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Risk factors in familial osteoarthritis: the GARP sibling study

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Summary

Purpose: To investigate the association between systemic and local risk factors and familial osteoarthritis (OA) at multiple sites.

Methods: Patients and their siblings had primary OA at multiple sites at middle age. OA diagnosis followed the American College of Rheumatology criteria. We recruited 345 controls (mean age 57 years (range 40–76), 64% women) by random sampling from the population by telephone and collected all data by questionnaires. Odds ratios (ORs) were adjusted for sex, age and body mass index (BMI) (kg/m^2), 95% confidence intervals (CIs95) were computed using robust standard errors with the intra-family effect taken into account.

Results: Three hundred and eighty-two patients (mean age 60 years [range 43–79]), 82% women had OA in the spine (80%), hands (72%), knees (34%) and hips (24%). In women, an association of familial OA with a young age at natural menopause (<45 years), OR = 2.6 (CI95 1.5–4.5) was found. Physically demanding jobs led to an increased risk of familial OA in men: OR = 2.6 (CI95 1.3–5.3). Familial OA was more prevalent in individuals with a BMI > 30, OR = 2.0 (CI95 1.3–3.2) compared to a BMI of <25. Taller persons had a lower risk of familial OA, OR = 0.33 (0.1–0.8) in the height category >180 cm relative to a height of <160 cm. A history of meniscectomy, increased the risk of familial OA at multiple sites with knee involvement, OR = 6.2 (CI95 3.0–12.7).

Conclusions: Systemic and local risk factors play a role in the etiology of familial OA at multiple sites.

Key words: Osteoarthritis, Generalized, Risk factors, GARP, Hip, Hand, Knee, Spine.

Osteoarthritis (OA) is a debilitating joint disorder with a multicausal etiology involving systemic and local risk factors. In this etiological model systemic risk factors, as age, sex, hormonal status, smoking, etc., which also include genetic factors, determine an individual's susceptibility to the impact of local risk factors, as obesity and occupations entailing high physical labor, with OA as a result in a certain joint[1]. Recently, genetic risk factors have been shown to be associated with OA, such as cytokine genes[2,3], matrillin gene[4], and frizzled-related protein (FRZB) gene[5,6]. Few data are available on the hypothesis whether, in patients with identified genetic risk factors, other systemic and local risk factors, contribute to OA development.

In the Ulm OA study, the investigators observed a positive association between knee OA and obesity, but this association was not found in the subset of patients with knee OA with concomitant polyarticular hand OA[7], a subset of OA with a strong familial predisposition, suggesting that in the presence of genetic risk factors, local factors have no additional contribution. A recent study, however, by Englund *et al.*, provided data suggesting interaction between genetic and local risk factors by demonstrating concomitant hand OA to increase the risk of knee OA after a meniscectomy[8]. Coggon *et al.* showed that the presence of concomitant Heberden nodes increased the risk of knee OA associated with obesity, but this was not so clear for hip OA[9].

In the present study we investigated that whether systemic and local risk factors are associated with OA in an OA phenotype, where genetic risk factors have been shown to be important. In earlier publications we demonstrated that familial OA at multiple sites is associated with FRZB gene[6] and higher innate *ex vivo* production of interleukin (IL)-1β[2]. A positive association with other systemic and local factors with familial OA at multiple sites would underscore the concept of a multicausal etiology of OA.

Materials and methods

The present study is part of the ongoing GARP (Genetics, Arthrosis and Progression) study, which was described earlier[10]. The GARP study is primarily aimed at the identification of genetic determinants of OA susceptibility and progression, so Caucasian sib pairs of Dutch ancestry with predominantly symptomatic OA at multiple sites were included. This well-characterized patient population enables us to investigate the role of systemic and local risk factors in familial OA at multiple sites.

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RECRUITMENT AND CLINICAL EVALUATION OF PATIENTS

One thousand eight hundred and seventy-four index patients (probands) aged between 40 and 70 years with symptomatic OA in the hands, knees or hips, diagnosed by rheumatologists, orthopedic surgeons and general practitioners in Leiden, The Hague, Delft, Haarlem and Amsterdam were informed of the ongoing study by mail. Of these 833 interested probands were screened by a mailed questionnaire for symptoms and signs of OA, medical history and a family history of OA. Subsequently, eligible probands with a positive family history in first-degree relatives ($n = 521$) were requested to introduce a sibling "with joint complaints", who was also addressed by a mailed questionnaire. Of these probands, 353 had at least one sibling with joint complaints. One hundred and thirty-nine of these siblings were either unwilling to participate ($n = 92$) or they did not meet the GARP criteria ($n = 47$), resulting in 214 eligible sib ships. After obtaining informed consent, all sib ships underwent a physical examination by a medical doctor (NR) at the outpatient clinic.

Patients with secondary OA and familial syndromes with a Mendelian inheritance pattern were excluded. Considered as secondary OA were as follows: (1) major congenital or developmental diseases and bone dysplasias, (2) major local factors such as severe scoliosis and hypermobility, (3) certain metabolic diseases associated with joint disease such as hemochromatosis and Wilson's disease, (4) inflammatory joint diseases such as rheumatoid arthritis, (5) other bone diseases such as morbus Paget and osteochondritis and (6) intra-articular fractures. Patients with a shortened life expectancy were also excluded. Crystal deposition arthropathies (unless in the case of severe polyarticular gout), and diabetes mellitus or thyroid conditions were not considered as exclusion criteria.

OA DIAGNOSIS

Probands and siblings were included in the GARP study with OA at multiple joint sites in the hands or with OA in two or more of the following joint sites: hand, spine (cervical or lumbar), knee, or hip. Both subjects were required to have symptomatic OA (as defined below) in at least one joint site. Subjects with symptomatic OA in just one joint site were required to have structural abnormalities in at least one other joint site defined by the presence of radiographic OA or the presence of two or more Heberden nodes, Bouchard nodes or squaring of at least one carpometacarpal (CMC) 1 joint on physical examination.

Symptomatic OA in the knee and hip was defined following the American College of Rheumatology (ACR) recommendations for knee and hip OA[11,12]. Knee OA was defined as pain or stiffness for most days of the prior month and osteophytes at joint margins of the tibiofemoral joint (X-ray spurs). Hip OA was defined as pain or stiffness in the groin and hip region on most days of the prior month in addition to femoral or acetabular osteophytes or axial joint space narrowing on radiograph. Joint prosthesis in the hips or the knees as a result of end-stage OA was included as OA in that particular joint. Spine OA (cervical and lumbar) was defined as pain or stiffness on most days of the prior month in the spine in addition to a Kellgren–Lawrence score of two in at least one disc or one apophyseal joint. OA in hand joints was defined according to the ACR criteria[13] as pain or stiffness on most days of the prior month in addition to three of the following four criteria: bony swelling of two or more of the 10 selected joints (bilateral distal interphalangeal (DIP) joints $2 + 3$, bilateral proximal interphalangeal (PIP) joints $2 + 3$ and CMC 1 joint), bony swelling of two or more DIP joints, less than three swollen metacarpal (MCP) joints and deformity of at least one of the 10 selected joints.

RADIOGRAPHS

Conventional radiographs of the hands (dorso-volar), knees (posterior–anterior [PA] in weight bearing/semi flexed and lateral supine), hips (PA, weight bearing), lumbar (PA and lateral, supine) and cervical spine (anterior–posterior, lateral and transbuccal) were obtained from all participants. Conventional radiographs were scored by a single experienced musculoskeletal radiologist (HK) for osteophytes in the knees and hips and joint space narrowing in the hips. In addition to the hands (DIPs, PIPs and CMC 1), the discs and apophyseal joints of the cervical and lumbar spine, the hips and tibiofemoral joints of the knees were also scored according to the Kellgren–Lawrence scale with the help of the original atlas[14]. This is a five-point scale, scoring system with ascending severity, based on the presence of osteophytes, joint space narrowing, sclerosis and degenerative cysts. A Kellgren–Lawrence score of ≥ 2 depicts OA in a particular joint.

The intra-reader variability for the different joint sites, scored by the Kellgren–Lawrence method, depicted by the intra-class correlation-coefficient (ICC) (95% confidence interval [CI95]) was for the hands 0.95 (0.92–0.96), for the knees (tibiofemoral) 0.92 (0.86–0.96), for the hips 0.95 (0.92–0.98), for the cervical spine (apophyseal and disc) 0.71 (0.52–0.84) and for the lumbar spine (apophyseal and disc) 0.67 (0.46–0.81). The intra-reader variability was based on the examination of radiographs of 40 subjects that were selected randomly throughout the duration of the study period and were blinded for any patient characteristics.

CONTROLS

Controls in the present study were frequency-matched to the probands only for age (±5 years) and geographic region. As the probands consisted of 162 women and 29 men, we aimed to recruit a minimal of 170 women and 100 men as controls. We excluded the siblings from the matching due to the intra-family effect. The controls were recruited by random sampling of the population by telephone using the Mitofsky–Waksberg method for random-digit-dialing[15], where random telephone numbers are generated and called. If a residence is contacted during the first attempt, the last two digits of that number are randomly varied and called, the Primary Sampling Unit (PSU). Within each PSU, a predetermined number of residential telephones K is sampled. In the present study K was 10 and a telephone number was abandoned after seven failed attempts made at different times to obtain a response. Callers were given detailed instructions for the telephoning procedure and were requested to inquire for a specific person in the household on the basis of the sex and age category of the required control. The controls who were willing to participate completed questionnaires similar to the questionnaires used in the GARP study. We did not further screen the control for the presence or absence of OA.

DATA ASSESSMENT IN GARP

Demographic characteristics, height, weight, smoking, marital status, hormonal status, job titles and the presence of OA symptoms were collected by standardized questionnaires and verified at the outpatient clinic.

Job title classification of physically demanding work was based on a revised classification scheme constructed according to a comprehensive occupational classification scheme, by Schellart, of physical and mental work demands into different categories according to a an expert judgment of job titles used in the Netherlands[16]. The category of physically demanding work is characterized by lifting of heavy objects, handling of heavy tools, stooping, frequently in combination with standing or walking. Examples of occupations in this category are jobs in construction work, the agricultural sector and industry. Job title classification was done simultaneously and blinded for patients and controls.

Natural menopause was defined as the age of natural cessation of menses; all women who were premenopausal at the time of either hysterectomy or ovariectomy were not included in these analyses. Women with a unilateral ovariectomy in the history were also not eligible, because this is known to be associated with an earlier age at menopause. Further, not included in these analyses were all women whose age at menopause could not be determined with certainty due to hormone supplements. In line with other studies on this subject, early menopause was defined as natural menopause before the age of 45[17].

STATISTICAL ANALYSIS

In the present study, all analyses were done by using the controls as comparator. Throughout the manuscript, the term OA refers to familial, symptomatic OA at multiple sites. In the subanalyses of risk factors with regard to specific joint sites, OA at each site was dichotomized according to the presence or absence of OA. Odds ratios (ORs) were calculated, using logistic regression, to adjust for age, sex and body mass index (BMI). ORs are presented with a CI95. To take into account the intra-family effect, robust standard errors were computed using the statistical program STATA 7.0. Continuous data were analyzed using Student's t test.

Results

STUDY POPULATION

After a clinical and radiographic evaluation, 382 patients (191 sib pairs) were included in the GARP study. The controls were recruited from 527 potential candidates from 1202 household contacts of the 3360 telephone numbers that were called. Of the 527 candidates, 376 (71%) were willing to participate and 345 returned a completed questionnaire.

The characteristics of the 382 patients with familial OA are shown in Table I. The mean age of the patients was 60 years (43–79). There was a small difference between the mean age of the patients and that of the controls who were 57 years (40–76), mean difference = 3.3 (CI95 2.1–4.6). The patients consisted for 82% of women in comparison to 64% women in the controls. All patients had structural abnormalities at multiple sites and nearly all patients (97%)