GENETIC INFLUENCES IN END-STAGE OSTEOARTHRITIS

SIBLING RISKS OF HIP AND KNEE REPLACEMENT FOR IDIOPATHIC OSTEOARTHRITIS

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From a prospective, cross-sectional survey of 402 patients who had a total hip (THR) or a total knee (TKR) replacement for idiopathic osteoarthritis (OA) at a major centre, we determined the prevalence of these replacements for idiopathic OA in their 1171 siblings and 376 spouses. Using spouses as controls, the relative risk of THR in siblings was 1.86 (95% CI 0.93 to 3.69). The relative risk for TKR in siblings *v* spouses was 4.8 (95% CI 0.64 to 36.4) whereas the risk for the combined outcome measure of THR or TKR was 2.32 (95% CI 1.22 to 4.43) when siblings and spouses over 64 years of age were compared. Using a threshold liability model (Falconer), the heritability of end-stage OA of the hip was estimated at 27%.

The increased risks of joint replacement for severe, idiopathic OA which we found in siblings suggest that genetic influences are important in end-stage OA of the hip and knee.

J Bone Joint Surg [Br] 1997;79-B:660-4.
Received 25 November 1996; Accepted after revision 11 March 1997

Osteoarthritis (OA) is the commonest disease of human joints[1] and is characterised by loss of articular cartilage and formation of periarticular bone. Although the diagnosis depends mainly on radiological changes,[2] the clinical spectrum is wide. The knee and the hip are commonly affected: in the UK, it is estimated that 34% of the population over 45 years of age have OA of the knee[3] while 19% over 55 years of age have OA of the hip.[4] Nearly two-thirds of those with knee OA and one-third with hip OA have symptoms related to their disease.[5] In 1996 more than 50 000 patients required a hip (THR) or a knee (TKR) replacement for OA under the National Health Service[6-9] and the unmet demand for TKR, in particular, exceeds the supply.[10]

Most cases of hip and knee OA are idiopathic. Risk factors have been established in relation to age, obesity, race, occupation, injury and joint deformity,[4,11] and some studies have implicated genetic factors. The relative risks of asymptomatic radiological OA in first-degree relatives of affected individuals are estimated at between 2 and 3.[11-14]

We report the results of a prospective, cross-sectional survey of hospitalised patients. Our aim was to establish the relative risks of advanced, symptomatic OA of the hip and knee in siblings of patients having total joint replacement for OA.

PATIENTS AND METHODS

Between August 1995 and April 1996, the medical records and radiographs of all patients who had had a primary or revision THR or TKR at our major centre were reviewed to determine the indications for joint replacement. Patients were excluded if the THR or TKR was not performed for idiopathic OA; if they had had revision surgery in which the indication for primary replacement was not noted; if they were not available for review postoperatively; and if they had no siblings over 40 years of age (the risk of THR or TKR to siblings under 40 years is minimal). In order to limit confounding from racial variation, non-Caucasian patients were also excluded. From a consecutive series of 721 THRs or TKRs, 319 cases were excluded for the above reasons (Table I). Of the remaining 402 patients who participated in the study, 393 were seen in person and nine were contacted by telephone. Overall, 256 patients had unilateral THR, 112 unilateral TKR, 8 bilateral THR, and 24 had bilateral TKR. Two patients had unilateral THR and contralateral TKR. Of these, 337 operations were primary replacements and 65 were revision arthroplasties.

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0301-620X/97/47437 $2.00

Table I. Patients excluded from survey

Reason	Number
No siblings living to 40 years of age	81
Not available for survey	
Refused	4
Discharged before review	63
Unwell	14
Patients already surveyed during a previous joint replacement episode during the study period	10
Non-Caucasian patients	8
Revision operation for which the indication for primary replacement was not stated	23
Other indications for TJR	
Rheumatoid arthritis	53
Intra-articular fracture	25
Congenital dislocation of the hip	18
Avascular necrosis	4
Slipped upper femoral epiphysis	3
Multiple epiphyseal dysplasia	3
Other	10

All the patients selected for the study were invited to answer a short questionnaire; this was supervised by one researcher (JC). The enquiry focused on the age, gender and history of any joint replacement for idiopathic OA in surviving and deceased full siblings and spouses of the patients. Siblings and spouses who had died before the first THR was performed at our centre in 1967 were eliminated from subsequent analyses. When patients had married more than once, details of the first spouse known to have lived to at least 40 years of age after 1967, and therefore potentially eligible for a total joint replacement, were taken. In a small number of cases, patients who had been discharged before the review were questioned by telephone.

Relative risk and heritability estimates for symptomatic OA of the hip and knee were derived using THR, TKR, and either of these procedures (TJR) as indicators of severe, symptomatic OA.

Relative risk to siblings (λ_s)**.** Risk estimates based on the joint replacement history of the siblings and spouses of the patients were obtained by the following equation:

$$\lambda_s = \frac{\%\ \text{Siblings with total joint replacement for idiopathic OA}}{\%\ \text{Spouses with total joint replacement for idiopathic OA}}$$

Confidence limits (CI; 95%) were calculated using an asymptotic approximation[15] provided in the Instat statistical package (GraphPad Software Inc, San Diego, California).

Heritability. This is a measure of the degree to which parental characteristics are transmitted to children. It is the ratio of additive genetic variance to the total disease variance between relatives.[16] Heritability (h^2) estimates are calculated by comparing the liability to TJR in siblings with that in the general population,[17] using spouses to represent the general population (see Appendix). We assumed that the liability to OA is distributed normally for both siblings and spouses.

RESULTS

Table II shows the age and gender distribution of probands, siblings and spouses. Lifetime prevalence and distribution of THR and TKR for idiopathic OA in these individuals are given in Table III. Prevalence figures include four siblings and one spouse known to be on the waiting list for THR or TKR, and two siblings with idiopathic OA who were unfit for THR. Sixteen probands lacked spouses, not being married, or being separated or widowed.

The relative risk and heritability estimates are given in Table IV.

DISCUSSION

Few studies have considered genetic factors in common subsets of hip and knee OA. Radiological surveys carried out in the north of England more than 40 years ago suggested that the risk of 'generalised OA' of joints, which included the hip and knee, was twice as high as expected in first-degree relatives of affected individuals.[12] A Swedish study established a relative risk of 2.1 for hip OA in siblings of patients with coxarthrosis[13] while another British survey obtained relative risks of 2.7 for knee OA in first-degree relatives of individuals with gonarthrosis.[11] A recent UK study on female twins obtained heritability estimates between 39% and 65% for the presence of radiological knee and hand OA.[14]

Existing studies are limited by their focus on asymptomatic OA of the hip and knee in family members. There are few longitudinal studies of OA for any joint[18] and it is impossible to predict the proportion of patients with asymptomatic disease who will eventually complain of symptoms and seek medical advice. Furthermore, there are difficulties in defining radiological OA, because of controversy as to the relative importance of fundamental features.[18-22]

Total joint replacement for OA is usually performed for patients who have severe symptoms and advanced radio-

Table II. Age and gender distribution of probands and their siblings and spouses (affected and unaffected by total hip or knee replacement for OA)

		Mean age in years (range)			Male:female (proportion)		
	Number	All	Affected	Unaffected	All	Affected	Unaffected
Probands	402	70.8 (46 to 91)	70.8 (46 to 91)	NA	169:233 (1:1.38)	169:233 (1:1.38)	NA
Siblings	1171	68.5 (48 to 95)	75.3 (58 to 93)	68.0 (48 to 95)	550:621 (1:1.13)	31:49 (1:1.58)	519:572 (1:1.10)
Spouses	376	68.0 (38 to 93)	74.7 (58 to 86)	67.8 (38 to 93)	215:161 (1:0.75)	8:5 (1:0.63)	207:156 (1:0.75)

Table III. Lifetime prevalence and distribution of THR and TKR for idiopathic OA in probands, siblings and spouses

Hip	Knee	Probands	Siblings	Spouses	Total
1	0	173	38	8	219
0	1	79	8	0	87
1	1	17	2	0	19
2	0	83	27	4	114
0	2	42	2	1	45
2	1	6	0	0	6
1	2	0	1	0	1
2	2	2	2	0	4
Total		402	80	13	495

logical changes. By comparing the prevalence of THR and TKR for idiopathic OA in siblings of affected individuals with a control group, we have estimated the risks to siblings of symptomatic OA of these joints.

Relative to a control group, siblings had nearly twice the risks of THR and nearly five times the risks of TKR for idiopathic OA. Because of the lack of controls with TKR, the 95% CIs for risks of TKR were broad. Sibling risks for the combined outcome measure of THR or TKR were significantly greater than those for controls (Table IV).

We also determined the risks for individuals older than 64 years of age to avoid the possibility that younger patients may have been denied arthroplasty because of their relative youth. The risks were greater when analyses were restricted to older siblings and spouses.

We used the prevalence data for THR and TKR obtained for siblings and spouses of subjects surveyed during the study, in an accepted model of multifactorial inheritance[17] (see Appendix) to estimate the contribution of genetic factors in the overall variance of idiopathic, end-stage OA between siblings ('heritability'). The results showed that between 27% and 31% of the disease variance of osteoarthritis of the hip and knee are likely to be genetically determined. These values contrast with the heritability estimates for other common disorders: schizophrenia (85%), asthma (80%), essential hypertension (62%) and ankylosing spondylitis (70%).[23] Heritability estimates specific to end-stage OA of the knee could not be determined because of a shortage of spouses with TKR.

Diagnosis of osteoarthritis. Patients chosen for a TJR for OA may be regarded as having crossed a threshold for severe, symptomatic disease. The diagnosis is usually rigorous, supported by clinical, radiological, operative and histological findings. Clinical criteria for THR or TKR are likely to be broadly similar across orthopaedic centres in the UK thereby allowing prevalences obtained for joint replacement in siblings and spouses to be related directly to corresponding prevalences of end-stage OA in these individuals. The coexistence of severe knee with severe hip OA has been previously documented and supports the need to consider combined risks for THR and TKR.[24]

Controls used for risk estimation. Disease association studies suggest that OA is a multifactorial disorder with environmental and genetic determinants.[11,25] Estimates of the risk to family members depend on the choice of controls.[26] To determine genetic factors in multifactorial disease, controls used in sibling studies should ideally resemble siblings with respect to environmental risk factors but differ from them in regard to possible genetic determinants. Furthermore, they should be representative of the general population in terms of their susceptibility to disease. Spouses of patients fulfil both these criteria and have been used previously as controls in family studies.[27] By their longstanding proximity to the patient, spouses and siblings share a common environment, similar positive or negative biases to TJR and, because siblings often live near each other, similar selection criteria for TJR at their local hospital. In our study, the use of spouses as controls is supported by the fact that the prevalence of THR among spouses over 64 years of age (4.3%) closely approximates published prevalence data relating to the general population over 64 years of age from the same region for 1991 (4.0%).[28]

Possible errors. Differences in the balance of known environmental and constitutional risk factors for hip and knee OA, including ageing, gender, occupation and obesity, could underlie increased relative risks seen in siblings of probands. Of these, increasing age is likely to be most important.[29] In our study, there is close matching for age between siblings and spouses (Table II). Because of an excess of females among probands, spouses were more likely than siblings to be male. If female gender was strongly associated with idiopathic OA of weight-bearing joints, then the increased relative risks obtained for siblings would lose relevance. A number of large surveys have not identified any significant differences in the prevalence of hip OA between men and women.[30-32] Finally, occupation and obesity could also affect the development of OA in

Table IV. Relative risks and heritability estimates obtained for total joint replacement of the hip (THR) or the knee (TKR) or both (TJR), for idiopathic OA in siblings compared with spouses of patients

Total joint replacement	Number of probands	Relative risk to all sibs and spouses	Relative risks to sibs and spouses over 64 yrs
THR	281	1.78 (0.92 to 3.45)	1.86 (0.93 to 3.69)
TKR	121	4.8 (0.64 to 36.4)	Insufficient numbers
TJR (either THR or TKR)	402	1.98 (1.11 to 3.51)	2.32 (1.22 to 4.43)
End-stage OA	Heritability (h^2)		
THR, all relatives included	27%		
THR or TKR, all relatives included	31%		

siblings and spouses. Although these factors were not evaluated in our survey, the use of large numbers of families is likely to have minimised any differences in their prevalence between siblings and spouses.

Another possible source of error is reliance on recollection by patients of their family history. It could be argued that patients are less likely to be aware of the medical history of their siblings than of their spouses, which would tend to decrease the risk estimates obtained. Inaccuracies could have occurred in recalling indications for TJR in family members. Approximately 80% of hip and knee replacements are performed for idiopathic OA (Table I), however, and there is likely to be family knowledge of unusual indications such as fracture or rheumatoid arthritis for spouses and siblings alike. Attempts at validation of the indications for joint replacement in siblings and spouses were abandoned after delays due to lack of medical records from other hospitals.

Variations in regional utilisation rates for TJR may give a spurious increase in the prevalence of THR and TKR among siblings as compared with spouses. Most spouses would have had their operations in the same region as the probands. Since the region involved in our study has one of the highest utilisation rates for THR and TKR in the UK,[7,8] siblings resident elsewhere are unlikely to be at greater risk of arthroplasty because of their location.

Conclusions. Our study suggests that there are significant familial tendencies toward symptomatic OA of the hip and knee. Despite the use of spouse-based controls to correct for environmental influences on disease, siblings had almost two to five times the relative risk of THR or TKR for idiopathic, end-stage OA. Nearly one-third of the variance of disease between siblings ('heritability') is likely to be genetic. Our results imply that there is an important role for genetic factors in a disease traditionally considered to reflect environmental factors leading to 'wear and tear'.

Although relative risks of two appear small, they are to be anticipated in common, multifactorial disorders in which disease prevalence among controls is high.[33] Indeed, similar risks have been established in family studies on non-insulin-dependent diabetes mellitus, in which genetic linkages have recently been made.[34] A genetic basis has already been described for rare subsets of hip and knee OA such as the epiphyseal dysplasias.[35] The familial tendencies which we describe emphasise the need to carry out genetic linkage studies to identify the genes which may underlie common subsets of hip and knee OA.

Mr J. Chitnavis was funded by the ME Davis Research Fellowship in Arthritis from the Royal College of Surgeons of England and also by the Norman Collison Foundation.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Appendix

Falconer's model of multifactorial inheritance assumes that there is a graded attribute, termed 'liability', which underlies disease causation. Liability to disease has both genetic and environmental components. Genetic components include *additive* genetic effects, secondary to the random assortment of genes and *non-additive* genetic effects secondary to genetic dominance. Individuals with disease lie beyond a 'threshold' point on the curve of liability. Although liability curves shows a normal distribution for both the general population (spouses) and siblings of affected individuals, the curve for the latter is shifted to the right because of increased mean liability for disease.

Heritability h given by

$h^2 = 2b$

where

$$b = \frac{x_g - x_s(1-(x_g^2 - x_s^2)\ (1-x_g/a))^{1/2}}{a + x_s^2\ (a - x_g)}$$

(the sign of the square root is taken so that $0 \leq b \leq 1$)

and b is the regression of siblings on index cases in terms of liability,

x_g is the deviation of the threshold from the mean for total joint replacement in the general population as represented by spouses of patients,

x_s is the deviation of the threshold from the mean for total joint replacement in the siblings of patients, and

a is the mean deviation of liability of affected individuals from the population mean.

It is assumed that liability to total joint replacement is normally distributed in both siblings and spouses. The formula above, however, takes account of unequal variances to disease in these two groups. x_g, x_s and a are derived from published tables using prevalence figures for total joint replacement determined from our study.

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