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Development of a prediction model for future risk of radiographic hip osteoarthritis

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SUMMARY

Objective: To develop and validate a prognostic model for incident radiologic hip osteoarthritis (HOA) and determine the value of previously identified predictive factors.
Design: We first validated previously reported predictive factors for HOA by performing univariate and multivariate analyses for all predictors in three large prospective cohorts (total sample size of 4548 with 653 incident cases). The prognostic model was developed in 2327 individuals followed for 10 years from the Rotterdam Study-I (RS-I) cohort. External validation of the model was tested on discrimination in two other cohorts: RS-II ($n = 1435$) and the Cohort Hip and Cohort Knee (CHECK) study ($n = 786$).
Results: From the total number of 28 previously reported predictive factors, we were able to replicate 13 factors, while 15 factors were not significantly predictive in a meta-analysis of the three cohorts. The basic model including the demographic, questionnaire, and clinical examination variables (area under the receiver-operating characteristic curve (AUC) = 0.67) or genetic markers (AUC = 0.55) or urinary C-terminal cross-linked telopeptide of type II collagen (*u*CTX-II) levels (AUC = 0.67) alone were poor predictors of HOA in all cohorts. Imaging factors showed the highest predictive value for the development of HOA (AUC = 0.74). Addition of imaging variables to the basic model led to substantial improvement in the discriminative ability of the model (AUC = 0.78) compared with *u*CTX-II (AUC = 0.74) or genetic markers (AUC = 0.68). Applying external validation, similar results were observed in the RS-II and the CHECK cohort.
Conclusions: The developed prediction model included demographic, a limited number of questionnaire, and imaging risk factors seems promising for prediction of HOA.

Introduction

The number of people affected with osteoarthritis (OA) is likely to increase due to the high prevalence of obesity and aging of the population while, to date, there are no curative treatment options which allow regeneration of damaged cartilage[1,2]. The current focus in OA research and clinical practice is on persons with radiographic symptomatic disease[3]. Despite extensive researches, modern therapies are largely palliative and only modestly effective. There is presently no disease-modifying OA drug with a consistent, documented effect despite several clinical attempts in late-stage phases. This reinforces the need for interventions in early OA or even before development of symptoms to develop preventive strategies[3]. Therefore, clinicians have the challenging task to identify those individuals that will develop OA as early as possible. Identification of high-risk individuals will be beneficial for efficient screening of novel therapeutic options, since follow-up time and number of

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individuals included in the studies can be reduced when only subjects are included which are at a high risk of developing OA.

Conventional risk prediction models, although well established in other disease areas, such as cardiovascular disease, have not been developed in OA and in particular not for hip osteoarthritis (HOA). Two recent studies reported on prediction models for incidence and progression of knee OA[4,5]. In the first study[4], three different models were evaluated for incident and progressive radiographic knee OA and symptomatic knee OA among a small high-risk cohort of 99 cases and 179 controls with 12 years of follow-up using conventional risk factors such as age, gender, body mass index (BMI), family history of OA, occupational risk, and joint injury. However, external validation of these models in the Osteoarthritis Initiative showed poor discrimination. In another study among Rotterdam Study (RS) participants[5], different risk prediction models were developed using basic risk factors (i.e., age, gender and BMI) and were compared with less conventional risk factors such as radiographic features, genetic risk score, and biochemical marker of urinary C-terminal cross-linked telopeptide of type II collagen (*u*CTX-II) levels. They showed that all risk factor groups by themselves had limited and rather similar predictive value, while the full model had useable predictive value and showed good external validation.

In the current study, we focus on prediction of incident HOA. A recent review highlighted the fact that HOA requires specific attention separate from other OA phenotypes, since its etiology is different from knee OA[6]. Surprisingly very little prospective data on HOA are available, since the majority of risk factor assessment has been done on cross-sectional data. In addition, no study has tried to make a prediction model for HOA using multiple risk factors, something that was recently highlighted to be essential for future monitoring and managing of HOA patients[6]. In the current manuscript, we therefore aimed to determine the value of various sets of risk factors, which were selected based on previous literature. These included anthropometric/demographic characteristics, routine questionnaire and clinical examination parameters, imaging risk markers, biochemical marker of *u*CTX-II, and genetic markers in HOA risk prediction. We attempted to validate the previously suggested risk factors for HOA in three large prospective cohorts, and then used that information to develop and validate a prognostic model for incident HOA. We used the first cohort of the large prospective population-based Rotterdam Study (RS-I) to develop the risk prediction model. The model was externally validated in the second cohort of the RS (RS-II), which is an independent cohort with similar population characteristics, and the Cohort Hip and Cohort Knee (CHECK) study, which is a study of people who for the first time consult the general practitioner for their joint complaints. Our study is the first to compare the value of different risk factor groups including the clinical, imaging, genetic, and biochemical markers in prediction of HOA and provides the first risk prediction model for incident HOA.

Methods

Study populations

The RS is a large prospective population-based cohort study of men and women aged 55 years and older in the municipality of Rotterdam, the Netherlands. The study design and rationale are described elsewhere in detail[7]. The first cohort (RS-I) was initiated in 1989 and included 7983 individuals. The second cohort (RS-II) was initiated in 2000 and included 3011 inhabitants who reached the age of 55 years after the baseline examination and persons aged 55 years or older who migrated into the research area. Written informed consent was obtained from all participants and the study was approved by the Medical Ethics Committee of the Erasmus Medical Center[7]. Baseline measurements were obtained through a home interview and visits to the research center for physical examinations and imaging and laboratory assessments. The present study includes the cohort's participants for whom hip radiographs at baseline and 10 years follow-up were present and scored. Patients with ankylosing spondylitis (AS), rheumatoid arthritis (RA), and subjects with a total hip replacement (THR) due to fracture were excluded from the study. After these exclusions, 2327 participants from RS-I were used to develop the risk prediction model and 1435 participants from RS-II were used for external validation of the model (Fig. 1).

The CHECK study included 1002 participants aged 45–65 years living in the Netherlands, with early symptomatic OA characterized by pain of knee and/or hip, entered the cohort in the period October 2002 to September 2005. They were included at or within 6 months of their first visit to the general practitioner for these symptoms[8]. Participants with a pathological condition that could explain the hip symptoms were excluded including intra-articular fractures, RA, congenital dysplasia, Perthes disease, subluxation, osteochondritis dissecans, septic arthritis, previous hip joint replacement, previous hip surgery, and individuals having only symptoms of bursitis or tendinitis. This left 786 participants with 8 years follow-up from the CHECK study for external validation of the risk prediction model (Fig. 1).

Outcome assessment

Weight-bearing antero-posterior radiograph of the pelvis was obtained at baseline and follow-ups and scored for the presence of a THR and OA according to the Kellgren and Lawrence (K&L) score[9]. Radiographic HOA was defined as a K&L score $\geq$2 of one or both joints or a THR. The incidence of HOA was defined as a K&L < 2 at baseline and THR or K&L $\geq$ 2 at follow-up. All subjects were free of HOA in both sides at baseline.

Risk factors

Previously suggested HOA risk factors or predictors that were available in RS were included in the study. These include age, obesity (BMI and waist to hip ratio (WHR)), gender, height, family history of OA, occupation, smoking, education, alcohol intake, diabetes, high blood pressure (HBP), joint pain (hip, knee, low back), hip joint morning stiffness, lower limb disability (LLD) index, and baseline measurement of total cholesterol, high-density lipoprotein cholesterol level (HDL), and C reactive protein (CRP), hip baseline K&L score (0 or 1), hand OA divided as finger OA and thumb OA, subtle acetabular dysplasia, cam morphology, femoral neck bone marrow density (BMD) at baseline, *u*CTX-II, and a genetic risk score (Supplementary Table I). The Supplementary Material describes the methods for measuring all of the risk predictors.

Statistical analysis

Age- and sex-adjusted generalized estimating equation (GEE) model (a logit model) was used to evaluate the association between the predictive factors and HOA incidence within each cohort, followed by a meta-analyses of the results.

Development of the risk prediction model

GEE model was used to fit the models for correlations between the right and left extremity in each individual using RS-I cohort. Using a backward elimination, we made a basic model that included the demographic, questionnaire, and clinical and routine laboratory examination variables. The variable that was least

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