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# Knee tissue lesions and prediction of incident knee osteoarthritis over 7 years in a cohort of persons at higher risk

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SUMMARY

*Objective:* Among high risk individuals, whether knee lesions in tissues involved in osteoarthritis (OA) can improve prediction of knee OA is unclear. We hypothesized that models predicting (1) incident osteophytes and (2) incident osteophytes and joint space narrowing can be improved by including symptoms or function, and further improved by lesion status.

*Design:* In Osteoarthritis Initiative (OAI) participants with normal knee X-rays, we assessed cartilage damage, bone marrow lesions (BMLs), and menisci. Cox proportional hazards models were used to develop risk prediction models for risk of each outcome. Nested models (increasingly larger baseline covariable sets) were compared using likelihood ratio tests and Schwarz Bayesian Information Criterion (SBC). Model discrimination used receiver operating characteristic (ROC) curves and area under the curve (AUC).

*Results:* In 841 participants [age 59.6, body mass index (BMI) 26.7, 55.9% women] over up to 7 years follow-up, each larger set improved prediction (+hand OA, injury, surgery, activities; +symptoms/function). Prediction was further improved by including cartilage damage both compartments, BMLs both compartments, meniscal tear, meniscal extrusion, sum of lesion types, number of subregions with cartilage damage, number of subregions with BMLs, and (concurrently) subregion number with cartilage damage, subregion number with BMLs, and meniscal tear. AUCs were ≥0.80 for both outcomes for number of subregions with cartilage damage and the combined model.

*Conclusions:* Among persons at higher risk for knee OA with normal X-rays, MRI tissue lesions improved prediction of mild as well as moderate disease. These findings support that disease onset is likely occurring during the "high-risk" period and encourage a reorientation of approach.



## Introduction

Current treatments for knee osteoarthritis (OA) may help symptoms but do not affect disease progression. Disease modification requires tackling the multi-faceted, downward spiral of joint tissue events that is progressive knee OA. Efforts to delay disease development and early-stage intervention may be more cost-effective than treatment of established OA[1,2]. The widely

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established definition of knee OA (radiographic Kellgren/Lawrence (KL) grade ≥2) hinges on unequivocal osteophyte presence. However, in knees graded KL 0 (normal) or KL 1 (possible osteophyte), knee tissue lesions are not infrequent in MRI studies, whether they include only persons at higher risk[3,4] or not[5,6]. Evidence is accumulating to support the hypothesis that these lesions are not incidental[3,4,7–13]. These lesions occur in tissues typically involved by the whole-organ disease of OA, i.e., cartilage, subchondral bone, and menisci; given this, they likely are not risk factors per se but may represent signs of disease. Whether they represent early OA is a challenging question to address at a study population level. Risk prediction modeling in this context enables evaluation of whether tissue lesion status improves the prediction of incident knee OA using the established definition (after considering known predictors), as would be expected if these lesions represent early disease.

To our knowledge, previous studies have not examined whether tissue lesion status can improve prediction of incident knee OA risk. Furthermore, previous studies of risk prediction models, while groundbreaking, were not limited to radiographically normal (KL 0) knees, the status of the vast majority of the high risk population. Zhang *et al.* developed a risk prediction model for incident knee OA (defined as KL ≥2), incorporating age, gender, body mass index (BMI), occupational kneeling/lifting, injury, and family history of OA; to validate the model, they used Osteoarthritis Initiative (OAI) and Genetics of Osteoarthritis and Lifestyle (GOAL) data[14]. In the Rotterdam Study (RS)-I (with validation in RS-II and the Chingford Study), Kerkhof *et al.* developed a prediction model for incident KL ≥2; questionnaire variables, genetic score, or a urinary biomarker did not improve prediction [comparing the area under a receiver operating characteristic (ROC) curve (AUC)] vs age, gender, and BMI[15]. The AUC was improved by adding baseline KL 1 (possible osteophytes)[15].

We undertook MR image readings in a cohort of OAI participants who were KL 0 in both knees (since risk of knee OA is increased by contralateral knee OA). We hypothesized that, in persons KL 0 in both knees, models for prediction of (1) incident KL ≥2 and (2) incident KL ≥2 and joint space narrowing can be improved by including baseline symptoms or function, and further improved by inclusion of knee lesion status, as would be expected if these lesions represented an early stage of disease. The widely established definition of knee OA (KL ≥2) is the basis of a large literature documenting impact and burden of knee OA. However, because KL = 2 knees may or may not progress beyond a mild stage, we included a secondary outcome, requiring the additional presence of joint space narrowing, corresponding with moderate disease.

## Methods

The OAI is a prospective, observational cohort study of persons with or at higher risk for knee OA, enrolled in Baltimore MD, Columbus OH, Pittsburgh PA, or Pawtucket RI, between February 2004 and May 2006. OAI incidence subcohort eligibility required characteristics associated with increased risk of developing knee OA [symptoms, overweight, injury, surgery, family history of total knee replacement (TKR), Heberden's nodes, repetitive knee bending, age 70–79 years] and absence of: symptomatic knee OA; inflammatory arthritis; severe bilateral joint space narrowing; TKR and severe contralateral narrowing; bilateral TKR or planned within 3 years; MRI contraindications; aide >50% of ambulation (except one cane); severe comorbidity; double-blind trial participation[16,17]. An additional requirement for our study was bilateral KL = 0 (by centralized readings) at the 12-month visit, our ancillary study's baseline MRI assessment (per the timing of the award of the grant that added other assessments to the 12-month evaluation and funded the MRI readings). The Institutional Review Board at each site approved the study.

### *Tissue lesions*

MR image acquisition utilized 3.0T Siemens Trio scanners at each site. Sequences included coronal intermediate-weighted (IW) turbo spin echo (TSE), sagittal IW TSE with fat-suppression, and 3D Dual Echo Steady State water excitation, acquired in the sagittal plane with coronal and axial multiplanar reconstructions; acquisition parameters are described in detail in the publicly available OAI manual[18].

We undertook right knee (left knee, if right knee images technically unacceptable) MRI readings in persons determined by the coordinating center to meet the KL criterion at the 12-month visit. Three expert musculoskeletal radiologists (MC, AG, FWR) used the MRI OA Knee Score (MOAKS)[19], blinded to hypotheses, KL criterion, and all study data. In terms of lesion assessment relevant to this study, with the exception of inter-rater reliability for tibial cartilage surface area, all measures of reliability were very good (0.61–0.8) or reached near-perfect agreement (0.81–1.0) according to the criteria developed by Landis and Koch[19,20]. The low prevalence of certain features in certain sub-regions may have adversely affected the kappa results hence the percent agreement was also calculated. All features relevant to this study were scored with overall percent agreement above 75% for both the intra- and inter-reader exercise (19). Paired images were read with chronology known[21]. Cartilage morphology was scored in four patellofemoral (PF) and 10 tibiofemoral (TF) subregions: **0**, normal; **1.0**, 1–10% area damaged, no full-thickness; **1.1**, 1–10% area, 1–10% full-thickness; **2.0**, 10–75% area, no full-thickness; **2.1**, 10–75% area, 1–10% full-thickness; **2.2**, 10–75% area, 10–75% full-thickness; **3.0**, >75% area, no full-thickness; **3.1**, >75% area, 1–10% full-thickness; **3.2**, >75% area, 10–75% full-thickness; **3.3**, >75% area, >75% full-thickness. Bone marrow lesions (BMLs) were scored in the same subregions: **0**, none; **1**, <25% of subregion; **2**, 25–50%; **3**, >50%. For each meniscus, three subregions were scored: **0**, normal; **1**, signal abnormality; **2**, horizontal tear; **3**, vertical tear; **4**, complex tear; **5**, root tear; **6**, partial maceration; **7**, progressive partial maceration; **8**, complete maceration. Extrusion was scored for each meniscus[22]: **0**, none; **1**, <50% extruded; **2**, ≥50% extruded[19,22].

For cartilage damage and BMLs: “any” was defined as score >0 in ≥1 TF or PF subregion; “both TF and PF” was defined as score >0 in ≥1 TF and ≥1 PF subregion; and “number of subregions” was number of TF and PF subregions with score >0. Meniscal tear was defined by any subregion score >1, and extrusion by any score >0. Sum of lesion types was the number of lesion types present (0–4). Maximum cartilage damage (surface area) was defined as most severely damaged cartilage across all knee subregions (0 = normal; 1 = MOAKS 1.0 or 1.1; 2 = MOAKS 2.0, 2.1, or 2.2; and 3 = MOAKS 3.0, 3.1, 3.2, or 3.3) and maximum cartilage damage (full thickness) as most severely damaged (0 = normal; 1 = 1.0, 2.0, or 3.0; 2 = 1.1, 2.1, or 3.1; 3 = 2.2 or 3.2; and 4 = 3.3). Maximum BML severity was defined as worst BML score across all subregions.

### *Predictors*

Predictors were also assessed at the 12-month visit. BMI was analyzed as a categorical variable [normal (reference category), overweight (BMI ≥ 25 and <30 kg/m$^2$), obese (BM I ≥ 30)]. Race was analyzed as African-American vs other. Family history of TKR for OA was defined by self-report for biological parent or sibling. Hand OA was assessed by: self-reported hard bumps on joints nearest fingertips; and exam, as ≥2 bony enlargements of distal interphalangeal or thumb interphalangeal joints in ≥1 hand. In the