under-ascertainment of RA cases in studies involving medical record review. However, the comprehensive and standardized approach to case ascertainment in this study makes this unlikely. While there is a possibility for misclassification of cases, particularly those with seronegative RA, patients included in this study met at least 4 1987 ACR criteria for RA and had no alternative diagnosis for their inflammatory arthritis in the medical records. While the increasing recognition and the need for early treatment of RA disease may affect diagnostic code-based estimates of RA incidence, we believe that defining RA onset based on accumulation of at least 4 1987 ACR classification criteria rather than a physician diagnosis may have minimized potential bias associated with variable awareness of RA disease among individual rheumatology providers. The rates of

radiographic testing have increased from earlier decades to more recent decades and may have contributed to increase in identification of erosions. However, this increase would be expected to affect RA patients regardless of RF status, and would not explain increased rates of erosions in RF-negative but not in RF-positive patients. Radiographs were interpreted by certified Mayo Clinic radiologists blinded to the study hypothesis, per routine protocol; thus radiographic interpretation is unlikely to bias the study results. Finally, the population of Olmsted County, Minnesota is ~90% white, suggesting that the results of our study may not be generalizable to other, more racially diverse populations. The rates of RF-positivity may vary across racial and ethnic groups. There was a marginal decrease in the proportion of white individuals in the 2005–2014 cohort in keeping with increasing diversity within the Olmsted County population. White patients have been previously noted to have lower percentages of RF-positive RA,[40] thus the borderline decline in the proportion of white individuals in Olmsted country would not be expected to explain the decline in incidence of RF-positive RA or otherwise influence the observed epidemiologic trends.

In summary, there has been an increase in RF-negative RA and decrease in RF-positive RA in recent years. In aggregate, the incidence of RA overall was stable during 2005–2014 compared to the previous decade. The changing prevalence of environmental factors, such as smoking, obesity, and others, may have contributed to these trends in seropositive disease in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:

Initial findings of this study were presented at the American College of Rheumatology meeting 2019.[41]

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Key messages:

What is already known about this subject?

- The overall age-standardized incidence rates of rheumatoid arthritis (RA) have been increasing globally since 1990.
- A decline in the incidence of rheumatoid factor (RF) positive RA has been reported in a European population in 1980–2000.

What does this study add?

- Our study shows decreasing incidence of RF-positive RA and increasing incidence of RF-negative RA in 2005–2014 as compared to the previous decades.
- In aggregate, the incidence of RA overall was stable during 2005–2014 compared to the previous decade.

How might this impact on clinical practice or future developments?

- Rising incidence of RF-negative RA suggests the need for increased awareness and timely recognition of RF-negative RA by physicians.
- The changing prevalence of environmental factors, such as smoking, obesity and others, may have contributed to decreasing incidence of RF-positive RA and increasing incidence of RF-negative RA in 2005–2014.

Table 1.

Patient characteristics by decade of rheumatoid arthritis (RA) incidence

Characteristic*	Decade of RA incidence			p value
	1985–1994 (N=240)	1995–2004 (N=344)	2005–2014 (N=427)	
Age at RA incidence, years	56.6 (16.6)	56.0 (15.5)	55.4 (15.4)	0.73
Female sex	160 (67%)	240 (70%)	291 (68%)	0.73
Race				0.08
- White	225 (94%)	321 (93%)	377 (88%)	
- American Indian/ Alaska Native	1 (0%)	2 (1%)	2 (0%)	
- Asian	8 (3%)	8 (2%)	16 (4%)	
- Black or African American	0 (0%)	3 (1%)	17 (4%)	
- Native Hawaiian/ Other pacific Islander	1 (0%)	1 (0%)	3 (1%)	
- More than one race	3 (1%)	5 (1%)	9 (2%)	
- Unknown	2 (1%)	4 (1%)	3 (1%)	
Smoking at RA incidence				0.002
- Never smoker	97 (40%)	161 (47%)	242 (57%)	
- Current smoker	51 (21%)	62 (18%)	64 (15%)	
- Former smoker	91 (38%)	121 (35%)	121 (28%)	
BMI at RA incidence, kg/m^2	27.0 (5.5)	28.1 (6.1)	29.6 (6.8)	<0.001
Obesity (BMI≥30 kg/m^2) at RA incidence	57 (24%)	114 (33%)	175 (41%)	<0.001
History of obesity at or before RA incidence	77 (32%)	147 (43%)	210 (49%)	<0.001
RF positive	166 (69%)	238 (69%)	216 (51%)	<0.001
Anti-CCP positive	33 (73%)	86 (49%)	197 (50%)	0.009
Not tested	195	170	30	
Erosion in the first year after RA incidence	33 (17%)	65 (21%)	96 (25%)	0.048
- RF positive	27 (19%)	50 (23%)	49 (25%)	0.47
- RF negative	6 (10%)	15 (16%)	47 (25%)	0.017
No radiograph	41	27	46	
Patients who underwent radiographic examination in the first year after RA incidence	199 (83%)	317 (92%)	381 (89%)	0.002
- RF positive	139 (84%)	221 (93%)	195 (90%)	0.012
- RF negative	60 (81%)	96 (91%)	186 (88%)	0.15

*Values in the table are mean (±SD) for continuous characteristics and N (%) for discrete characteristics

Abbreviations: RA = Rheumatoid Arthritis; BMI= Body Mass Index; RF = Rheumatoid Factor; anti-CCP = anti-cyclic citrullinated antibody

Table 2.

Incidence rates of rheumatoid arthritis by 1987 American College of Rheumatology criteria per 100,000 population (95% CI)

Group	Decade of RA incidence	Female	Male	Total
Overall	1985–1994	48 (41, 56)	32 (25, 40)	40 (35, 46)
	1995–2004	55 (48, 63)	30 (24, 36)	43 (38, 48)
	2005–2014	53 (47, 59)	29 (24, 34)	41 (37, 45)
RF positive	1985–1994	33 (27, 40)	23 (17, 30)	28 (24, 33)
	1995–2004	39 (33, 45)	19 (15, 24)	30 (26, 33)
	2005–2014	26 (22, 30)	15 (12, 19)	21 (18, 24)
RF negative	1985–1994	15 (11, 19)	9 (5, 12)	12 (9, 15)
	1995–2004	16 (13, 20)	10 (7, 14)	13 (11, 16)
	2005–2014	26 (22, 31)	14 (11, 18)	20 (18, 23)

Abbreviations: RA = Rheumatoid Arthritis; RF = Rheumatoid Factor