

Arthritis as a Risk Factor for Incident Coronary Heart Disease in Elderly Japanese-American Males

The Honolulu Heart Program

Mitsumasa Kishimoto, M.D., Ph.D., Jeffrey Greenberg, M.D., M.P.H., Ryan Lee, B.S., Kamal H. Masaki, M.D., Randi Chen, M.S., Beatriz L. Rodriguez, M.D., Ph.D., Patricia L. Blanchette, M.D., M.P.H., Michael H. Pillinger, M.D., and J. David Curb, M.D.

Abstract

Background: Arthritis is the most common chronic disease in the elderly. Studies show that rheumatoid arthritis is a risk factor for cardiovascular morbidity and mortality, and osteoarthritis is associated with an unfavorable cardiovascular risk factor profile.

Methods: At the Honolulu Heart Program's fourth examination in 1991 to 1993, arthritis status was assessed among a cohort of 3741 Japanese-American males, ages 71 to 93 years. Arthritis was determined by self-report of physician diagnosis, and subjects were divided into two groups: current arthritis and no current arthritis. Eight years of follow-up data are available for incident coronary heart disease (CHD) in 2777 subjects free of CHD at baseline. Age-adjusted rates of incident CHD and means of cardiovascular risk factors were compared in each group. Cox proportional hazards models were used to calculate

relative risks, adjusting for common cardiovascular risk factors, alcohol, and use of aspirin or NSAIDs, or both.

Results: There were 279 cases of incident CHD in the cohort over 8 years; in those with arthritis, 11.7% developed incident CHD, compared to 9.8% in those without arthritis ($p = 0.24$). Age-adjusted rates of incident CHD in those with and without arthritis were 20.5 and 18.0 per 1000 person-years, respectively ($p = 0.25$). Arthritis was not significantly associated with CHD risk factors. Arthritis was not a significant independent predictor of incident CHD (relative risk, 1.06; 95% CI, 0.74 to 1.51).

Conclusions: Arthritis, and most probably osteoarthritis, may not be associated with most CHD risk factors or 8-year incident CHD in elderly Japanese-American males.

Mitsumasa Kishimoto, M.D., Ph.D., is from the Division of Rheumatology, NYU School of Medicine, NYU Hospital for Joint Diseases, New York, New York, and the Department of Rheumatology, Kameda Medical Center, Kamogawa, Chiba, Japan. Jeffrey Greenberg, M.D., M.P.H., is from the Division of Rheumatology, NYU School of Medicine, NYU Hospital for Joint Diseases, New York, New York. Ryan Lee, B.S., is from the Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii. Kamal H. Masaki, M.D., Patricia L. Blanchette, M.D., M.P.H., and J. David Curb, M.D., are from the Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawaii, and the Honolulu Heart Program, Kuakini Medical Center, Honolulu, Hawaii. Randi Chen, M.S., and Beatriz L. Rodriguez, M.D., Ph.D., are from the Honolulu Heart Program, Kuakini Medical Center, Honolulu, Hawaii. Michael H. Pillinger, M.D., is from the Division of Rheumatology, NYU School of Medicine, NYU Hospital for Joint Diseases, New York, New York.

Correspondence: Mitsumasa Kishimoto, M.D., Kameda Medical Center, 929 Higashicho Kamogawa city, Chiba, Japan 296-8602; kishimotomitsumasa@yahoo.co.jp.

Arthritis is one of the most prevalent diseases in the elderly population, and the most frequent cause of disability in the United States.^{1,2} Several studies suggest rheumatoid arthritis (RA) increases the risk of coronary heart disease (CHD) and CHD-related death.³⁻⁹ Osteoarthritis (OA), the most common joint disease in the United States and globally,¹⁰ has also been associated with an unfavorable cardiovascular risk profile. In addition, studies suggest patients with OA may be at increased risk of developing CHD.¹¹⁻¹⁴ However, studies also suggest this risk is higher in patients with RA than OA. There are few published data on arthritis as an independent risk factor for incident CHD. The objective of our study was to assess the relationship of self-reported arthritis status and incident CHD in a large cohort of elderly Japanese-American males who were part of the Honolulu Heart Program longitudinal cohort.

Materials and Methods

Study Population

The Honolulu Heart Program is a long-term prospective epidemiological study of cardiovascular disease. The original

cohort consisted of 8006 Japanese-American males living on the island of Oahu, Hawaii, in 1965, who were recruited using the World War II Selective Service Registration file. Details on the selection process of this cohort were previously published by Worth and Kagan in 1970.¹⁵ Eligible males were born between 1900 and 1919 (ages 45 to 68 years at the first examination in 1965 to 1968).¹⁶ The entire cohort has undergone a total of eight examinations, occurring in 1965, 1968, 1971, 1991, 1994, 1997, 1999, and 2001. This study was approved by the Institutional Review Board of Kuakini Medical Center. Procedures followed were in accordance with institutional guidelines and written informed consent was obtained from all participants.

This report is based on data obtained from the fourth examination of the cohort conducted from 1991 to 1993. At the fourth examination, 3741 males aged 71 to 93 years were assessed (80% of survivors). Of these, 1085 were ages 71 to 74; 1529 were ages 75 to 79; 707 were ages 80 to 84; and 420 were ages 85 to 93 years. Eighty-five percent of the examinations were performed at the Honolulu Heart Program clinic (n = 3192). A significant percentage of examinations were conducted at home (n = 489, or 13% of those examined) or at a nursing home (n = 60, or 1.6% of those examined).¹⁷

Data Collection

The fourth examination included demographic information, psychosocial and medical interviews, cognitive function testing, a 12-lead electrocardiogram, a pulmonary function test, anthropometry, blood pressure measurements, and fasting blood and 2-hour oral glucose tolerance tests.

Morbidity and mortality surveillance was conducted by the monitoring of hospital records from all Oahu hospitals, review of obituaries in local newspapers, the medical examiner's office, and death certificates. Medical records for all deaths and selected morbidity outcomes (including CHD) were reviewed by a trained physician panel using standardized criteria, and a final diagnosis was assigned. Data collection is believed to be essentially complete for surveillance outcomes. Attrition for this cohort is very low; at the fourth examination, only five males were lost to follow-up.

Measurement of Arthritis Status

The medical interview included questions about several diseases, including arthritis. Subjects were asked whether they had ever been hospitalized for or had a physician tell them they had arthritis. Arthritis was defined as any type of arthritis, but data are not available for specific types. Possible responses included: no arthritis, current arthritis under medical care, current arthritis not under medical care, or arthritis only in the past.

Definition of Incident Coronary Heart Disease

Incident CHD was defined as new angina pectoris, definite myocardial infarction, percutaneous transluminal catheter angioplasty or coronary artery bypass graft surgery, and

CHD death or sudden death within one hour. For this report, data on incident CHD were available through December 1998 (8-year follow-up after the fourth examination).

Definition of Other Key Variables

Covariates were selected because of their potential relationship with either arthritis or with incident CHD. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Physical Activity Index (PAI) was based on the method used in Framingham and the Honolulu Heart Program,¹⁸ which consists of multiplying the approximate oxygen consumption of five different levels of activity with the reported number of hours a day engaged in activity. Hypertension was defined as systolic blood pressure 140 mmHg or greater, or diastolic blood pressure 90 mmHg or greater, or taking anti-hypertensive drugs. Diabetes mellitus was defined by modified American Diabetes Association criteria (1997), as fasting glucose greater or equal to 126 mg/dL, or 2-hour post-load glucose greater or equal to 200 mg/dL, or taking medications (insulin or oral hypoglycemics).¹⁹ Current smoking status and alcohol consumption (ounces per month) were determined by self-report. Use of aspirin (ASA) or a nonsteroidal anti-inflammatory drug (NSAID), or both, was determined by direct observation; participants were instructed to bring in all medications taken during the previous 2 weeks.

At the fourth examination, blood specimens were taken by venipuncture after an overnight fast of at least 12 hours. Procedures for taking and preparing blood specimens for laboratory analysis were standardized by guidelines of the lipid standardization laboratory of the Centers for Disease Control and Prevention (CDC, Atlanta, Georgia). Lipid concentrations were measured as part of the Cooperative Lipoprotein Phenotyping Study at the University of Vermont.²⁰ Plasma fibrinogen concentrations were measured with a clot-based end point using a BBL fibrometer (Becton-Dickinson, Baltimore, Maryland).²¹

Data Analysis

Data on arthritis were available for 3614 subjects (97% of those examined). Those with arthritis only in the past (n = 82) and prevalent cases of CHD at the fourth examination (n = 755) were excluded, leaving 2777 subjects with current arthritis free of CHD at baseline for this analysis. Subjects were divided into two groups: those with current arthritis and those without current arthritis, as defined above. Age-adjusted means of cardiovascular risk factors were compared in those with and without current arthritis using ANOVA (analysis of variance) for continuous variables. Chi-square tests were used for categorical variables. Unadjusted and age-adjusted rates of incident CHD, expressed per 1000 person-years of follow-up, were calculated according to current arthritis status.

We assessed the association between current arthritis status and incident CHD with three separate Cox proportional hazards models. The first adjusted for age alone. The second

Table 1 Age-Adjusted Means of Cardiovascular Risk Factors by Current Arthritis Status

Risk Factors	No Arthritis	Arthritis	P
Age (years)	77.8	77.5	0.195
Body Mass Index (kg/m ²)	23.3	23.8	0.003
Physical Activity Index	31.0	30.9	0.627
Total Cholesterol (mg/dL)	190.6	190.0	0.720
HDL Cholesterol (mg/dL)	51.8	50.5	0.083
Hypertension	73.3%	75.2%	0.414
Diabetes Mellitus	26.0%	22.5%	0.134
Current Smoking	8.0%	5.2%	0.579
Fibrinogen (mg/dL)	303.9	308.1	0.218
Alcohol Intake (ounces/month)	19.5	19.1	0.848
ASA or NSAID Use, or Both	21.4%	39.6%	< 0.001

Chi-square tests used for categorical variables. ANOVA used for continuous variables. Means reported for all continuous variables.

model adjusted for age, BMI, PAI, hypertension, diabetes mellitus, HDL cholesterol, total cholesterol, and smoking status. The third model included the above variables as well as fibrinogen, alcohol use, and ASA or NSAID use, or both. Since subjects with dementia or cognitive impairment may provide unreliable information regarding medical history, Cox proportional hazards models were repeated after excluding subjects with dementia or cognitive impairment (Cognitive Abilities Screening Instrument score less than 74) (n = 425), leaving 2352 subjects for analysis.²² All statistical analyses were done with SAS software, version 8 (SAS Institute, Cary, North Carolina).

Results

The overall prevalence of all arthritis (current and past) in this cohort was 16.6% (600/3614), and current arthritis was 14.7% (518/3532). Age-adjusted means of cardiovascular risk factors demonstrated no significant differences between subjects with and without current arthritis, except subjects with arthritis were heavier [BMI, 23.8 (standard error, 0.155) vs. 23.3 (standard error, 0.064), p = 0.003] and more likely to use ASA or NSAIDs, or both (39.6% vs. 21.4%, p < 0.001) (Table 1). Thus, current arthritis status was not associated with most traditional cardiovascular risk factors in this cohort.

There was a total of 279 cases of incident CHD in the cohort over the 8-year follow-up period. Those with cur-

Table 3 Cox Proportional Hazard Models for Association Between Current Arthritis and 8-Year Incident CHD

Cox Model*	Relative Risk for Current Arthritis		
	Relative Risk	95% CI	P
1	1.23	0.90-1.68	0.21
2	1.12	0.79-1.58	0.53
3	1.06	0.74-1.51	0.76

*Model 1, Adjusted for age; Model 2, Adjusted for age, BMI, physical activity index, hypertension, diabetes mellitus, HDL cholesterol, total cholesterol, smoking status; Model 3, Adjusted for age, BMI, physical activity index, hypertension, diabetes mellitus, HDL cholesterol, total cholesterol, smoking status, fibrinogen, alcohol intake, and ASA and/or NSAID use.

Table 2 Rates of 8-year Incident Coronary Heart Disease by Current Arthritis Status in Subjects Free of CHD at Baseline

	No Current Arthritis	Current Arthritis
Number of Participants	2374	403
Total Number of Cases of Incident CHD Over 8 Years of Follow-Up	232 (9.8%)	47 (11.7%)
Unadjusted Rates of Incident CHD per 1000 Person Years	17.6	20.8
Age-Adjusted Rates of Incident CHD per 1000 Person Years	18.0	20.5

rent arthritis were slightly more likely to develop incident CHD over the 8-year follow-up (11.7%, 47/403), compared to those without arthritis (9.8%, 232/2374); however, this difference was not statistically significant (p = 0.24). Age-adjusted rates of incident CHD were 20.5 per 1000 person-years in those with current arthritis, compared with 18.0 in those without current arthritis (p = 0.25) (Table 2).

We used three separate Cox proportional hazards models with 8-year incident CHD as the outcome (Table 3). In the first model, the relative risk for incident CHD associated with current arthritis was 1.23 (95% CI, 0.90 to 1.68) after adjustment for age alone. In model 2, adjustment for traditional cardiovascular risk factors did not alter the relative risk (RR, 1.12; 95% CI, 0.79 to 1.58). Further adjustment for fibrinogen, alcohol use, and ASA or NSAID use, or both, did not modify this association (RR, 1.06; 95% CI, 0.74 to 1.51). The results did not change significantly when Cox models were repeated after excluding subjects with dementia or cognitive impairment (n = 425) (Table 4).

Discussion

The relationship between CHD and arthritis is of significant clinical interest. Both arthritis and CHD are major causes of morbidity and mortality. These two most common forms of arthritis, RA and OA, have each been implicated as playing a role in CHD in affected patients.

In this prospective cohort study of elderly Japanese-

Table 4 Cox Proportional Hazard Models for Association Between Current Arthritis and 8-Year Incident CHD, Excluding Those with Dementia and Cognitive Impairment

Cox Model*	Relative Risk for Current Arthritis		
	Relative Risk	95% CI	P
1	1.32	0.95-1.84	0.10
2	1.25	0.87-1.80	0.22
3	1.18	0.82-1.71	0.38

*Model 1, Adjusted for age; Model 2, Adjusted for age, BMI, physical activity index, hypertension, diabetes mellitus, HDL cholesterol, total cholesterol, smoking status; Model 3, Adjusted for age, BMI, physical activity index, hypertension, diabetes mellitus, HDL cholesterol, total cholesterol, smoking status, fibrinogen, alcohol intake, ASA and/or NSAID use.

American males, we found no significant increase in incident CHD in patients with arthritis. The lack of association persisted even after adjustment for a number of potential confounders, such as coronary risk factors and alcohol use. Overall, our cohort had a relatively low incidence of CHD, compared to other populations. In elderly Japanese-American males of the Honolulu Heart Program, the age-adjusted incidence of CHD was 20.5 per 1000 person years. A 44-year and 64-year follow-up study from the NHLBI's (National Heart, Lung, and Blood Institute) Framingham Heart Study (FHS), shows the average annual rates of a first major cardiovascular event ranging from 7/1000 in males ages 35 to 44 years to 68/1000 at ages 85 to 94.²³ In our study, participants aged 85 to 93 years had an incidence of CHD of 29 per 1000 person years follow-up, which was much lower than the incidence of CHD in the Framingham study population. The relatively low rate of CHD among our subjects may relate to either genetics or environment, as Syme and colleagues have reported a gradient of CHD mortality among Japanese males living in Japan (lowest), Hawaii (intermediate), and San Francisco (highest).²⁴ It is possible that our failure to observe an association between arthritis and CHD relates to the fact that we were studying a low-risk cohort for CHD. Additional studies would be needed to assess this proposition.

The Nurses' Health Study, a large prospective cohort of females, showed subjects with RA had a significantly increased risk of myocardial infarction but not stroke in comparison to those without RA.⁸ A large population-based cohort in Sweden followed from 1964 to 1995 revealed a higher risk of death from coronary artery disease in RA patients.⁶ Other studies support RA as an independent risk factor for CHD.^{3-5,7,9} In contrast to RA, the data on OA as a risk factor for CHD are less clear. Data from the Third National Health and Nutritional Examination Survey (NHANES III)¹¹ and other studies¹²⁻¹⁴ indicate U.S. adults with OA have a significantly higher prevalence of cardiovascular risk factors (increased BMI, hypertension, diabetes mellitus, physical activity, lipid profile, etc.) than the non-arthritic population, which may place OA patients at risk for developing CHD. Indeed, a recent study suggests that the 10-year risk of CHD in patients with RA and OA are about equal.²⁵ On the other hand, some additional studies suggest that OA may not be associated with CHD.²⁶ Based on the available information, our data did not permit us to rigorously determine the precise arthritis diagnoses of our study patients. However, data from the Framingham and other studies suggest that the prevalence of OA and RA in the elderly population, and spondyloarthropathies in the general population are approximately 31%, 2%, and 2%,^{10,27,28} respectively, indicating that most of our population may have had OA. Thus, our data suggest that OA was not a risk factor for CHD in our population. Whether this lack of association between OA and CHD is a universal phenomenon or a unique feature of our population cannot be determined from the available data set.

The etiology of any association between systemic inflam-

mation and CHD is not well understood. Theories for the pathological association between CHD and autoimmune diseases, such as RA and systemic lupus erythematosus, include increased expression of cellular adhesion molecules, recruitment of inflammatory cells, atherogenic side effects of anti-rheumatic medications, and the lack of appropriate down-regulation of pro-inflammatory processes, leading to atherosclerosis.²⁹⁻³¹ OA is often classified as a non-inflammatory disease. However, osteoarthritic joints may become inflamed, and numerous studies show that inflammatory cytokines play a role in stimulating chondrocytes to increase transcription of cartilage-degrading enzymes, such as matrix metalloproteinases.^{32,33} Spector and coworkers recently reported serum C-reactive protein levels are directly correlated with the risk of radiographic knee OA progression, providing evidence that inflammation may play a role in the trajectory of OA.³⁴ If OA does result in low-level systemic inflammation, our data suggest that, at least in our population, that inflammation was not sufficient to result in increased CHD.

One concern regarding our methodology was that, by excluding subjects with prevalent CHD, we may have been introducing bias by excluding a population that might have an altered rate of arthritis. As expected, subjects with arthritis were more likely to use an ASA or NSAID, or both. However, they did not have a higher prevalence of cardiovascular risk factors, except for a higher BMI, supporting the hypothesis that obesity predisposes to the development of OA.^{35,36} The Honolulu Heart Program population is relatively lean compared to other populations in the U.S., where the average BMI is 26.6 in adult males.³⁷ Previous studies suggest that obesity is correlated with a lower level of physical activity and fitness, a known predictor of mortality from cardiovascular causes.³⁸⁻⁴⁵ A higher level of physical fitness is associated with lower resting heart rate, blood pressure, total cholesterol, and lower rates of smoking.⁴¹ In our population, although the BMI was slightly higher in the arthritic group, there was no correlation between arthritis and the PAI, suggesting that a higher BMI may not have limited physical activity levels in arthritic patients, in contrast to the studies mentioned above.^{44,45} This may also explain the absence of a significant association between arthritis and other cardiovascular risk factors and incident CHD. Finally, although increased ASA or NSAID use among arthritis patients might have masked an increasing CHD via cardioprotective effects or, alternatively, in the case of at least some NSAIDs, might have led to an increase in CHD,⁴⁶ we observed no difference between arthritis and control groups even after adjusting for the use of these agents.

This study has several limitations. First, the study focuses on older Japanese-American males, limiting generalizability. However, previous studies from the Honolulu Heart Program have been relevant to other populations and of significant value to the advancement of science. As noted earlier, the study did not define the type of arthritis in subjects. However, the National Institutes of Health (NIH, Bethesda, Maryland) estimates the prevalence of OA is about 10 times that of

RA.⁴⁷ According to these estimates, our data most likely predominantly reflect OA. Since some prior studies suggest that the risk of CHD and CHD-related events is lower in OA than RA, our data pool may have been less likely to capture a strong association between arthritis and CHD. Whether RA was a risk factor for CHD in our population cannot be independently determined. Finally, the study gathered data about arthritis by self-report, and such data might be expected to include nonspecific joint complaints, and, therefore, potentially overestimate the presence of arthritis. On the other hand, many subjects may not consult a physician for mild joint pains, and as a consequence may not be able to affirmatively answer questions regarding a physician diagnosis of arthritis. While the validity of using self-reports to estimate true prevalence of arthritis is unknown in this cohort, and the lack of association between arthritis and incident CHD could be due to a type I error related to misclassification of arthritis, both Bombard and associates and the CDC have shown that self-reported data can be reliably used to study the prevalence of arthritis.^{1,2,48} Patient self-reporting of a diagnosis of arthritis received from a physician, as in our study, was particularly reliable in the Bombard study.⁴⁸ In addition, NHANES III also identified comorbid medical conditions mainly by subjects' self-report rather than by physical examination. NHANES suggests self-reported measures can be quite reliable, based on studies conducted on other diseases. For example, sensitivity and specificity of self-reported hypertension in NHANES III has been assessed, and deemed valid for use in surveillance for the U.S. population.⁴⁹

Our study also has many strengths. This is a population-based study with large numbers and good compliance rates. The follow-up period of 8 years is relatively long. This is a unique, stable population of elderly Japanese-American males with a very low out-migration rate. Surveillance for the outcome (incident CHD) is essentially complete, since this is an island population and subjects do not generally leave the area for medical care.

Conclusions

Our study results suggest that arthritis may not be associated with cardiovascular risk factors in elderly Japanese-American males. Furthermore, arthritis may not be a risk factor for incident CHD in this cohort. Although these observations probably relate to OA, our data do not permit formal stratification. The differences between our results and those observed in other populations may provide insight into the mechanisms through which arthritis is, or is not, associated with CHD.

Disclosure Statement

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