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Determinants of Mortality Among Postmenopausal Women in the Women's Health Initiative Who Report Rheumatoid Arthritis

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Objective. **Rheumatoid arthritis (RA) patients have an increased risk of cardiovascular disease (CVD) and mortality. We measured anti–cyclic citrullinated peptide (anti-CCP) antibody levels and determined use of disease-modifying antirheumatic drugs (DMARDs) among women in the Women's Health Initiative (WHI). Using these data, we undertook this study to assess total mortality over 10 years of followup among white, black, or Hispanic women with self-reported RA in the WHI.**

Methods. **Using stored baseline serum, we measured anti-CCP, rheumatoid factor (RF), and antinuclear antibodies (ANAs) in 9,988 women who reported having RA. Based on a previous chart review study, probable RA was defined as either self-reported RA and anti-CCP positivity, or anti-CCP negativity and DMARD use. Cox proportional hazards regression was used to model the relationship of self-reported RA, DMARD exposure, and anti-CCP positivity to total mortality, using followup data through April 2009.**

Results. **At baseline, the mean age was 62.8 years; 24.5% of subjects were black and 10% were Hispanic. Prevalence of anti-CCP positivity was 8.1% (n = 812), and 217 women were anti-CCP negative but had reported use of DMARDs; therefore, 1,029 women (of 9,988) were classified as having probable RA, and 8,958 were classified as unlikely to have RA (with data on DMARD use missing for 1 subject). Age-adjusted mortality rates were ~2-fold higher for anti-CCP–positive women, with 20.2 deaths per 1,000 person-years, as compared to 11.4 deaths per 1,000 person-years among anti-CCP–negative women with self-reported RA who never used DMARDs. Among women who did not report any arthritis at baseline, we found 8.3 deaths per 1,000 person-years. The increased risk among anti-CCP–positive women with RA was not explained by age, RF positivity, ANA positivity, or DMARD use.**

Conclusion. **Anti-CCP–positive RA was associated with substantial excess mortality among postmenopausal women in the WHI. This result was not explained by the risk factors we measured.**

Rheumatoid arthritis (RA) patients have shortened life expectancies (1), with ~1.5-fold higher mortality rates as compared to controls (1,2). Excess mortality is largely attributed to cardiovascular disease (CVD) (3) and is greater in cohorts with existing RA than in inception cohorts, since the risk increases with both the duration and the severity of RA (4,5). Mortality is higher among men with RA as compared with women, and it is also higher among subjects of older ages (6). Studies have demonstrated that excess mortality may be

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declining over time, possibly as a result of decreases in disease severity and/or improved drug therapies (especially introduction of medications earlier in the course of the disease and use of new biologic agents) (4,7–10). No clinical trial has been carried out long enough to assess mortality as an outcome (11–13), but observational data suggests that methotrexate may reduce both CVD and mortality (14).

The specific pathophysiology of excess mortality has not been firmly established despite numerous observational studies over the past 60 years. Possible explanations include accelerated aging, persistent inflammation related to severity of RA (based on measurements of both rheumatoid factor [RF] and anti–cyclic citrullinated peptide [anti-CCP] antibodies), higher levels of specific cytokines, T cell abnormalities, other immunologic changes, and secondary fibrosis, thrombosis, and amyloid deposition among other factors (15–22). Infectious diseases, B cell lymphoma, and renal and pulmonary diseases have also been reported to occur in excess in RA patients (23,24).

Few large epidemiologic cohort studies have included RA as a specific outcome because of the relatively low incidence and prevalence of RA and because of difficulties documenting reported RA diagnoses (25). The availability of anti-CCP antibody assays that are both sensitive (70–75%) and highly specific (95%) for RA has provided an opportunity to include RA as an outcome in large epidemiologic cohort studies in which RA patients were not deliberately selected from clinic or community registries (26–28).

In the Women's Health Initiative (WHI), a review of hospital and other medical records in 2 WHI clinical centers revealed that classification of self-reported RA according to anti-CCP positivity/negativity and use (or not) of disease-modifying antirheumatic drugs (DMARDs) at baseline or during the study yielded a high positive predictive and negative predictive value for physician-validated diagnosis of RA. Few women who were anti-CCP negative and were not taking DMARDs had clinical evidence of RA (29). Further, 286 women in 2 centers reported a history of RA at either baseline or followup. Study physicians reviewed the medical records as well as the information provided by the physicians who were treating the patients; the study physicians validated 42 cases as probable RA, 20 of which (47.6%) were anti-CCP positive. However, of the 244 cases that were validated as not being cases of RA, 5 (2.0%) were anti-CCP positive, resulting in an 80% positive predictive value. In contrast, the positive predictive value of anti-CCP positivity and DMARD use was 100%, the positive predictive value of RF positivity was 44%, and the positive predictive value of self-reported DMARD use alone was 62%.

The focus of this report is a detailed evaluation of total mortality over 10 years of followup among 9,988 women in the WHI who reported RA, stratified by likely clinical RA, reported risk factors, use of DMARDS, and serum markers measured at baseline only, including anti-CCP (measured with a second-generation assay [anti–CCP-2]), RF, and antinuclear antibodies (ANAs). Future reports will focus on cytokines, genetics, and specifically, the risk of coronary heart disease (CHD).

PATIENTS AND METHODS

Participants and data collected in the WHI. Previous reports have described the WHI. Briefly, 161,808 women were enrolled in 40 clinical centers from 1993 through 1997. The mean age of the participants at baseline was 62.8 years, and 64.5% were white (30). At baseline, 76,192 women (47.1%) reported having arthritis. At baseline or followup visits, 16,461 women (10.2%) reported having a history of RA. In all, 15,188 women reported having RA at baseline or followup visits, 9,988 (65.8%) of whom were included in the present study.

Priority in the sampling frame was given to women with reported RA who had a CHD event during the 10-year followup, as well as to women of black and Hispanic race/ethnicity, and to women who had DNA available for genetic analysis. The sample included 100% of women (1,650) who reported having RA at baseline and followup, 72% of women (4,007 of 5,578) who self-reported having RA at baseline only, 63% of women (2,625 of 4,134) who reported having RA at followup but another form of arthritis at baseline, and 45% of women (1,706 of 3,826) who reported having RA at followup but no arthritis at baseline. The final sample included 6,487 white, 2,442 black, and 1,058 Hispanic women (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38268/abstract). Seven hundred thirteen American Indians, 4,190 Asian/Pacific islanders, and 2,362 women of other ethnicities and those for whom blood samples were missing were excluded. Much of the analysis presented in this report is restricted to women who reported having RA at baseline or baseline and followup (78% of eligible WHI women [5,657 of 7,228]), since there was a lack of followup blood samples and limited information on subsequent DMARD use after baseline. This also helped avoid bias that could arise from shorter followup times. Weighted and unweighted analyses are included, with the weights based on the specific sampling fractions noted above. There was little difference in weighted/unweighted results for participants who had RA at baseline or at baseline and followup because of the very high percentage (78%) of such patients who were included in the study.

At the baseline examination, women were asked about severity of joint pain and swelling of joints during the 4 weeks prior to the examination, but they were not asked to specify the specific joint or number of joints that were affected. Joint-related symptoms varied from none to severe. Women pro-

vided information on their current health status, disability, physical functioning, and employment status (31). Detailed pharmacologic drug histories were also obtained, both at baseline and followup, every 3 years in the clinical trial and at the third year of followup in the observational study, including information about drugs used in the treatment of RA (DMARDs). Eligible DMARDs included hydroxychloroquine, sulfasalazine, minocycline, methotrexate, leflunomide, azathioprine, cyclosporine, gold, cyclophosphamide, antirheumatic biologic agents, oral steroids, tumor necrosis factor α inhibitors, and interleukin-1 antagonist (29). The data are not detailed enough to provide accurate dose-related drug history.

Serum biomarkers. Using baseline serum samples stored at −70° and not previously thawed, anti–CCP-2, RF, and ANA assays were performed in the Rheumatology Clinical Research Laboratory at the University of Colorado. Briefly, anti-CCP (IgG) antibodies were measured using commercially available second-generation (anti–CCP-2) enzyme-linked immunosorbent assay kits (Diastat; Axis-Shield Diagnostics). A positive cutoff value of ≥5 arbitrary units (AU)/ml was used, which has been demonstrated to be >98% specific for RA (29). Nephelometry (Dade-Behring) was used to measure RF quantitatively by the reactivity of the diluted test serum with heterologous IgG in solution. This provided continuously variable quantitative results in international units. The positive cutoff value for the anti–CCP-2 and RF assays was set so that 5% of a population of 490 randomly selected healthy anonymous blood donors had positive results, as per the American College of Rheumatology (ACR) 1987 criteria for RA (32). All autoantibody-positive sera (anti–CCP-2 and/or RF) were retested under blinded conditions, along with 5% of the negative sera, with >97.5% agreement in repeat testing (29) to ensure quality control of the data.

A 2-step process was used to test for ANA. First, an autoimmune enzyme immunoassay ANA screening test (Bio-Rad) was used to test serum samples using the methods and reagents specified by the manufacturer. Positivity for this assay was determined based on in-house experiments and a level that was >95% sensitive for patients with systemic lupus erythematosus (SLE) who were positive for ANA by indirect immunofluorescence (IIF) and who met ≥4 of 11 ACR criteria for classification of SLE (33), as well as a level that was >95% sensitive for patients with a variety of other non-SLE rheumatic diseases known to be positive for ANA by IIF. Second, all samples that were positive on enzyme immunoassay testing were subsequently tested using IIF and HEp-2 nuclei, and final ANA positivity was determined based on ≥1+ immunofluorescence intensity at a titer of ≥1:320. No followup blood samples were evaluated.

Two other comparison groups were included in the analysis: 1) women who reported having arthritis but not RA (n = 57,572), and 2) women who had never reported arthritis (n = 76,160) at baseline. No study-specific blood tests were done for those 2 comparison groups.

Other variables included in this analysis and measured in all of the women enrolled in the WHI have been previously shown to be related to morbidity and mortality, including cigarette smoking (none, past, current), hypertension, diabetes, and CHD at baseline, current levels of physical activity, waist circumference, reported general health, age, education, and ethnicity. These variables have been described in previous WHI publications (34,35).

Deaths were identified by semiannual or annual followup with the patients' family, friends, and medical care providers, as well as through the National Death Index and obituaries. Only ~1–2% of participants were lost to followup. Cardiovascular-related and cancer-related morbidities were adjudicated centrally. Cardiovascular-related deaths included death from CHD, stroke, congestive heart failure, and other CVDs. Other cause-specific deaths were classified according to the underlying cause of death.

Statistical analysis. The study included 9,988 women who were sampled from 15,188 eligible WHI participants who had reported RA at baseline or during followup. Sampling fractions varied by whether participants reported RA at baseline or followup only, CHD status, and race/ethnic group. To correctly represent the WHI RA population, sampling weights (1/sampling fraction) were determined for each woman and incorporated in the analyses.

As noted, among women who reported RA, probable RA cases were defined as anti-CCP–positive women (whether exposed to DMARDs or not) or anti-CCP–negative women with reported DMARD use, based on our previous chart review (36). Women who reported having RA but who were not anti-CCP positive and were not exposed to DMARDs were classified as not having RA. The analysis was designed first to compare probable RA versus unlikely RA among women who reported RA. Other comparison groups included the group of remaining women who reported having a form of arthritis other than RA and the group of women who reported no arthritis during the study; no blood tests were performed for these 2 additional comparison groups. Results utilize variables measured at baseline only, except when noted for DMARD use. Age-adjusted mortality rates and 95% confidence intervals (95% CIs) were calculated using direct methods, with the entire WHI population as the standard population. Cox proportional hazards regression models were used to assess the association between mortality and risk factors. Time to the event was defined as the time from baseline to the date of death or to the end of followup, which ever occurred first. Analyses were performed with SAS version 9.3 (SAS Institute). All models were 2-sided with an alpha level of 0.05.

RESULTS

Among women who self-reported RA, 812 (8.1%) were anti-CCP positive, and 467 of those women (57.5%) reported taking DMARDs at any time during followup. Of 9,179 women who reported RA but were anti-CCP negative, 673 (7.3%) were receiving DMARDs. The prevalence of anti-CCP positivity and DMARD use was much higher among women who reported RA at baseline than among women who reported RA at followup examinations only. When the analysis was restricted to women reporting RA at baseline, 612 were anti-CCP positive, and of those, 407 (67%) reported DMARD use.

Table 1. All-cause mortality stratified by anti-CCP positivity and DMARD use at baseline in women who reported a history of RA*

	No. of patients	No. of patients who died	Age-adjusted death rate (95% CI)	Age-adjusted death rate excluding patients who reported having RA at followup only (95% CI)
Unweighted				
Probable clinical RA				
Anti-CCP positive	812	162	20.2 (15.6–26.1)	21.3 (16.0–28.5)
Anti-CCP negative and DMARD use	217	42	17.5 (10.6–29.5)	16.6 (9.8–29.2)
Clinical RA unlikely				
Anti-CCP negative and no DMARD use	8,951†	1,120	11.4 (10.3–12.5)	12.8 (11.3–14.6)
Weighted				
Probable clinical RA				
Anti-CCP positive	1,082	201	18.7 (14.9–23.5)	21.3 (16.5–27.7)
Anti-CCP negative and DMARD use	282	55	17.8 (11.4–28.0)	16.3 (10.2–27.0)
Clinical RA unlikely				
Anti-CCP negative and no DMARD use	13,812	1,540	10.0 (9.2–10.9)	12.3 (11.0–13.7)
Arthritis history at baseline among those without reported RA‡				
Total	133,732	12,585	8.7 (8.5–9.0)	–
Arthritis	57,572	6,398	9.2 (8.9–9.6)	–
No arthritis	76,160	6,187	8.3 (7.9–8.6)	–

* Age-adjusted death rates are per 1,000 person-years. RA = rheumatoid arthritis; 95% CI = 95% confidence interval.
† Anti–cyclic citrullinated peptide (anti-CCP) measurements are missing for 7 subjects, and data on use (or not) of disease-modifying antirheumatic drugs (DMARDs) are missing for 1 subject.
‡ Not included in study sample for biomarker testing.

Mortality by reported RA. Over 10 years, 13% of the women in the study sample (1,325 of 9,988) died. Of those, 14% self-reported RA at both baseline and followup (233 of 1,649), 16% self-reported RA at baseline only (633 of 3,996), and 10.5% self-reported RA at followup only (456 of 4,331). Median time to death was ~8 years for those who reported RA at baseline, 6.6 years for those who reported RA at both baseline and followup, and 6.4 years for those who reported RA at followup only.

Anti-CCP positivity and DMARD use. In the total study sample, age-adjusted death rates over 10 years of followup were higher for women with probable RA (i.e., anti-CCP positive or anti-CCP negative and taking DMARDs), than for women who reported RA but were not likely to have RA (i.e., anti-CCP negative and no DMARD use) (Table 1 and Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38268/abstract). Results were similar in weighted analyses, particularly for the increased death rates among anti-CCP–positive women. Death rates were also lower among women who did not report RA, particularly for women who reported no arthritis at baseline (Table 1).

Age-specific death rates increased across age groups for both anti-CCP–positive and anti-CCP–negative women, but remained substantially higher for anti-CCP–positive women within each age group (data not shown). Among anti-CCP–positive women, mortality rates were lower among black women as compared to white or Hispanic women. Due to the small number of nonwhite anti-CCP–positive women, 95% CIs were wide (see Supplementary Table 2, available on available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38268/abstract). Based on anti-CCP levels at baseline, there was no significant difference in the percent of women who died: for anti-CCP levels of <31 AU/ml, 20.7%; for anti-CCP levels of 31–75 AU/ml, 16.3%; for anti-CCP levels of 75–102 AU/ml, 19.7%; and for anti-CCP levels of >102 AU/ml, 16.7%.

Among participants who reported RA at baseline (or baseline and followup), the prevalence of RF positivity was ~20% (1,152 of 5,657) in baseline serum samples, and it was higher among anti-CCP–positive versus anti-CCP–negative women (69% versus 12%) (Table 2). Approximately half of the RF-positive women were anti-CCP negative and did not take DMARDs (i.e., they were unlikely to have clinical RA based on our validation study [29]). The overall prevalence of ANA was 15.6% (881 participants), similar to the prevalence found in a recent US population study (36). Of ANA-positive women, 16% were anti-CCP positive and 31% were RF positive; however, two-thirds of the ANA-positive women were anti-CCP negative and RF negative (Table 2) and therefore probably did not have clinical RA.

Table 2. Prevalence of anti-CCP positivity, RF positivity, and ANA positivity and age-adjusted death rates among women who reported RA at baseline or at baseline and followup (n = 5,657)*

Anti-CCP	RF	ANA	No. of patients	Age-adjusted death rate (95% CI)
−			5,042	13.0 (11.5–14.7)
+			612	21.4 (16.0–28.5)
	−		4,492	12.8 (11.2–14.6)
	+		1,152	17.9 (14.4–22.4)
		−	4,768	13.7 (12.1–15.5)
		+	881	14.7 (11.3–19.4)
−	−	−	3,802	12.5 (10.9–14.5)
+	−	−	75	20.9 (9.9–48.3)
−	+	−	487	14.5 (10.0–21.1)
−	−	+	597	13.3 (9.4–18.9)
+	+	−	395	23.3 (16.5–33.0)
+	−	+	13	30.5 (7.9–136.8)
−	+	+	142	19.5 (11.2–36.0)
+	+	+	128	14.4 (6.7–31.7)

* Age-adjusted death rates are per 1,000 person-years. Anti-CCP = anti–cyclic citrullinated peptide; RF = rheumatoid factor; ANA = antinuclear antibody; RA = rheumatoid arthritis; 95% CI = 95% confidence interval.

Finally, age-adjusted death rates were higher among anti-CCP–positive and RF-positive women but not higher among ANA-positive women (Table 2). Age-adjusted death rates were not significantly higher among those who were anti-CCP positive/RF positive as compared to those who were anti-CCP positive/RF negative, and the age-adjusted death rates were not elevated among those who were anti-CCP negative/RF positive, suggesting that anti-CCP positivity rather than RF positivity was the correlate of increased death rates. Very few participants were anti-CCP positive/ANA positive. Death rates were also elevated among those with RF positivity and ANA positivity, but the sample size was small. Surprisingly, the death rate was only slightly higher for women who were anti-CCP positive/RF positive/ANA positive, compared with women who were negative for anti-CCP, RF, and ANA (i.e., 14.4 deaths per 1,000 person-years versus 12.5 deaths per 1,000 person-years).

Mortality stratified by DMARD and/or methotrexate use. Among women who reported RA at baseline in weighted analysis, 68% (337 of 493) of those who reported methotrexate use at baseline were positive for anti-CCP, whereas only 40% (125 of 313) of those who reported use of other DMARDs at baseline were positive for anti-CCP, and only 4.5% (291 of 6,422) of women who reported RA at baseline and with no use of DMARDs were positive for anti-CCP. Mortality was similar among those who used DMARDs and those who did not use DMARDs and among those who used methotrexate and those who used any DMARDs. However, mortality was higher among anti-CCP–positive women as compared to anti-CCP–negative women in the comparison between those who used methotrexate and those who did not, as well as between those who used DMARDs and those who did not (Table 3).

Causes of death. The distribution of the causes of death among those who reported RA at baseline was similar for those with probable RA (i.e., anti-CCP–positive women and anti-CCP–negative women who used DMARDs) and those unlikely to have RA (i.e., anti-CCP–negative women with no DMARD use) (data not shown). Total CVD, including CHD and stroke, and all cancers were the leading causes of death. There was also little difference in the distribution of causes of death in this study as compared to the distribution of causes of death in the WHI overall. However, the number of deaths among anti-CCP–positive women is small and limits interpretation of the distribution of causes

Table 3. Age-adjusted death rates through 2009 stratified by methotrexate and DMARD use among women who reported RA at baseline or at baseline and followup (weighted)*

Anti-CCP	Medication	No. of patients	No. (%) of patients who died	Age-adjusted death rate (95% CI)
+	Methotrexate use	337	68 (20.1)	21.3 (14.5–31.6)
+	No methotrexate use, any DMARD use	125	30 (23.8)	22.0 (12.1–40.7)
+	No methotrexate use, no DMARD use	291	64 (22.0)	21.6 (14.3–33.0)
−	Methotrexate use	156	22 (14.3)	13.1 (6.9–26.7)
−	No methotrexate use, any DMARD use	188	34 (18.2)	15.5 (9.1–27.7)
−	No methotrexate use, no DMARD use	6,131	860 (14.0)	12.4 (11.1–13.9)

* Age-adjusted death rates are per 1,000 person-years. Results are stratified by disease-modifying antirheumatic drug (DMARD) use at baseline, not including prednisone. Of 76,160 patients who never reported arthritis, 6,187 (8.1%) died, with an age-adjusted death rate of 8.3 (95% confidence interval [95% CI] 7.9–8.6). RA = rheumatoid arthritis; anti-CCP = anti–cyclic citrullinated peptide.

Table 4. Age-adjusted death rates stratified by baseline variables, anti-CCP status, and DMARD use in patients with self-reported RA, excluding history of RA at followup only (weighted)*

	Anti-CCP positive		Anti-CCP negative and DMARD use at baseline		Anti-CCP negative and no DMARD use at baseline		
Baseline measurement	Weighted total	Age-adjusted death rate (95% CI)	Weighted total	Age-adjusted death rate (95% CI)	Weighted total	Age-adjusted death rate (95% CI)	Age-adjusted death rates among patients who never reported RA (95% CI)
Age, years							
50–59	262	9.2 (6.3–13.5)	74	4.9 (1.9–12.8)	1,894	5.3 (4.4–6.3)	3.2 (3.1–3.3)
60–69	313	17.8 (13.8–22.9)	102	16.0 (10.2–25.3)	2,617	10.6 (9.5–11.8)	7.4 (7.2–7.6)
70–79	178	43.8 (34.9–55.1)	69	32.7 (21.7–49.3)	1,713	24.7 (22.5–27.1)	17.6 (17.1–18.1)
Ethnicity							
Black	149	12.1 (6.4–23.3)	31	17.6 (6.1–52.5)	979	11.5 (9.3–14.3)	10.8 (9.8–12.0)
Hispanic	41	22.6 (8.5–62.8)	4	0	322	7.3 (4.6–11.4)	7.1 (5.8–8.8)
White	563	20.3 (15.8–26.1)	210	18.3 (11.4–29.7)	4,928	9.9 (9.1–10.9)	8.6 (8.3–8.9)
Education completed							
High school or less	194	24.2 (16.0–37.1)	58	13.3 (4.8–39.7)	1,752	10.2 (8.7–11.9)	9.7 (9.1–10.3)
Some college	306	16.3 (11.1–23.9)	94	25.3 (13.9–47.1)	2,486	10.5 (9.2–11.9)	9.0 (8.6–9.5)
College or more	243	17.0 (11.4–25.7)	92	14.0 (6.1–32.5)	1,929	9.52 (8.2–11.1)	7.9 (7.6–8.3)
Smoking							
Never	303	14.9 (10.1–22.4)	105	15.7 (7.7–32.6)	3,120	8.7 (7.7–9.9)	6.9 (6.6–7.3)
Past	360	18.7 (13.5–26.0)	121	20.9 (11.6–38.3)	2,506	10.2 (8.9–11.6)	9.5 (9.1–9.9)
Current	81	27.8 (15.4–50.5)	18	0	491	20.0 (15.6–25.6)	19.3 (17.7–21.1)
General health							
Excellent/very good	191	12.1 (7.7–19.6)	89	7.3 (6.3–8.5)	2,521	7.3 (6.3–8.5)	6.7 (6.4–7.0)
Good	350	18.3 (13.0–26.1)	124	10.1 (8.9–11.6)	2,477	10.1 (8.9–11.6)	10.2 (9.7–10.7)
Fair/poor	205	29.9 (20.1–44.6)	31	17.5 (14.9–20.5)	1,190	17.5 (14.9–20.5)	19.0 (17.6–20.5)
Diabetes							
No	712	17.8 (14.0)	219	9.1 (8.3–10.0)	5,623	9.1 (8.3–10.0)	8.1 (7.9–8.4)
Yes	41	32.3 (16.1–66.7)	25	21.4 (17.4–26.4)	600	21.4 (17.4–26.4)	18.9 (17.3–20.6)
CHD at baseline							
No	687	17.5 (13.7–22.5)	224	8.9 (8.1–9.8)	5,329	8.9 (8.1–9.8)	8.2 (7.9–8.4)
Yes	66	33.3 (18.0–63.2)	21	19.2 (16.0–23.3)	900	19.2 (16.0–23.3)	15.9 (14.6–17.4)
Physical function score on the SF-36							
≤85	589	20.2 (15.6–26.2)	208	12.1 (11.0–13.3)	4,143	12.1 (11.0–13.3)	11.0 (10.6–11.4)
>85	134	13.6 (7.7–24.1)	35	6.4 (5.3–7.6)	1,939	6.4 (5.3–7.6)	6.2 (5.9–6.6)
Waist circumference, cm							
≤88	460	16.3 (12.0–22.4)	134	8.7 (7.7–9.8)	3,113	8.7 (7.7–9.8)	7.6 (7.3–7.9)
>88	291	22.6 (16.2–31.6)	108	11.5 (10.2–12.8)	3,092	11.5 (10.2–12.8)	10.5 (10.0–10.9)
Total METs per week							
<2.5	264	22.9 (15.7–33.4)	89	13.6 (11.9–15.7)	1,847	13.6 (11.9–15.7)	11.0 (10.4–11.6)
2.5–18.4	359	18.6 (13.3–26.3)	124	9.4 (8.3–10.7)	3,040	9.4 (8.3–10.7)	8.5 (8.1–8.8)
≥18.5	129	13.4 (7.7–24.6)	31	7.4 (6.0–9.1)	1,326	7.4 (6.0–9.1)	7.0 (6.6–7.5)
Hypertension							
No	479	18.3 (13.7–24.5)	146	7.7 (6.8–8.8)	3,490	7.7 (6.8–8.8)	7.3 (7.0–7.6)
Yes	270	20.1 (13.9–29.1)	96	13.3 (11.8–14.9)	2,678	13.3 (11.9–14.9)	11.3 (10.8–11.8)

* Age-adjusted death rates are per 1,000 person-years. Eight hundred twelve patients were anti–cyclic citrullinated peptide (anti-CCP) positive, 217 patients were anti-CCP negative and used disease-modifying antirheumatic drugs (DMARDs) at baseline, 8,951 patients were anti-CCP negative and had not used DMARDs at baseline, and 122,275 never reported rheumatoid arthritis (RA). 95% CI = 95% confidence interval; CHD = coronary heart disease; SF-36 = Short Form 36; METs = metabolic equivalents.

of death. (See Supplementary Table 3 for further data on causes of death, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38268/abstract.)

Risk factors. Death rates over 10 years were substantially higher among anti-CCP–positive women who reported cigarette smoking, diabetes, less physical activity, poor health, history of CHD, or poor physical function on the Short Form 36 (31,37) (Table 4). Women who were anti-CCP positive had higher total mortality within each of these attributes as compared to women who had never reported RA or who reported a history of RA but were anti-CCP negative and were not taking DMARDs (and thus presumably did not have

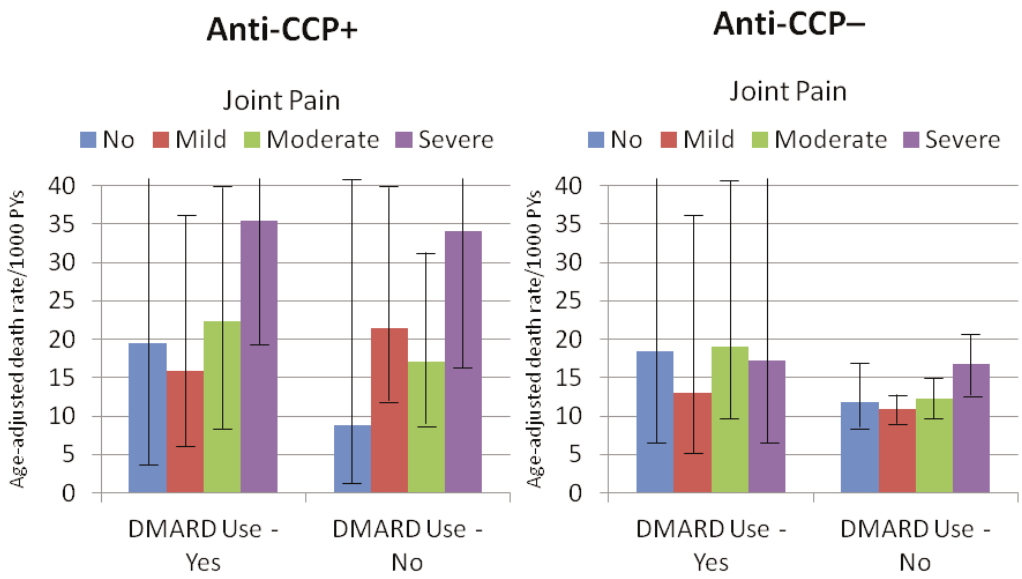

Figure 1. Age-adjusted death rates, stratified by joint pain and disease-modifying antirheumatic drug (DMARD) use, among anti–cyclic citrullinated peptide (anti-CCP)–positive women who reported rheumatoid arthritis (RA) at baseline (left) and anti-CCP–negative women who reported RA at baseline (right). Values are the mean ± SD. PY = person-years.

clinical RA). Reported health status (i.e., excellent to poor) was a very powerful predictor of mortality across all groups. Approximately 25% of anti-CCP–positive women reported poor health as compared to 7% of women who did not report RA, with death rates that were increased >4-fold for anti-CCP–positive women who reported poor health compared with women who reported excellent health and who never reported RA.

Joint pain. A positive correlation between age-adjusted death rates and joint pain reported during the 4 weeks prior to baseline interview was found, especially among anti-CCP–positive women (Figure 1). Among

Table 5. Cox proportional hazards regression model predicting total mortality among women who reported RA at baseline or at baseline and followup (weighted)*

Measurement at baseline	HR (95% CI)			
	Anti-CCP positive and DMARD use	Anti-CCP positive and no DMARD use	Anti-CCP negative and DMARD use	Anti-CCP negative and no DMARD use
Log WBC count, per 1 SD	2.9 (1.2–7.3)	2.4 (1.3–4.7)	4.3 (1.5–12.3)	1.9 (1.5–2.4)
Age, per year	1.1 (1.1–1.2)	1.1 (1.1–1.1)	1.1 (1.1–1.2)	1.1 (1.1–1.1)
Ethnicity				
Black vs. white	0.3 (0.1–0.8)	0.5 (0.3–1.0)	1.2 (0.4–3.5)	1.1 (0.9–1.3)
Hispanic vs. white	0.2 (0.0–1.3)	0.9 (0.2–3.8)	1.8 (0.9–3.8)	0.7 (0.5–1.1)
Ever smoked vs. never smoked	0.9 (0.6–1.6)	1.8 (1.0–3.0)	1.0 (1.0–1.1)	1.3 (1.1–1.5)
Hypertension, yes or no	1.0 (0.6–1.7)	1.2 (0.8–2.0)	1.4 (0.5–3.8)	1.2 (1.0–1.4)
Diabetes, yes or no	3.4 (1.4–8.4)	1.2 (0.5–2.8)	1.2 (0.5–3.2)	2.2 (1.8–2.7)
Education				
Completed college vs. high school or less	0.4 (0.2–0.7)	0.7 (0.4–1.2)	2.3 (1.0–5.6)	0.9 (0.8–1.1)
Some college vs. high school or less	0.5 (0.3–0.9)	0.8 (0.5–1.3)	1.1 (0.5–2.2)	1.1 (0.9–1.3)
Joint pain				
Mild vs. none	1.4 (0.3–7.4)	3.3 (0.7–16.1)	0.5 (0.2–1.9)	1.0 (0.7–1.3)
Moderate vs. none	1.3 (0.2–6.8)	2.3 (0.5–11.6)	0.5 (0.2–1.9)	1.0 (0.8–1.3)
Severe vs. none	3.0 (0.6–15.8)	3.6 (0.7–18.7)	0.4 (0.1–1.6)	1.3 (1.0–1.7)

* The analysis excludes women who reported rheumatoid arthritis (RA) at followup only. Of 322 anti–cyclic citrullinated peptide (anti-CCP)–positive subjects who used disease-modifying antirheumatic drugs (DMARDS), 166 died. Of 290 anti-CCP–positive subjects who did not use DMARDs, 59 died. Of 183 anti-CCP negative subjects who used DMARDs, 33 died. Of 4,566 anti-CCP–negative subjects who did not use DMARDs, 655 died. HR = hazard ratio; 95% CI = 95% confidence interval; WBC = white blood cell.

anti-CCP–positive women, severe joint pain was associated with significant 2-fold higher age-adjusted death rates versus those with no joint pain or mild joint pain. Among those with severe joint pain, death rates were much higher among anti-CCP–positive women (35.5 deaths per 1,000 person-years), as compared to anti-CCP–negative women with no DMARD use who reported RA (17.2 deaths per 1,000 person-years), women who reported arthritis but not RA (12.1 deaths per 1,000 person-years), or women who did not report arthritis (11.4 deaths per 1,000 person-years) (i.e., there was an approximate 3-fold difference across severe joint pain symptoms by anti-CCP–positive status). Furthermore, age-adjusted death rates varied significantly, over 4-fold, among women who were anti-CCP positive and had severe joint pain as compared to women with no history of arthritis and no joint pain at baseline.

Kidney function. The original WHI did not include measures of kidney function. Therefore we evaluated creatinine levels in a subset of participants (n = 789) (599 of those [76%] were positive for anti-CCP in this study). The mean ± SD creatinine level was 0.59 ± 0.20 mg/dl, with a level of 1.3 mg/dl in the 99th percentile, and creatinine levels were similar among anti-CCP–positive and anti-CCP–negative women. Age-adjusted death rates increased as blood creatinine levels increased. The percentage of deaths was higher among women with creatinine levels in the higher quartiles for both anti-CCP–positive women (15.7% in the lowest quartile versus 31.1% in the highest quartile) and for anti-CCP–negative women (20.8% in the lowest quartile versus 30.6% in the highest quartile). However, confidence limits are wide because the number of deaths in this subsample was small.

White blood cell (WBC) counts. Higher WBC counts were an independent predictor of mortality. For anti-CCP–positive women, age-adjusted death rates increased linearly and significantly from ~11.9 (95% CI 4.2–41.5) per 1,000 person-years among women with WBC counts <4.08 to 35.6 (95% CI 22.9–57.4) per 1,000 person-years among women with WBC counts >8.3 (P = <0.0001). The same was true for anti-CCP–negative women who were not exposed to DMARDs, with age-adjusted death rates of 8.7 (95% CI 6.0–12.8) per 1,000 person-years among women with WBC counts <4.08 to 19.2 (95% CI 14.9–24.8) per 1,000 person-years among women with WBC counts >8.3 (P = 0.0001). Results were similar in weighted and unweighted analyses (data not shown).

Multivariable models. In multivariable-adjusted Cox proportional hazards regression models of the total sample, probable RA was a significant predictor of mortality as compared to no history of RA (hazard ratio [HR] 2.8 [95% CI 2.2–3.5] among anti-CCP–positive women with DMARD use at baseline, 2.2 [95% CI 1.7–2.7] among anti-CCP–positive women with no DMARD use at baseline, and 1.8 [95%CI 1.4–2.5] among anti-CCP–negative women with DMARD use at baseline [data not shown]). Women who reported RA but were not likely to have RA (i.e., anti-CCP–negative women who were not receiving DMARDs) also had a significantly increased risk of total mortality (HR 1.3 [95% CI 1.2–1.4]), compared with women who did not report a history of RA.

Risk factors for mortality were then compared within categories defined by anti-CCP status and DMARD use (Table 5). Among anti-CCP–positive women who had used DMARDs at baseline, significant predictors of mortality were (log) WBC count, age, and diabetes. Among anti-CCP–positive women, HRs for severe joint pain and high WBC count were similar among those exposed to DMARDs and those not exposed to DMARDs. In contrast, among anti-CCP–negative women who used DMARDs (a small sample), joint pain severity was unrelated to mortality, although elevated WBC count remained a powerful predictor of mortality. Among anti-CCP–negative women who had not used DMARDs (i.e., women who were unlikely to have RA [the largest sample in this study]), both severe joint pain and WBC count were independent predictors of the risk of mortality (Table 5). These women likely have osteoarthritis. Results were not modified by inclusion of specific cytokine or chemokine levels or distribution of shared epitope (results not shown).

DISCUSSION

The large sample size of postmenopausal women in the WHI has provided a unique opportunity to determine the prevalence of and risk factors for mortality among women with probable RA (defined as anti-CCP positivity or use of DMARDs), women who reported RA at baseline but were not likely to have RA, women who reported other arthritis (osteoarthritis), and women who did not report any arthritis at baseline and followup. This is the first large longitudinal study to evaluate anti-CCP levels, RF levels, risk factors, and mortality.

The important result of this analysis was that anti-CCP positivity is associated with a substantial 2–2.5-fold increased risk of total mortality in multivariate models that included many risk factors and lifestyle

factors associated with mortality, and this result was statistically independent of the baseline use of DMARDs, including methotrexate. Key risk factors, such as elevated WBC count, smoking, diabetes, and fair/poor health status, increased mortality among women who were anti-CCP positive. Therefore, epidemiologic and genetic studies of RA need to distinguish between anti-CCP–positive and anti-CCP–negative RA (38).

It is possible that other unmeasured risk factors or residual confounding could explain the excess mortality associated with anti-CCP positivity. A clinical trial that specifically measures the effect of anti-CCP positivity independent of other risk factors would be necessary to prove independent effects of anti-CCP on mortality. DMARDs, such as methotrexate, or more recently biologic agents, substantially reduced symptoms and seemed to offer total (14) and cardiovascular (39,40) risk protection in observation trials. In addition, low-dose methotrexate is currently being tested in a secondary prevention trial of CHD with the presumption that the reduction in inflammation and C-reactive protein levels will reduce cardiovascular morbidity and mortality (41). When subjects were first enrolled in the WHI (1993–1997), certain biologic agents were generally not available; therefore, we have no information on the use of these new biologic agents and mortality as they pertain to this study. Possibly because of short followup and smaller sample size, no clinical trial to date has shown that these new agents decreased total mortality or CHD among RA patients, despite their great success in reducing symptoms.

Excess mortality has also been noted in other inflammatory diseases even when treatment has successfully reduced levels of important biologic markers of disease (as in well-treated human immunodeficiency virus [HIV] patients). Persistence of inflammation and secondary changes in thrombotic markers, such as D-dimer, were reported to be very strong predictors of total mortality in a well-treated population of HIV patients (42). Persistent inflammation could contribute to an increase in fibrosis in many organs, such as the heart, lung, and kidneys, as well as an increased risk of thrombogenesis and mortality (43–51). The possibility that inflammatory-type amyloid (serum amyloid A [SAA]) contributes to excess mortality should also be evaluated (52). The relationship of lipoproteins and markers of thrombosis and fibrinolysis with CHD incidence is a topic for future study. New technologies using magnetic resonance imaging and positron emission tomography imaging provide opportunities to evaluate the extent of fibrosis in different organs and amyloid deposition secondary to levels of SAA as potential contributors to excess mortality in RA. It will be important to determine whether newer therapies reduce not only morbidity but also excess mortality (53). The substantial excess mortality associated with anti-CCP positivity in combination with other risk factors supports the notion that prevention and control of risk factors among RA patients is needed.

This study has several important limitations. The WHI is not a random population-based study. The failure to identify any effect of DMARDs or methotrexate on mortality may be due, in part, to longer duration of disease prior to entry into the WHI and use of selected DMARDs for the more severe and persistent disease. Despite the large number of minority participants in the overall study sample, the number of anti-CCP–positive minority participants (n = 301) limited detailed race-specific analysis. The lower age-adjusted mortality for anti-CCP–positive black women needs further analysis in larger sample sizes of black women. Finally, the WHI was not an inception cohort of RA women. We do not know the age at onset of RA, duration of disease, or prior treatment before enrollment in the WHI. The mean age of 63 years suggests that most of the women likely had RA for 10 or more years prior to study entry. We have no information about men.

In summary, among a large sample of postmenopausal women in the WHI, self-reported RA was associated with higher mortality, but only a small fraction of these subjects had probable RA. The increased risk of death among anti-CCP–positive women was not explained by age, RF positivity, ANA positivity, or DMARD use. Traditional risk factors (e.g., smoking, diabetes), kidney disease, joint pain, health status, or WBC count also did not provide statistically significant explanations for the increased risk among anti-CCP–positive women, despite the independent associations of these risk factors with higher mortality. Further longitudinal studies of RA and clinical trials should focus on identifying the specific determinants of excess mortality, especially among the anti-CCP–positive RA population, and whether further modification of systemic inflammation and/or reduction in fibrosis and thrombogenesis will decrease mortality.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kuller had full access to all of the

data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kuller, Mackey, Walitt, Deane, Holers, Robinson, Moreland.

Acquisition of data. Kuller, Mackey, Deane, Holers, Robinson, Sokolove, Moreland.

Analysis and interpretation of data. Kuller, Mackey, Walitt, Deane, Holers, Robinson, Sokolove, Chang, Liu, Parks, Wright, Moreland.

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