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Coffee, Tea, and Caffeine Consumption and Risk of Rheumatoid Arthritis

Results From the Iowa Women's Health Study

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Objective. **To evaluate whether coffee, tea, and caffeine consumption are risk factors for rheumatoid arthritis (RA) onset among older women.**

Methods. **These factors were evaluated in a prospective cohort study that was initiated in 1986 and that included 31,336 women ages 55–69 years without a history of RA. Risk factor data were self-reported using a mailed questionnaire. Through 1997, 158 cases of RA were identified and validated against medical records. The relative risk (RR) and 95% confidence interval (95% CI) were used as the measures of association and were adjusted for age, alcohol use, smoking history, age at menopause, marital status, and the use of hormone replacement therapy.**

Results. **Compared with those reporting no use, subjects drinking ≥4 cups/day of decaffeinated coffee were at increased risk of RA (RR 2.58, 95% CI 1.63–4.06). In contrast, women consuming >3 cups/day of tea displayed a decreased risk of RA (RR 0.39, 95% CI 0.16–0.97) compared with women who never drank tea. Caffeinated coffee and daily caffeine intake were not associated with the development of RA. Multivariable adjustment for a number of potential confounders did not alter these results. The associations of RA onset with the highest categories of decaffeinated coffee consumption (RR 3.10, 95% CI 1.75–5.48) and tea consumption (RR 0.24, 95% CI 0.06–0.98) were stronger in women with seropositive disease compared with those with seronegative disease (RR 1.54, 95% CI 0.62–3.84 and RR 0.93, 95% CI 0.27–3.20, respectively).**

Conclusion. **Decaffeinated coffee intake is independently and positively associated with RA onset, while tea consumption shows an inverse association with disease onset. Further investigations of decaffeinated coffee and tea intake as arthritis risk factors are needed to verify these findings and explore their biologic basis.**

Both genetic and environmental factors are thought to be important in the pathogenesis of rheumatoid arthritis (RA). A variety of environmental risk factors have been evaluated as potential etiologic agents in RA, including cigarette smoke (1–7), exogenous estrogen use (as an oral contraceptive and as hormone replacement therapy) (1,8), and some nutrients (9–12).

Heliövaara et al recently reported an association between coffee consumption, rheumatoid factor (RF) status, and subsequent RA onset (13). In a cross-sectional survey of subjects without arthritis, the number of cups of coffee consumed daily was directly proportional to the prevalence of RF positivity. In the same study, subjects consuming ≥4 cups/day of coffee were more than twice as likely to develop seropositive RA in the course of followup compared with those drinking less than that amount. Although the specific type of coffee (caffeinated versus decaffeinated) was not specified in this provocative study, this was the first investi-

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gation to suggest an association between coffee consumption and RA.

In this report, we focus on the evaluation of coffee, tea, and caffeine consumption as potential risk factors for RA using a large, prospective cohort of older women. We specifically examine the types of coffee consumed, assessing relationships between these exposures of interest and RA onset.

PATIENTS AND METHODS

Study cohort and followup. The Iowa Women's Health Study (IWHS) is a prospective cohort study established in 1986, initially enrolling 41,836 Iowa women between the ages of 55 years and 69 years. Characteristics of this well-studied cohort have been described previously (14–17). Self-reported items on the baseline questionnaire included demographic data (race, education, marital status, usual occupation), medical history, reproductive history, anthropometrics, lifestyle factors, and dietary intake. Followup questionnaires were mailed in 1987, 1989, 1992, and 1997, and response rates for living eligible subjects were 91%, 90%, 83%, and 79%, respectively.

Assessment of coffee, tea, and caffeine intake. Coffee, tea, and caffeine intake were ascertained once at baseline in 1986 using a 127-item semiquantitative food frequency questionnaire nearly identical to that used in the Nurses' Health Study (18). Subjects were asked to report their average intake of coffee (decaffeinated and caffeinated, separately) and tea over the past year. Total coffee intake was determined by calculating the sum of daily caffeinated and decaffeinated coffee consumption. Daily caffeine intake was estimated from the average use of caffeinated coffee (136 mg/cup), tea (64 mg/cup), and cola drinks (46 mg/bottle or can) as reported on the food frequency questionnaire. This method was found to be both reliable and valid in this population. Specifically, in a prior study involving a subset of the IWHS cohort, the 3-month and 2-year test–retest levels of caffeine intake were strongly correlated ($r = 0.95$ and $r = 0.88$, respectively). The levels of self-reported caffeine intake on the initial food frequency questionnaire and the average of five 24-hour dietary recalls in a subset of the IWHS cohort were also strongly correlated ($r = 0.82$) (19).

Identification of RA cases. On the 1992 IWHS questionnaire, respondents were asked, "Have you ever been told by a doctor that you have rheumatoid arthritis?" and "If yes, age at first diagnosis?" Of the 32,336 women responding to this question, 2,487 women self-reported a new diagnosis of RA after 1986, marked that they were not sure of an RA diagnosis, or had missing data with respect to age at RA onset. On the 1997 IWHS questionnaire, respondents were asked, "Since July 1992, were you diagnosed for the first time by a doctor as having rheumatoid arthritis?" This questionnaire identified an additional 684 potential incident RA cases.

All 3,171 women (those responding "yes" or "not sure" or who answered "yes" but were missing age at onset) with potential incident RA (onset after 1986) were contacted by mail to confirm their responses, to obtain names and addresses of all physicians whom they had seen about their RA, and to obtain consent for release of their medical records. Reminder postcards were sent after the initial letter, followed by a second mailing. Nonrespondents to this supplemental questionnaire were contacted by telephone. For deceased subjects, next-of-kin were contacted.

Of the 3,171 respondents who stated they were diagnosed as having RA on either the 1992 or 1997 IWHS questionnaire, only 53 participants or next-of-kin (1.7%) could not be located. An additional 162 (5.1%) refused to participate and 70 (2.2%) responded but did not provide consent for release of medical records. A large proportion of respondents ($n = 1,659$, or 52.3%) refuted their original "yes," "not sure," or missing responses (>55% of the refuted responses were for "not sure" or missing data). This yielded an overall contact rate of 98.3% and an overall participation rate of 91.0% (2,886/3,171).

RA case validation. Medical records were requested from identified physicians to validate the diagnosis of RA for each consenting subject who confirmed his or her original self-report. Physicians were asked to complete a brief questionnaire and provide all medical, laboratory, and radiographic records pertinent to the diagnosis. Medical records were obtained for 1,186 (96.7%) of the 1,227 potential incident RA cases.

A combination of two trained reviewers, from a group including rheumatologists, rheumatology advanced practice nurses, and a rheumatology physician assistant, independently reviewed all medical records to determine RA case status using the "ever" (since cohort baseline) satisfaction of 4 of 7 American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria (20,21). Discordance between the two primary reviewers was adjudicated by a third reviewer. Although medical records were requested on all potential cases, any diagnosis of "definite RA" provided by a physician identified as a board-certified/eligible rheumatologist was also considered a validated case.

Since early clinical manifestations of RA may influence exposure patterns, we conservatively defined the date of RA onset as the first date of an RA symptom leading to the eventual satisfaction of ACR criteria or a rheumatologist's diagnosis of RA. Thus, women with RA symptom onset or diagnosis before January 1, 1987 were considered prevalent cases and were excluded from analysis. Women with self-limited polyarticular arthritis (i.e., viral arthritis) or alternative diagnoses such as gout were also excluded. Review of these 1,186 sets of records resulted in 158 validated RA cases. Clinical characteristics of the 158 validated cases were obtained from medical record reviews and questionnaires completed by the respondents' physicians.

Data analysis. From the original cohort, we excluded women who did not complete either the 1992 or 1997 followup questionnaires due to death or nonresponse ($n = 6,201$), or who reported that they had been diagnosed as having RA and gave a diagnosis date of before January 1, 1987 ($n = 2,102$; no attempt at validation). This left 30,362 women who reported no history of RA on the 1992 and/or the 1997 questionnaires. Women who marked "not sure" of an RA diagnosis on the 1992 questionnaire but who reported "no" to RA questions on further investigation ($n = 816$) were also included in the at-risk cohort. Thus, the final analysis cohort ($n = 31,336$) included women with no history of RA ($n = 30,362$), women who were

added back to the cohort (n = 816), and women who had validated RA (n = 158). Each woman accumulated person-years of followup from the date of receipt of the 1986 baseline questionnaire to the date of RA symptom onset or until September 30, 1992 (for women who died after this date or who did not respond to the 1997 questionnaire) or August 31, 1997 (for the remaining women).

Statistical methods. Subjects reporting physiologically implausible values for daily caloric intake (>5,000 kcal/day or <600 kcal/day) and those with ≥30 missing responses on the food frequency questionnaire were excluded from analysis (6 cases and 1,810 noncases). Based on the possible responses to the survey questionnaire, coffee use (caffeinated, decaffeinated, and total) was a priori categorized into no regular use, ≤1 cup/day, 2–3 cups/day, and ≥4 cups/day. Tea use was similarly categorized into no regular use, <0.6 cup/day, 0.6–3.0 cups/day, and >3.0 cups/day (0.6 cup/day corresponds to a survey response of 4 cups/week). Caffeine intake was categorized into quartiles of daily use. Risk ratios (RRs), 95% confidence intervals (95% CIs), and trend tests (categorical variable modeled as a continuous variable) were used to describe associations between coffee, tea, and caffeine consumption and risk of RA, and were estimated using Cox proportional hazards regression (22). All analyses were adjusted for age.

Multivariable models were constructed to determine the impact of potentially confounding variables on the association between coffee (regular, decaffeinated, and total), tea, and caffeine consumption and RA incidence. Variables included in the multivariable models were those previously associated with RA in this cohort and included age, marital status (currently married, separated/divorced, widowed, never married), smoking history (never, former/<20 pack-years, former/≥20 pack-years, current/<20 pack-years, current/≥20 pack-years), alcohol use (none, <3 gm/day, ≥3 gm/day), age at menopause, and the use of hormone replacement therapy (never, former, current). Subgroup analyses were performed to examine associations between the same predictor variables and the development of RF-positive and RF-negative disease. Additionally, to eliminate the potential confounding effect of tobacco use, we repeated our analysis after eliminating women with any history of smoking. All analyses were conducted using SAS for Windows, version 8.0 (SAS Institute, Cary, NC).

RESULTS

During 334,463 person-years of observation of the 31,336 women in the cohort with no history of RA in 1986, 158 women developed incident RA that met our validation criteria. Concordance between the two primary reviewers for case validation prior to consensus or adjudication was 90.6%. RA diagnosis was based either on cumulative satisfaction of ACR RA criteria (n = 146, 92.4% of total cases) and/or on diagnosis by a respondent's rheumatologist (n = 139, 88.0% of total cases). The noncases included 31,178 IWHS subjects. Table 1 summarizes the demographic and other relevant characteristics of RA cases and noncases at baseline. With the exception of smoking history and marital status, there were no striking differences in these baseline characteristics between the two groups.

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

	RA cases (n = 158)	Non-RA cases (n = 31,178)
Age, mean ± SD years	61.1 ± 3.9	61.5 ± 4.2
Age at menopause, mean ± SD years	46.3 ± 7.0	47.7 ± 6.4
Body mass index, mean ± SD kg/m^2	26.8 ± 4.6	26.8 ± 4.9
White race, %	99.4	99.4
Marital status, %		
Currently married	85.5	78.2
Separated/divorced	4.4	4.1
Widowed	7.6	15.2
Never married	2.5	2.5
Education, %		
Not high school graduate	14.6	17.2
High school graduate	45.6	41.8
Vocational education/ some college	27.8	27.2
College graduate or more	12.0	13.8
Place of residence, %		
Farm	16.6	19.8
Rural area or city with population of <2,499	31.2	28.7
City with population of 2,500–10,000	17.8	17.2
City with population of >10,000	34.4	34.3
Alcohol use, %		
Never	54.0	53.3
<3 gm/day	19.7	22.0
≥3 gm/day	26.3	24.7
Any use of coffee, %	67.1	69.2
Hormone replacement therapy use, %		
Never	54.4	61.2
Former	34.8	27.3
Current	10.8	11.5
Any oral contraceptive use, %	19.2	20.2
Smokers, %		
Never	57.1	67.0
Former	20.8	19.4
Current	22.1	13.6

* RA = rheumatoid arthritis.

Table 2 displays the clinical characteristics of the 158 validated RA cases. The mean age at onset was 68 years. Nearly 90% of the cases were seen by a rheumatologist. Approximately 60% of cases had seropositive disease, while RF status was unknown in 7.6% (12 cases). The mean elapsed time between the baseline survey and RA symptom onset was 6.1 ± 3.0 years (data not shown).

Table 3 summarizes the major results of this study. Using our a priori consumption cutpoints, caffeinated coffee, total coffee, and daily caffeine intake were not associated with the development of RA. There was a modest inverse correlation between caffeinated and decaffeinated coffee consumption (r = −0.32). There

Table 2. Clinical characteristics of validated RA cases*

	All cases (n = 158)	RF+ (n = 97)	RF− or unknown (n = 61)†
Age at onset, mean ± SD years	67.8 ± 4.9	67.4 ± 4.7	68.4 ± 5.1
Time from onset to diagnosis, mean ± SD months	13.4 ± 2.17	14.4 ± 23.6	11.9 ± 18.4
ACR criteria satisfied, mean ± SD	4.6 ± 1.1	5.0 ± 0.9	4.0 ± 1.2
With rheumatoid nodules, %	14.2	16.6	10.2
With radiographic bone erosions, %	49.7	46.9	54.2
With RA diagnosed by a rheumatologist, %	89.7	87.6	93.2
Cumulative use of RA medications, %			
Nonsteroidal antiinflammatory drugs	97.4	100.0	93.2
Oral glucocorticoids	66.4	62.5	72.9
Methotrexate	51.0	50.0	52.5
Hydroxychloroquine	51.0	51.0	50.8
Intraarticular glucocorticoids	37.4	39.6	33.9

* RF = rheumatoid factor; ACR = American College of Rheumatology (see Table 1 for other definitions).
† Includes 12 cases with unknown RF status.

was a positive association between decaffeinated coffee use and RA risk. Compared with those reporting no decaffeinated coffee use, subjects drinking ≥4 cups/day of decaffeinated coffee were at increased risk of RA (RR 2.58, 95% CI 1.63–4.06). In contrast, there was an inverse association with tea use. Compared with women reporting no tea use, women drinking >3 cups/day of tea were at a decreased risk of RA (RR 0.39, 95% CI 0.16–0.97). Simultaneous inclusion of decaffeinated coffee and tea intake in the same multivariable model did not change the magnitude of the estimated risks (RR 2.40, 95% CI 1.49–3.86 and RR 0.37, 95% CI 0.14–1.03

Table 3. Relative risks (RRs) and 95% confidence intervals (95% CIs) for associations of rheumatoid arthritis with intake of coffee (decaffeinated, caffeinated, and total), tea, and caffeine, Iowa Women's Health Study, 1986–1997

			Age adjusted			Multivariable adjusted*		
Nutrient	Cases	Person-years	RR	95% CI	*P* trend	RR	95% CI	*P* trend
Total coffee, cups/day								
None	13	32,390	1.00	Referent		1.00	Referent	
≤1	37	79,763	1.16	0.62–2.18		1.39	0.68–2.82	
2–3	28	64,984	1.04	0.54–2.01		1.10	0.52–2.32	
≥4	74	137,044	1.34	0.74–2.42	0.27	1.56	0.80–3.06	0.21
Caffeinated coffee, cups/day								
None	48	92,028	1.00	Referent		1.00	Referent	
≤1	49	87,740	1.07	0.72–1.60		1.23	0.80–1.88	
2–3	26	76,291	0.63	0.39–1.02		0.72	0.43–1.20	
≥4	29	58,122	0.95	0.60–1.51	0.30	0.98	0.60–1.61	0.46
Decaffeinated coffee, cups/day								
None	56	133,816	1.00	Referent		1.00	Referent	
≤1	43	99,530	1.05	0.71–1.57		1.13	0.74–1.72	
2–3	25	54,430	1.12	0.70–1.80		1.11	0.67–1.84	
≥4	28	26,405	2.58	1.63–4.06	0.001	2.44	1.52–3.89	0.003
Tea, cups/day								
None	64	131,972	1.00	Referent		1.00	Referent	
<0.6	42	83,900	1.01	0.68–1.49		1.09	0.73–1.63	
0.6–3.0	41	71,841	1.18	0.80–1.75		1.23	0.81–1.87	
>3.0	5	26,468	0.39	0.16–0.97	0.43	0.35	0.13–0.97	0.50
Caffeine, mg/day								
<29.1	42	78,219	1.00	Referent		1.00	Referent	
29.2–153.7	46	78,393	1.09	0.72–1.66		1.28	0.81–2.01	
153.8–376.5	27	78,794	0.61	0.38–0.99		0.69	0.41–1.17	
>376.5	37	78,775	0.87	0.56–1.35	0.18	0.94	0.58–1.52	0.33

* Adjusted for age, marital status, smoking history, alcohol use, age at menopause, and use of hormone replacement therapy.

Table 4. Potential confounding factors for the association of rheumatoid arthritis with decaffeinated coffee consumption*

	Decaffeinated coffee consumption, cups/day			
	None	≤1	2–3	≥4
Age, mean ± SD years	61.2 ± 4.2	61.6 ± 4.2	61.5 ± 4.2	60.7 ± 4.0
Age at menopause, mean ± SD years	47.6 ± 6.4	48.0 ± 6.2	47.8 ± 6.3	47.4 ± 6.6
Body mass index, mean ± SD kg/m^2	26.8 ± 5.0	26.7 ± 4.8	26.8 ± 4.7	26.7 ± 4.9
Marital status, %				
Currently married	78.1	77.9	80.7	81.2
Separated/divorced	14.7	15.4	14.1	13.5
Widowed	4.5	4.1	3.1	3.8
Never married	2.7	2.6	2.1	1.5
Education, %				
Not high school graduate	17.3	14.1	15.5	17.2
High school graduate	42.9	40.9	41.9	43.0
Vocational education/some college	27.0	28.6	28.1	28.0
College graduate or more	12.8	16.4	14.5	11.8
Place of residence, %				
Farm	20.3	20.0	19.5	16.8
Rural area or city with population of <2,499	29.0	28.1	26.8	29.7
City with population of 2,500–10,000	16.9	17.1	17.3	18.3
City with population of >10,000	33.8	34.8	36.4	35.2
Alcohol use, %				
Never	56.8	53.7	48.6	44.3
<3 gm/day	19.6	23.1	24.6	24.0
≥3 gm/day	23.6	23.2	26.8	31.8
Smokers, %				
Never	64.8	72.6	66.9	53.6
Former	18.4	18.4	22.1	25.3
Current	16.8	9.0	11.0	21.1
Hormone replacement therapy use, %				
Never	62.8	59.7	59.6	59.9
Former	11.2	12.5	11.2	11.7
Current	26.0	27.9	29.2	28.4
Any oral contraceptive use, %	19.1	19.8	20.3	20.8

* Differences in means and proportions across levels of decaffeinated coffee consumption are significant ($P < 0.05$) for all variables except body mass index and oral contraceptive use.

for the highest category of decaffeinated coffee and tea intake, respectively). Of note, there was no correlation between decaffeinated coffee and tea intake ($r = -0.04$). Additionally, for both decaffeinated coffee and tea use, there was no clear evidence of a dose response; instead, the adverse risk or protective effect appeared to be confined to the highest category of decaffeinated coffee and tea intake, respectively.

Using the published coffee consumption cut-points (≤3 cups/day and ≥4 cups/day) proposed by Heliövaara et al (13), and adjusting for multiple potential confounders, we again reexamined the associations of caffeinated, decaffeinated, and total coffee intake with RA. As in our prior analysis, a higher intake of caffeinated coffee was not associated with disease onset (RR 1.04, 95% CI 0.69–1.56). Subjects consuming ≥4 cups/day of decaffeinated coffee were at increased risk (RR 2.48, 95% CI 1.64–3.74) compared with those drinking less. However, in contrast to our initial analysis, subjects in the highest category of total coffee intake were at greater risk for RA onset (RR 1.55, 95% CI 1.11–2.15) compared with those drinking less.

Table 4 shows the distribution of potential confounding variables across 4 levels of decaffeinated coffee intake. There were few notable associations, except that women who drank greater amounts of decaffeinated coffee were also more likely to use alcohol and to be current smokers. Multivariable adjustment for age, marital status, smoking history, age at menopause, and the use of hormone replacement therapy did not alter our primary findings (Table 3). The association of decaffeinated coffee and tea intake with RA remained robust even after the simultaneous addition of oral contraceptive use, daily caloric intake, education, occupation, body mass index, and place of residence to the model (data not shown). When we confined the analysis to those who had never smoked, our results were again unchanged. Specifically, those who had never smoked

Table 5. RRs and 95% CIs for the development of RF-positive and RF-negative rheumatoid arthritis, Iowa Women's Health Study, 1986–1997*

		Age adjusted			Multivariable adjusted†		
	Cases	RR	95% CI	*P* trend	RR	95% CI	*P* trend
RF-positive subjects (n = 94)							
Decaffeinated coffee, cups/day							
None	31	1.00	Referent		1.00	Referent	
≤1	28	1.22	0.73–2.03		1.25	0.74–2.11	
2–3	16	1.27	0.70–2.32		1.25	0.68–2.33	
≥4	19	3.10	1.75–5.48	0.001	2.64	1.46–4.79	0.006
Tea, cups/day							
None	42	1.00	Referent		1.00	Referent	
<0.6	25	0.94	0.57–1.54		1.06	0.64–1.76	
0.6–3.0	25	1.10	0.67–1.80		1.20	0.72–2.02	
>3.0	2	0.24	0.06–0.98	0.26	0.26	0.06–1.09	0.43
RF-negative subjects (n = 47)‡							
Decaffeinated coffee, cups/day							
None	21	1.00	Referent		1.00	Referent	
≤1	14	0.94	0.47–1.85		1.04	0.51–2.14	
2–3	6	0.74	0.30–1.83		0.71	0.26–1.92	
≥4	6	1.54	0.62–3.84	0.77	1.63	0.64–4.12	0.68
Tea, cups/day							
None	16	1.00	Referent		1.00	Referent	
<0.6	15	1.37	0.67–2.81		1.32	0.64–2.76	
0.6–3.0	13	1.49	0.71–3.09		1.36	0.63–2.94	
>3.0	3	0.93	0.27–3.20	0.55	0.67	0.15–2.91	0.86

* See Tables 2 and 3 for definitions.
† Adjusted for age, marital status, smoking history, alcohol use, age at menopause, and use of hormone replacement therapy.
‡ Subjects excluded from the analysis included 12 with unknown RF status, those reporting extreme values for total daily energy intake, and/or those with ≥30 missing responses on the food frequency questionnaire. Excluded subjects included 3 who were RF-positive and 2 who were RF-negative (1 patient with unknown RF status also had ≥30 missing questionnaire responses).

and who were in the highest category of decaffeinated coffee use were at increased risk of RA incidence (RR 2.52, 95% CI 1.32–4.83) compared with women reporting no regular decaffeinated coffee intake.

Associations between decaffeinated coffee consumption, tea intake, and the development of RF-positive and RF-negative disease are summarized in Table 5. Women in the highest category of decaffeinated coffee consumption were at substantially increased risk of developing seropositive disease (RR 3.10, 95% CI 1.75–5.48). This association remained significant after adjustment for multiple potential confounders. Women in the highest category of tea intake (RR 0.24, 95% CI 0.06–0.98) were at decreased risk of RF-positive RA, an association that changed little with multivariable adjustment. In contrast, RRs for the development of seronegative disease in the highest categories of decaffeinated coffee and tea use were nonsignificant (RR 1.54, 95% CI 0.62–3.84 and RR 0.93, 95% CI 0.27–3.20, respectively).

DISCUSSION

In this prospective cohort study of older women, the consumption of decaffeinated coffee was independently and positively associated with an increased risk for the development of RA, while tea intake was inversely associated with disease onset. The magnitude of the association between decaffeinated coffee intake and RA, as well as between tea consumption and RA, was even more pronounced in the development of seropositive disease. Our results do not support an association between caffeinated coffee or caffeine intake and the development of RA. Strengths of this study include the prospective cohort design, rigorous case validation using ACR criteria, community setting, and validated assessment of our exposure variables.

In their recent Finnish cohort study of RA onset (13), Heliövaara and colleagues reported an increased risk of RA (RF-positive and RF-negative cases combined) among individuals who consumed ≥4 cups/day of coffee (RR 1.69, 95% CI 1.02–2.80). Using the same coffee consumption cutpoints (≤3 cups/day and ≥4 cups/day) as Heliövaara et al, we found a similar association between higher levels of total daily coffee consumption and RA onset (RR 1.55, 95% CI 1.11–2.15).

In contrast to the Finnish cohort study, we examined the effects of decaffeinated and caffeinated coffee

separately. Using these same cutpoints (≤3 cups/day and ≥4 cups/day), we found no evidence of an association between caffeinated coffee intake and RA, suggesting that in our study the association of total coffee intake with RA onset is primarily explained by decaffeinated coffee use. Anecdotal reports suggest that the prevalence of decaffeinated coffee consumption is low in Finland (23), and is therefore unlikely to explain the results reported by Heliövaara and colleagues. It is not known whether the presence or absence of caffeine per se explains the increased risk observed with coffee consumption in these two studies, as opposed to a by-product related to the preparation and/or processing of the coffee products consumed by study subjects. For example, diterpene cafestol, which is found in relatively high concentrations in unfiltered coffee brews (a preparation technique common in Finland) (13), has been associated with high serum cholesterol levels (24). Heliövaara et al (13) suggest that diterpene cafestol may play an etiologic role in RA based on the associations of coffee intake with both RF production and hyperlipidemia found in their study. The frequency with which the IWHS subjects used unfiltered coffee preparations, and whether the frequency of such use differed by coffee types, is not known.

In the Finnish study, daily coffee intake significantly predicted the development of RF-positive (RR 2.2, 95% CI 1.13–4.27), but not RF-negative, disease. In examining the effect of both decaffeinated coffee and tea intake, we similarly observed more pronounced associations with seropositive disease compared with those seen with seronegative disease. The stronger association seen in seropositive RA may reflect more severe disease (25) or perhaps a diagnosis less subject to misclassification.

Although there are no known mechanisms that explain the associations between RA risk and exposures to tea and decaffeinated coffee, there are epidemiologic data that may provide some insight. Prior to the mid-1970s (the time period coinciding with this cohort's exposure), the primary method of extracting caffeine from coffee involved the direct application of industrial solvents. Over the last century, chemicals used for this purpose have included benzene, trichloroethylene, carbon tetrachloride, acetone, ammonium hydroxide, sulfuric acid, ethyl acetate, and methylene chloride (26). While solvent residues are normally reduced to trace levels by steaming the coffee beans, it is conceivable that chronic ingestion of even small amounts could have a negative biologic effect on humans. Many of these solvents have been implicated in a number of connective tissue diseases, including scleroderma, undifferentiated connective tissue disease, lupus, and RA (27). Tea, in contrast to coffee brews, displays both antiinflammatory and antioxidant properties (28). Antioxidants have been shown to impart a protective effect against RA onset in two separate case–control studies (9,10).

There are potential limitations to this study. We assessed dietary measures, including coffee and tea intake, in the entire study cohort only once, at the time of the 1986 baseline survey. While this methodology was shown to be valid and reliable over the short term (19), a single measurement may not accurately estimate cumulative consumption (29) or variations in coffee consumption over a person's lifetime. In this cohort, coffee consumption accounted for 79% of all caffeine intake (15). The high correlation of baseline caffeine intake with later levels of intake in an IWHS validation substudy (19) suggests that our single measurement of coffee consumption at least mirrored subsequent levels of use.

Our study cohort included elderly, predominantly white women with elderly onset RA from a well-defined geographic region. While restricting our study to elderly white women from one geographic area may limit the generalizability of our results, this cohort provides unique insight into the potential role of environmental exposures in the demographic group (elderly women) most commonly affected by RA.

Another potential weakness relates to the fact that we did not have the opportunity to clinically examine each RA case. However, our rigorous case validation methods, including high participation rates by respondents and physicians, as well as the requirement that all cases meet ACR criteria based on medical record review and/or confirmation by a board-certified rheumatologist, make it very unlikely that we have incorrectly classified subjects as RA cases. Concordant with the high proportion of cases confirmed by a rheumatologist (89%), most validation studies of diagnostic criteria use subspecialist report as the gold standard (30,31). Although it is possible that individuals with milder RA or those not seeking medical attention may have gone unrecognized, the extremely large number of noncases in the comparison group makes false negatives a substantially less important concern for this epidemiologic analysis.

Finally, it cannot be concluded with certainty that the associations between decaffeinated coffee consumption, tea intake, and RA are due directly to the exposures of interest or to some other unknown confounding factor (or factors) closely associated with their use. In prior epidemiologic investigations, both male sex and

cigarette smoking have been found to be significantly associated with coffee consumption (32). Our cohort selection and the results of our subgroup analysis of those who had never smoked indicate that these were not significant codeterminants of the observed associations. In other investigations, decaffeinated coffee consumption has been linked to lower body mass index and a high intake of cruciferous vegetables (33). In separate analyses, we found no significant associations between these variables and the development of RA (data not shown).

In summary, we present evidence that decaffeinated coffee intake is significantly and positively associated with RA onset among elderly women, while tea intake shows an inverse association. Given the economic and health-related impact of RA, coupled with the global popularity of coffee and tea, these findings have potential public health implications. Future investigations of coffee and tea as potential RA risk factors are required to verify and further explore the biologic basis of our findings. Based on our results, consumption of tea and decaffeinated coffee should be considered possible disease determinants in future research focused on RA etiology.

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REFERENCES

1. Vessey M, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking, and other factors in relation to arthritis. Contraception 1987;35:457–64.
2. Uhlig T, Hagen K, Kvien T. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. J Rheumatol 1999;26:47–54.
3. Symmons DPM, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DGI, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case control study in Norfolk, England. Arthritis Rheum 1997;40:1955–61.
4. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis: results from a nationwide study of disease-discordant twins. Arthritis Rheum 1996;39:732–5.
5. Saag KG, Cerhan J, Merlino L, Criswell LA, Mikuls T, Burma M, et al. Cigarette smoking and risk of elderly onset rheumatoid arthritis: results from the Iowa Women's Health Study [abstract]. Arthritis Rheum 2000;43 suppl 9:S167.
6. Karlson EW, Lee I-M, Cook NR, Manson JE, Buring JE, Hennekens CH. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. Arthritis Rheum 1999;42:910–7.
7. Heliövaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. J Rheumatol 1993;20:1830–5.
8. Merlino LA, Cerhan JR, Criswell LA, Saag KG. Female reproductive factors and the risk of elderly onset rheumatoid arthritis [abstract]. Arthritis Rheum 2000;43 suppl 9:S134.
9. Comstock G, Burke A, Hoffman S, Helzlsouer K, Bendich A, Masi A, et al. Serum concentrations of alpha tocopherol, beta carotene, and retinol preceding the diagnosis of rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis 1997;56:323–5.
10. Heliövaara M, Knekt P, Aho K, Aaran R-K, Alfthan G, Aromaa A. Serum antioxidants and risk of rheumatoid arthritis. Ann Rheum Dis 1994;53:51–3.
11. Linos A, Kaklamanis E, Kontomerkos A, Koumantaki Y, Gazi S, Vaiopoulos G, et al. The effect of olive oil and fish consumption on rheumatoid arthritis: a case control study. Scand J Rheumatol 1991;20:419–26.
12. Van de Laar M, van der Korst J. Rheumatoid arthritis, food, and allergy. Semin Arthritis Rheum 1991;21:12–23.
13. Heliövaara M, Aho K, Knekt P, Impivaara O, Reunanen A, Aromaa A. Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis. Ann Rheum Dis 2000;59:631–5.
14. Folsom A, Kaye S, Prineas R, Potter J, Gapstur S, Wallace R. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am J Epidemiol 1990;131:794–803.
15. Folsom A, McKenzie D, Bisgard K, Kushi L, Sellers T. No association between caffeine intake and postmenopausal breast cancer incidence in the Iowa Women's Health Study. Am J Epidemiol 1993;138:380–3.
16. Folsom A, Mink P, Sellers T, Hong C, Zheng W, Potter J. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. Am J Public Health 1995;85:1128–32.
17. Bisgard K, Folsom A, Hong C, Sellers T. Mortality cancer rates in nonrespondents to a prospective study of older women: 5-year follow-up. Am J Epidemiol 1994;139:990–1000.
18. Willett W, Sampson L, Browne M, Stampfer M, Rosner B, Hennekens C, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127: 188–99.
19. Munger R, Folsom A, Kushi L, Kaye S, Sellers T. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. Am J Epidemiol 1992;136:192–200.
20. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
21. MacGregor A, Silman A. A reappraisal of the measurement of disease occurrence in rheumatoid arthritis. J Rheumatol 1992;19: 1163–5.
22. Cox D. Regression models and life tables (with discussion). J R Stat Soc B 1972;34:187–220.
23. Heliövaara M, Aho K, Knekt P, Reunanen A, Aromaa A. Coffee or decaf [letter]? Ann Rheum Dis 2001;60:87.
24. De Roos B, Katan M. Possible mechanisms underlying the cholesterol-raising effect of the coffee diterpene cafestol. Curr Opin Lipidol 1999;10:41–5.
25. Van Zeben D, Hazes J, Zwinderman A, Cats A, van der Voort E, Breedveld F. Clinical significance of rheumatoid factors in early rheumatoid arthritis: results of a follow up study. Ann Rheum Dis 1992;51:1029–35.
26. Ramalakshmi K, Raghavan B. Caffeine in coffee: its removal. Why and how? Crit Rev Food Sci Nutr 1999;39:441–56.

27. Garabrant D, Dumas C. Epidemiology of organic solvents and connective tissue disease. Arthritis Res 2000;2:5–15.
28. Yang C, Wang Z. Tea and cancer. J Natl Cancer Inst 1993;85: 1038–49.
29. Hughes J, Oliveto A. A systematic survey of caffeine intake in Vermont. Exp Clin Psychopharmacol 1997;5:393–8.
30. Hernandez-Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, et al. Exogenous sex hormones and the risk of rheumatoid arthritis. Arthritis Rheum 1990;33:947–53.
31. MacGregor A, Bamber S, Silman A. A comparison of the performance of different methods of disease classification for rheumatoid arthritis: results of an analysis from a nationwide twin study. J Rheumatol 1994;21:1420–6.
32. Schreiber G, Robins M, Maffeo C, Masters M, Bond A, Morganstein D. Confounders contributing to the reported associations of coffee or caffeine with disease. Prev Med 1988;17:295–309.
33. Leviton A, Allred E. Correlates of decaffeinated coffee choice. Epidemiology 1994;5:537–40.