Mortality in osteoarthritis

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ABSTRACT

Mortality has not been a major area of investigation in osteoarthritis. The author conducted a systematic review and identified seven studies that provided data on either mortality or survival in persons with osteoarthritis; an additional two articles with relevant data were identified through review of reference lists. Studies included persons with radiographic evidence of osteoarthritis as well as clinical samples of patients with osteoarthritis. Results were pooled using the method of best evidence synthesis. Overall, there was moderate evidence of increased mortality among persons with osteoarthritis compared with the general population. Increased cause-specific mortality was observed in some studies from cardiovascular and gastrointestinal disorders. Risk factors for mortality in persons with osteoarthritis included an increased burden of osteoarthritis, advanced age, and presence of comorbid conditions. Possible explanations for the excess mortality include reduced levels of physical activity among persons with osteoarthritis due to involvement of lower limb joints and presence of comorbid conditions, as well as adverse effects of medications used to treat symptomatic osteoarthritis, particularly non-steroidal anti-inflammatory drugs.

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Mortality has not been a major area of investigation in osteoarthritis; the major areas of impact of osteoarthritis are effects on functional limitation, physical disability and health care utilization and costs. Danielsson commented that death rates were higher than expected in persons with radiographic osteoarthritis of the knees but not of the hips; however, no specific data were presented and no discussion of these findings was presented (1, 2). In his classic monograph published over 30 years ago, John Lawrence stated the following: "Mortality statistics give little help in ascertaining the prevalence of this disease. In England and Wales, … the mortality during the last 20 years has varied from 5 to 8 per million. This is only a third of the mortality from rheumatoid arthritis, a much less common disease." (3).

The first study of mortality in patients with osteoarthritis in the U.S. was published by Monson and Hall in 1976 (4). They examined mortality in a systematic sample of 617 patients admitted to the Robert Breck Brigham Hospital in Boston between 1930 and 1960 and compared this with the age- and sex-specific mortality in the white population of the United States. Patients were admitted to hospital primarily for bed rest and physical therapy. Relative survival rates for both sexes were similar to the general population for the first 10 years after hospitalization but then declined and were lower than the general population thereafter; no statistical analysis was provided. The standardized mortality ratio (SMR), a comparison of the number of observed to expected deaths, was 111 (Table I). The most common cause of death was arteriosclerotic heart disease, accounting for 40 percent of deaths; the SMR for this cause was 157 (Table II). Cause-specific mortality due to gastrointestinal disorders, which accounted for only 6 percent of deaths among the patients with osteoarthritis, was increased by a factor of over two (SMR of 239) compared with the general population. There was a direct association between aspirin usage and a higher SMR from gastrointestinal causes among osteoarthritis and rheumatoid arthritis patients combined: the SMR increased from 110 to 240 to 380 across groups defined as none, occasional, and daily aspirin usage during their index hospitalization. There was no association between aspirin use and either a reduction or increase in the SMR from arteriosclerotic heart disease.

Reva Lawrence and colleagues examined mortality in persons with radiographic evidence of osteoarthritis of the

Table I. Mortality studies in osteoarthritis.

Study	Year of study	Location	Source	No. of persons with OA	Mean age	Mean duration of follow-up (years)	% women	SMR	Info on causes of death?	Data on risk factors?
Monson and Hall (4)	1976	MA, USA	Hospital-based	617	--	M: 10.3 F: 11.2	72.6	111	Yes	No
Lawrence *et al*. (5)	1989	USA	NHANES-I, and NHEFS cohorts	255 (knee only)	--	--	67.5	M: 1.17* F: 1.45*	No	Age and knee pain only
Cerhan *et al*. (6)	1995	USA	Radium dial-painting workers	296 (all women)	57.1	28§	100	--	Yes	Yes
Watson *et al*. (7)	2003	UK	GPRD registry	163,274	-- F: 4.8	M: 4.7	62.3 F: 15.9^	M: 19.5^	CV only	No
Haara *et al*. (8, 9)	2003, 2004	Finland	Population-based	Not specified (prevalence rates only)	--	15-17	--	OA in any finger joint was not associated with mortality	CV only	Yes
Kumar *et al*. (10)	2007	UK	Clinic-based	485	--	15§	66.2	--	CV only	No

* listed as crude relative risk (RR); §total number of follow-up years; ^ listed as standardized incidence rate (per 1000 patient-years) of all-cause mortality.

Table II. Causes of death in patients with OA (% total deaths).

	Monson & Hall 1976 (4)	Cerhan *et al*. 1995 (6)	Watson *et al*. 2003 (7)	Kumar *et al*. 2007 (10)
Total no. deaths	338/617 (54.8%)	55/296 (18.6%)	--	154/485 (31.8%)
Cardiovascular	51.2	36	M: 11.9^ F: 7.6^	35.7; aRR=1.96 (1.21-3.25)
(Myocardial Infarction)	--	--	M: 8.3^ F: 4.4^	--
Stroke	--	11	--	--
Cerebrovascular disease	13	--	M: 5.9^ F: 3.2^	--
Cancer	11.8	36	--	aRR=1.00 (0.62-1.61)
(Lymphatic and hematopoietic)	(0.6)	--	--	--
Renal	2.7	--	--	--
Respiratory	5.9*	0.5	--	--
Pulmonary	--	--	--	
Pneumonia	--	--	--	
Infection	--	--	--	
Musculoskeletal diseases	1.2	--	--	--
GI	6.5*	0.7	--	--
Poisonings or accidents	--	7	--	--
Other/unknown	7.7	7.8	M: 0.8^ F: 0.5^	--
Total percent	100.0	100	NA	NA

* listed as exceeding expected no. of expected deaths (SMR>1); ^ listed as standardized incidence rates (per 1000 patient-years).

knee using data from the First National Health and Nutrition Examination Survey (NHANES-I), conducted between 1971 and 1975, and the NHANES-I Epidemiologic Follow-up Survey (NHEFS), conducted between 1982 and 1984 (5). A total of 2384 persons aged 55 to 74 who had radiographs of the knees performed during NHANES-I and were successfully traced in the NHEFS were included in this analysis. The crude mortality ratio was 38.9 percent and 30.1 percent among men and women with radiographic evidence of osteoarthritis of the knee compared to 31.6 percent and 17.5 percent among men and women without radiographic evidence of osteoarthritis of the knee; the age-adjusted sex-specific relative risks for death were 1.17 and 1.45, respectively (Table I and Fig. 1).

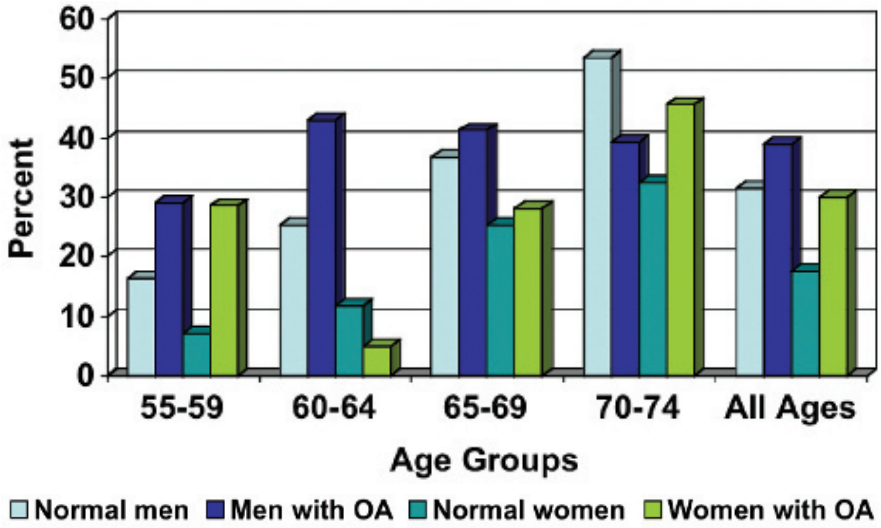

Fig. 1. Mortality in persons with radiographic osteoarthritis of the knee at baseline during NHANES-I by age and sex. Data from reference 5 (Tables 7-8).

The increased mortality was statistically significant in women only; this was largely due to excess mortality among women aged 55 to 59 during NHANES-I. Among persons with radiographic evidence of osteoarthritis of the knees during NHANES-I, the age-adjusted sex-specific relative risks for death were 1.27 and 1.23 for men and women, respectively, for those who reported frequent knee pain compared to those who did not report frequent knee pain; these increased relative risks were not statistically significant in either sex (Table III). Cause-specific mortality was not examined in this cohort, nor was the relative risk adjusted for risk factors for radiographic osteoarthritis such as overweight or use of aspirin or non-steroidal anti-inflammatory drugs for treatment of symptoms in those with radiographic osteoarthritis.

Cerhan and colleagues examined mortality in a sample of 296 women who had been employed in the U.S. radium dial-painting industry between 1915 and 1945 and participated in a cohort study on the long-term effects of radium that was conducted between 1955 and 1985 (6). When women entered the study, they underwent radiographs of the entire body as well as a clinical examination and an assessment of total body burden of radium; the sample selected for this analysis was limited to women with low radium exposure. The authors read six radiographs for each woman: lateral cervical and lumbar

Table III. Predictors of all-cause mortality in patients with OA (hazard ratios with 95% confidence intervals).

	Lawrence *et al.* (5)	Cerhan *et al.* (6)	Haara *et al.* (8, 9)
Total no. deaths	--	55	
Age	M: 1.17* ($p>0.05$) F: 1.45* ($0.01<p<0.05$)	1.61 (1.25-2.08)	
42-49		Reference group	
50-59		1.26 (0.52-3.07)	
60-69		3.37 (1.32-8.59)	
70-76		3.92 (1.17-13.13)	
Pain (yes/no)	M: 1.27* ($p>0.05$) F: 1.23* ($p>0.05$)		
Hip OA		1.93 (0.60-6.25)	
Knee OA (bilateral)		2.20 (1.03-4.69)	
MTP OA		1.66 (0.89-3.09)	
No. joints with OA		1.48 (1.18-1.87)	
No. joint groups with OA		1.56 (1.24-1.97)	
No. structures with OA		1.49 (1.14-1.94)	
No. joints with OA- hands		1.37 (1.09-1.73)	
No. joints with OA- cervical discs		1.31 (1.02-1.68)	
No. joints with OA- lumbar discs		1.18 (0.91-1.53)	
Advanced (grade 3 or 4) thumb carpometacarpal OA			M: 1.32* (1.03-1.69)
Symmetrical DIP OA			M: 0.89* (0.68-1.16) F: 1.23* (1.01-1.51)
Tobacco use (ever)		1.78 (0.66-4.78)	
Systolic blood pressure ≥155		5.55 (1.63-18.89)	
Diabetes		4.99 (2.21-11.26)	
Cardiovascular disease		2.84 (1.21-6.71)	
Stroke		2.67 (0.64-11.10)	
Body Mass Index > 29.9		0.57 (0.22-1.92) (BMI ≥29.9)	

*listed as relative risk (RR)

spine, bilateral hands, knees and feet and a single view of the pelvis. A total of 55 joints comprising 18 joint groups were graded for osteoarthritis using the Kellgren-Lawrence scales. In univariate analyses, all summary measures of total body osteoarthritis were associated with reduced survival (Table III). In addition, the presence of osteoarthritis of the hands, bilateral knees and cervical disc degeneration was associated with reduced survival, while the presence of osteoarthritis of the hips and feet and lumbar disc degeneration was not. In age-adjusted Cox proportional hazard models, the relative hazard for reduced survival was 1.45 (95% confidence interval 1.12, 1.87) per standard deviation increase in the number of joint groups affected by radiographic osteoarthritis; the hazard ratio remained stable after adjustment for body mass index, diabetes, smoking, and alcohol use. Involvement of individual joint groups, however, was no longer significantly associated with reduced survival after adjustment for these confounders. The authors suggested that the reduced survival might be attributed to either lower levels of physical activity or the use of medications by the women with more joint groups affected by osteoarthritis.

Watson and colleagues examined all-cause mortality and the incidence of all vascular events including sudden death and vascular death among patients with rheumatoid arthritis, osteoarthritis, and no arthritis aged 40 and above using the U.K. General Practice Research Database (7). A total of 61,517 men and 101,757 women with a clinical diagnosis of osteoarthritis were included in the analysis. The rates of age-adjusted all-cause mortality per 1000 patient-years were 19.5 and 15.9 in men and women with osteoarthritis and 20.6 and 17.3 in men and women with no arthritis, respectively (Tables I and II). There were no apparent numerical differences between the rates of age-adjusted sudden and vascular death between these groups. There are a number of limitations to these data that were discussed by the authors, including 1) the diagnosis of osteoarthritis was recorded by a general practitioner and was not validated based on published classification criteria, and

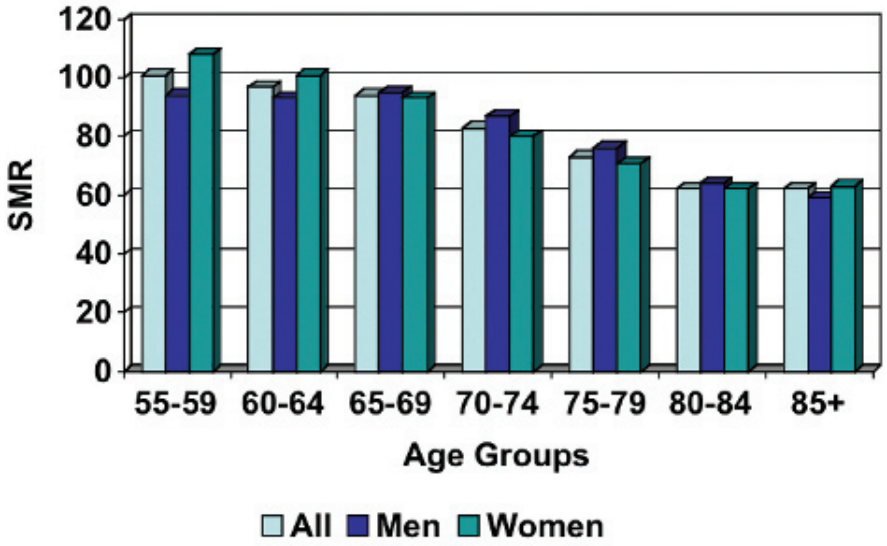

Fig. 2. Standard mortality ratios (SMR) for 55,957 persons aged 55 and above who underwent total knee arthroplasty in Sweden between 1980 and 2002. SMRs for all persons aged 65 and above, men aged 70 and above, and women aged 65 and above were statistically significantly reduced below 100. Data from reference 24 (Table II).

2) some individuals with asymptomatic radiographic osteoarthritis would be misclassified into the "no arthritis" group leading to a bias towards the null. In addition, persons with soft-tissue and/or periarticular pain might be misdiagnosed with osteoarthritis, leading to dilution of the effect of osteoarthritis on mortality. Hence, while the results are not consistent with an increased mortality rate among persons with a clinical diagnosis of osteoarthritis followed in general practice compared with persons without an arthritis diagnosis, they need to be interpreted with caution.

Haara and colleagues used data from the Mini-Finland Health Survey to examine the association between osteoarthritis of the finger joints or the carpometacarpal joint of the thumb and all-cause mortality (8, 9). The Mini-Finland Health Survey was a stratified two-stage cluster survey conducted between 1977 and 1980; radiographs of the hands were performed in 3595 people with symptoms or findings of a musculoskeletal disease and read for features of osteoarthritis using Kellgren-Lawrence grading scales. All deaths that occurred through 1994 were identified; the association between radiographic osteoarthritis and mortality was examined using multiple variable Cox proportional hazards models adjusting for age, education, history of workload, smoking and body mass index. Women with symmetrical radiographic osteoarthritis involving distal interphalangeal joints had an increased risk of death (RR=1.23 [95% confidence intervals 1.01, 1.51]) (Table III). Women with osteoarthritis in any finger joint and men with either osteoarthritis in any finger joint or symmetrical DIP joint osteoarthritis did not have a significantly increased adjusted risk of mortality (8). Furthermore, neither men nor women with radiographic evidence of thumb carpometacarpal joint osteoarthritis had an increased risk of mortality (9).

Kumar and colleagues examined all-cause mortality and mortality due to ischemic heart disease and malignancy among patients with rheumatoid arthritis and their same-sex siblings and a comparison group of patients with lower limb osteoarthritis seen at Freeman Hospital, Newcastle-upon-Tyne, U.K. (10). A total of 257 patients with rheumatoid arthritis, 371 same-sex siblings, and 485 patients with osteoarthritis were included in the analysis; date and cause of death were obtained from the Office on National Statistics. Compared to normative data from the Health Survey for England, the patients with osteoarthritis had an increased risk for death due to ischemic heart disease (RR=1.96 [95% confidence intervals 1.21, 3.25]) but not from malignancy (RR=1.00 [95% confidence intervals

0.62, 1.61]) (Table II). The authors felt that lower levels of physical activity due to disability among the patients with lower limb osteoarthritis, and the use of nonsteroidal anti-inflammatory drugs explained the increased risk of death from ischemic heart disease. Of note, there was no apparent increase in all-cause mortality or reduction in cumulative survival rate in the patients with osteoarthritis compared to the same-sex siblings of the patients with rheumatoid arthritis.

These data, derived from both population-based epidemiologic and clinical studies, provide moderate evidence, based on the method of best evidence synthesis (11), that radiographic and symptomatic osteoarthritis, particularly affecting the knees or in the construct of generalized osteoarthritis, is associated with increased mortality, especially due to acute cardiovascular and gastrointestinal causes. Some but not all studies included adjustment for potential confounding variables known to be associated with both osteoarthritis and premature mortality, including body mass index and smoking. The possible effects of other known or unrecognized confounding variables, however, cannot be excluded, particularly given the small effect on overall all-cause mortality.

The increased death rate from ischemic heart disease may be explained in part or entirely by decreased levels of physical activity among patients with lower limb osteoarthritis and the use of nonsteroidal anti-inflammatory drugs for management of symptoms rather than osteoarthritis *per se* (12-14). The use of non-steroidal anti-inflammatory drugs also explains, at least in part, the increased mortality due to gastrointestinal causes (15, 16). Another potential explanation is that genes associated with the development of radiographic osteoarthritis may be associated as well with reduced survival, possibly mediated by the biomarker of shortened leukocyte telomeres (17-21).

One bright spot, however, is the improved survival among patients with hip osteoarthritis who have undergone total hip arthroplasty (22.23) and among patients with knee osteoarthritis who have undergone total knee arthroplasty (24), particularly those aged 70 and above (Fig. 2). This is probably attributable to selection of relatively healthy elderly patients for surgery as anesthesiologists and surgeons are likely not to offer surgery to those with serious comorbid medical conditions.

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