Mortality and other outcome measures in osteoarthritis

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Chapter 6

Mortality in osteoarthritis patients

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ABSTRACT

OBJECTIVE

To investigate whether all-cause and cardiovascular mortality is increased in patients who have consulted primary or secondary health care with osteoarthritis (OA) symptoms and signs.

METHODS

383 patients with symptomatic OA at multiple sites from the 'Genetics ARthrosis and Progression' (GARP) study (mean age 60 years, 82 % women, 3693 person years of follow-up) and 459 patients with primary hand, knee or hip OA from the 'Osteoarthritis Care Clinic' study (mean age 61, 88 % women, 1890 person years of follow-up) were followed. Standardized mortality ratios (SMRs) with 95% confidence intervals (CI) were calculated for all-cause mortality and causes of deaths in comparison to the general population. Cox proportional hazard ratios (HR) with 95% CI were used to associate baseline characteristics with all-cause mortality.

RESULTS

In GARP 26 patients died, while 48 deaths were expected (SMR 0.54 (0.37-0.79)). The SMR was 0.47 (0.29-0.76) in women and 0.73 (0.39-1.35) in men. Similar results were found in the Osteoarthritis Care Clinic study (SMR 0.45 (0.25-0.82)). Malignancy and cardiovascular disease were the main causes of deaths in GARP. Male sex (HR 3.04 (1.38-6.69)), increasing age (HR 1.10 (1.05–1.16) and self-reported cancer (HR 8.29 (3.12-22.03) were associated with increased mortality in GARP.

CONCLUSION

Patients consulting health care for their OA are not at higher risk of death than the general population. These results suggest that the management of OA patients may not need to focus specifically on the treatment of cardiovascular risk factors and comorbidities.

INTRODUCTION

Osteoarthritis (OA) is a common disease with rising prevalence. Recently, increased all-cause mortality was found among subjects surveyed from the general population with hip and knee pain and radiographic OA signs.[1] Next to atherosclerosis, diabetes, walking disability and use of NSAIDs may explain a possible association between OA and mortality.[1,2] For clinical practice this could mean that management of patients with OA should focus on effective treatment of cardiovascular risk factors and comorbidities.[1,3]
Therefore, we investigated whether OA patients who present themselves in health care with OA experience an increased mortality and whether this is due to cardiovascular causes.

PATIENTS AND METHODS

Study design

We investigated two prospective observational cohorts of OA patients.
The 'Genetics ARthrosis and Progression'(GARP) cohort comprised 192 Caucasian sibling pairs (384 patients) with symptomatic primary OA at multiple sites in the hand or in at least 2 of the following sites: hand, knee, hip or spine, that were diagnosed by rheumatologists, orthopaedic surgeons and general practitioners.[4] They were included between August 2000 and March 2003, after informed consent. Twenty patients with shortened life expectancy were excluded; eleven older than 75 years at time of inclusion and nine with poor health. The study was approved by the medical ethical committee.
The 'Osteoarthritis Care Clinic'(OCC) cohort consisted of 460 consecutive patients who were diagnosed by the rheumatologist with primary hand, knee or hip OA and referred to the clinical nurse specialist for education between August 2005 and April 2009.[5]

Demographics and clinical characteristics

Demographic characteristics, smoking status and comorbidities (verified by a physician) were collected by standardized questionnaires. Self-reported pain and functional limitations were assessed by subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for knee and hip, and the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index for hand.
WOMAC subscales ,VAS format (range 0-100, higher scores=worse outcome), were available of 383 GARP patients. A Likert scale (0=none to 4=extreme) was used for the AUSCAN subscales pain (range 0-20) and function (range 0-36) (in 351 GARP and all OCC patients).

Follow-up and assessment of mortality

Observation time started on date of inclusion and ended on either November 2nd 2011, date of death, emigration or loss to follow-up, whichever occurred first (complete follow-up for 98% of the cohort). Person-years were counted for all participants.

Vital status was verified by using municipal registries (Gemeentelijke Basis Administratie) and primary causes of death of GARP patients by the Central Bureau of Statistics Netherlands (CBS), national repository for death certificates. These data were compared with causes of deaths (coded to ICD-10 classification) in the general population.

Data analysis

Standardized Mortality Ratios (SMR) with 95% confidence intervals (CI) were calculated for all-cause mortality and cause-specific mortality, using STATA version 10.1 (Statacorp, College station, TX). For expected numbers of deaths from age and sex specific mortality data of the general population, we used the mid of the follow-up time as reference year.

'Healthy cohort' effects may occur due to exclusion of patients with shortened life span, Since this effect ebbs away after a couple of years, enabling unbiased analyses [6], SMRs were also calculated by delaying the start of follow-up.

Associations between characteristics of patients at baseline and all-cause mortality in GARP were studied using univariate and multivariate Cox proportional hazards models, adjusting for age and sex. To take a potential family effect into account in GARP, shared frailty was applied in the Cox proportional hazard models (using STATA), assuming that observations of siblings have the same frailty. However, the variance of shared frailty was very small and including it had a negligible influence on the hazard ratios. We therefore decided to perform the analyses without the family effect using SPSS version 20 (SPSS Inc, Chicago,IL).

RESULTS

Population descriptions

For the present analysis 383 patients from the GARP cohort (mean age 60 years, 82% women, see supplementary Appendix 1, available online) were included (one patient only seen at baseline and lost to follow-up), accounting for 3693 person-years of follow-up (median 9.9 years, range 1.83-11.9 years). In the OCC cohort 459 patients (mean age 61 years, 88% women, supplementary Appendix 1)

were included (one patient only evaluated at baseline and lost to follow-up) and accounted for 1890 person-years of follow-up (median 3.9 years, range 0.87-6.8 years).

Mortality

In GARP, 26 OA patients (16 females, 10 males) died during follow-up, resulting in a SMR of 0.54, 95% CI 0.37 - 0.79. The SMR was lower in women than in men (Table 1). In patients from the OCC cohort we found similar results (Table 1).
No excess mortality was observed in our two cohorts of OA patients when compared to the general population.

Causes of death

In the GARP study 21 of the 26 deaths occurred due to either cancer (most common cause of death in women) or cardiovascular disease (most common cause of death in men) (Table 1).

Healthy cohort effect and sib pairs

A potential healthy cohort effect was investigated in GARP. The SMR did not increase when the start of follow-up was delayed. (Figure 1)
The SMRs calculated separately for probands and siblings, did not differ.

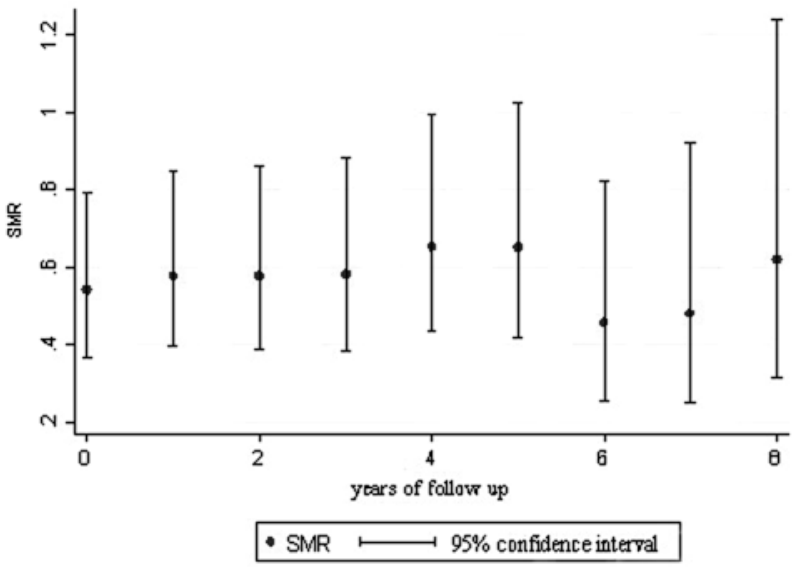

Figure 1. The Standardized Mortality Ratio (SMR) with 95% confidence interval bars calculated by delaying the year follow-up started in the GARP study

Table 1. Mortality and causes of death in 2 patient cohorts with primary osteoarthritis, compared with the Dutch population

Cohort	Cause of death	All patients		SMR (95% CI)	Men		SMR (95% CI)	Women		SMR (95% CI)
		Observed	Expected		Observed	Expected		Observed	Expected	
GARP	All causes	26	48	0.54 (0.37-0.79)	10	14	0.73 (0.39-1.35)	16	34	0.47 (0.29-0.76)
		9	14	0.66 (0.34-1.26)	5	4	1.13 (0.47-2.72)	4	9	0.43 (0.16-1.15)
	Cancer	12	20	0.59 (0.33-1.04)	3	6	0.54 (0.17-1.66)	9	15	0.61 (0.32-1.17)
	All causes	11	24	0.45 (0.25-0.82)	3	5	0.66 (0.21-2.06)	8	20	0.40 (0.20-0.81)

Risk factors associated with mortality

Univariate analysis revealed that male sex, increasing age and self-reported cancer were associated with increased mortality in the GARP cohort. In multivariate analysis male sex, age and self-reported cancer were associated with increased mortality. Hip OA was associated with mortality in the univariate analysis, but no longer when adjusted for sex and age. The WOMAC questions on walking, walking on flat surfaces and pain when walking, were not associated with mortality. A strong trend can be seen for smoking (Table 2).

Table 2. Univariate and multivariate analysis of hazard ratios with 95% confidence intervals (95% CI) for mortality in 383 osteoarthritis patients

Characteristic at baseline	Univariate Model HR (95% CI)	Multivariate Model HR (95% CI)*
Male sex	3.04 (1.38-6.69)	2.67 (1.21-5.90) ‡
Age, years	1.10 (1.05-1.16)	1.10 (1.04-1.16) §
BMI, kg/m^2	0.98 (0.90-1.07)	0.97 (0.88-1.07)
Knee OA**	0.73 (0.31-1.73)	0.59 (0.25-1.41)
Hip OA***	2.31 (1.06-5.03)	1.55 (0.70-3.45)
AUSCAN pain#	0.95 (0.87-1.04)	0.98 (0.89-1.07)
AUSCAN function#	0.98 (0.93-1.03)	0.99 (0.94-1.04)
WOMAC pain#	0.99 (0.97-1.01)	0.99 (0.97-1.01)
WOMAC function#	0.99 (0.98-1.01)	1.00 (0.98-1.01)
Smoking	1.99 (0.87-4.58)	2.14 (0.91-5.04)
Cardiovascular disease	0.62 (0.08-4.54)	0.43 (0.06-3.18)
Diabetes	1.77 (0.42 - 7.47)	1.14 (0.27-4.88)
Cancer	8.29 (3.12-22.03)	13.56 (4.69-39.19)

*Adjusted for age, sex, unless stated otherwise
‡Adjusted for age
§Adjusted for sex
**patients without knee OA as the reference category
***patients without hip OA as the reference category
#HR's given per unit standardised score
HR, hazard ratio; BMI, body mass index; OA, osteoarthritis; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

DISCUSSION

In two observational cohorts of OA patients who consulted health care for their OA, no increased mortality rate was found. Risk factors for death were male sex, age and the co-morbid condition of cancer, but no OA-associated factors. These results suggest that management of OA patients may not need to focus specifically on treatment of cardiovascular risk factors and comorbidities.

Evidence concerning mortality in OA has been contradictory. Hochberg's review concluded on an increased risk of death in OA with moderate evidence due to methodological problems, such as lack of adjustment for confounding variables.[7] Additionally, patients with hip and knee OA undergoing arthroplasty experienced prolonged survival. Our results are in line with these studies.[8,9]

Our findings do not support the results by Nuesch et al, who found excess mortality,[1] which may be due to differences in study populations. The British cohort included subjects with knee or hip OA, recruited via general population survey, whereas our cohorts included patients with knee or hip OA, but also hand and spine OA, who actively consulted health care from a medical specialist or general practitioner for their OA complaints.

We hypothesized that subjects who actively sought care for OA would be especially at risk for mortality, because these patients suffer from severe forms of OA. However our study results do not support this hypothesis. Several explanations can be given. These patients may be healthier because they possess behavioural traits which distinguish them from other OA patients who do not seek health care. These personality traits may also prompt them to pursue a healthy life-style and seek early care for diseases.

Both GARP and OCC participants were more often overweight when compared to the general population.[5,10] Though patients are not actively screened for metabolic syndrome, patients with OA who consult health care will also receive care for other known medical conditions, which could result in lowered mortality rates. Since we did not find a specific cause of death which stood out, nor an effect of OA-related factors, these explanations seem more likely than an effect of OA per se on mortality.

Our study has limitations. First, in a prosthetic study it has been suggested that reduced mortality may be explained by preoperative selection of healthier people.[11] To preclude that our results may have resulted from exclusion of patients with a shortened life span in GARP, we tested the presence of this 'healthy cohort' effect and did not find it. Exclusion of patients above 75 years is unlikely to have biased our SMR, as the number of deaths in age- matched general population would have been high as well. We also coped with this limitation by replication in the OCC cohort.

Second, the reliability of the death certificates, often filled in late at night, is limited. However, this misclassification will occur to our OA patients and control population alike.

Self-reported diseases can also be misclassified.

Finally, cardiovascular disease, the WOMAC function and BMI were not associated with mortality in our GARP cohort. These negative findings may be due to the limited number of events that occurred. Many unknown factors may act as confounders for the association between some factors and mortality (e.g. influence of NSAIDs for the association between physical function and mortality). Unfortunately, due to the limited number of events in our cohorts, we were unable to investigate the extensive list of potential confounders in this study.

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TABLES

Appendix 1. Baseline characteristics of patients in the GARP study and 'Osteoarthritis Care Clinic' patients

Baseline characteristics	GARP patients (n = 383)	'Osteoarthritis Care Clinic' patients (n = 459)
Women (n (%))	314 (82)	404 (88)
Age (mean (SD))	60 (7.6)	61 (9.8)
Hand OA (n (%))	276 (72)	438 (95)
Knee OA (n (%))	130 (34)	101 (22)
Hip OA (n (%))	93 (24)	NA
BMI >25 (kg/m^2 (%))	237 (62)	225 (60)
Smoking (n (%))	206 (54)	164 (40)
AUSCAN pain (range 0-20)	6 (0-19)	10 (0-20)
AUSCAN function (range 0-36)	10 (0-33)	18 (0-36)
WOMAC pain (range 0-100)	24 (0-96)	NA
WOMAC function (range 0-100)	20 (0-96)	NA
Cardiovascular disease (n (%)) *	23 (6)	NA
Diabetes (n (%))*	18 (5)	NA
Cancer (n (%))*	13 (3)	NA

*Self-reported
Values are medians plus range unless stated otherwise.
BMI, body mass index; OA, osteoarthritis; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.