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Novel statistical methodology reveals that hip shape is associated with incident radiographic hip osteoarthritis among African American women

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SUMMARY

Introduction: Hip shape is a risk factor for the development of hip osteoarthritis (OA), and current methods to assess hip shape from radiographs are limited; therefore this study explored current and novel methods to assess hip shape.
Methods: Data from a prior case–control study nested in the Johnston County OA Project were used, including 382 hips (from 342 individuals). Hips were classified by radiographic hip OA (RHOA) status as RHOA cases (baseline Kellgren Lawrence grade [KLG] 0 or 1, follow-up [mean 6 years] KLG $\geq$ 2) or controls (KLG = 0 or 1 at both baseline and follow-up). Proximal femur shape was assessed using a 60-point model as previously described. The current analysis explored commonly used principal component analysis (PCA), as well as novel statistical methodologies suited to high dimension low sample size settings (Distance Weighted Discrimination [DWD] and Distance Projection Permutation [DiProPerm] hypothesis testing) to assess differences between cases and controls.
Results: Using these novel methodologies, we were able to better characterize morphologic differences by sex and race. In particular, the proximal femurs of African American women demonstrated significantly different shapes between cases and controls, implying an important role for sex and race in the development of RHOA. Notably, discrimination was improved with the use of DWD and DiProPerm compared to PCA.
Conclusions: DWD with DiProPerm significance testing provides improved discrimination of variation in hip morphology between groups, and enables subgroup analyses even under small sample sizes.

Introduction

Hip osteoarthritis (OA) is a growing public health problem, and led to the majority of the more than 450,000 hip replacements in the United States in 2012 with total aggregate charges of more than 25 billion US dollars[1]. Although sex differences are less marked for hip OA than for OA at other sites[2–4], women compared with men, and African Americans compared with whites, were more likely to have hip symptoms (women 39.5% vs men 31.8%; African American 37.1% vs white 36.0%), radiographic hip OA (RHOA, women 29.5% vs men 25.4%; African American 32.1% vs white 26.6%), and

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symptomatic hip OA (women 11.1% vs men 8.3%; African American 12.0% vs white 9.2%) in the Johnston County Osteoarthritis Project[5]; African American women had the highest weighted prevalence of symptomatic hip OA among the four race by sex subgroups, at 12.2%.

Bone morphology has recently garnered interest as a risk factor for the development of OA. Joint shape is of particular interest in relation to hip OA, given known OA risk factors such as dysplasia and femoroacetabular impingement as well as developmental factors which impact anatomy specifically at this joint. Our group and others have reported on associations between baseline hip shape (analyzed using modes generated from principal component analysis [PCA]) and incident RHOA, symptomatic RHOA, clinical hip OA, and total hip replacement[6–10]. Specifically, in our prior analysis[10], we found several modes of shape variation that differed by race and sex, 2 modes that were associated with incident RHOA among men only (none in women), and 3 modes that were associated with incident symptomatic RHOA[10]. Smaller subgroup analyses were limited due to small sample sizes.

To date, such analyses have relied upon principal component-based methods, which are limited in their ability to optimally discriminate between shape variants, particularly when the dimensionality of the model is much greater than the number of available hips for study. For example, in our prior paper, we described a 60-point (120-dimension) model of proximal femur shape in 382 hips, but we were prevented from exploring subgroups such as African American women or men due to small numbers in our sample ($n = 49$ and 16, respectively). Therefore, in this paper, we sought to optimize discriminant ability between hip shape variants by utilizing novel statistical methodology based in machine learning and designed for such high dimensionality low sample size (HDLSS) settings, which allows simultaneous consideration of the entire hip shape rather than separate discrete components (i.e., individual mode scores). We describe analyses using four categories by sex and race, and compare case hips that developed incident RHOA to control hips that did not use these recently developed statistical methods, allowing improved discrimination and more conclusive results.

Methods

The data were from a case–control study nested in the Johnston County Osteoarthritis Project, including 382 hips from 342 individuals as previously described[10]. In brief, participants had standardized supine anteroposterior pelvis radiographs at baseline and at follow-up (mean of 6 years later). These radiographs were read paired and blinded to clinical status and chronological order by a single musculoskeletal radiologist. At baseline, all hips had a Kellgren Lawrence grade (KLG) of 0 or 1. Case hips ($n = 190$) developed RHOA, defined as KLG ≥ 2 at follow-up, while control hips ($n = 192$) remained KLG 0 or 1 at follow-up. For all hips, the shape of the proximal femur was defined on baseline pelvis radiographs using a 60-point model with high reliability as previously detailed[9,10]; left hip radiographs were mirrored to mimic right hips such that all hips could be included in a single shape model.

This paper employs three cutting edge statistical methods applicable to high dimensional low sample size contexts and with minimal assumptions: Object Oriented Data Analysis[11], which advocates treating each shape as a data object (essentially one data point) and improves statistical power; Distance Projection Permutation (DiProPerm)[12] hypothesis testing, which is a nonparametric permutation based test which preserves that improved power; and the Distance Weighted Discrimination (DWD)[13] machine learning algorithm which identifies a separating direction between classes.

For the current analysis, in order to fully exploit advantages of these multivariate analysis techniques, we first transformed the 2-dimensional curves into a 120-dimensional vector for each hip by combining x- and y-coordinate (pixel coordinates normalized for size) values of each curve into one vector. After statistical analysis was performed on these 120-dimensional vectors, each vector was transformed back into x- and y-coordinates to allow plotting of femur shape through 2-dimensional curves. Investigation of the association of femur shape with various characteristics was based on hypothesis testing for the difference between two distributions (e.g., cases and controls) with a significance level set at 0.05. Analyses of association followed four steps (see Methodology Supplement for details) in a manner that allowed comparison of the traditional PCA approach with the novel DWD and DiProPerm approach. First, scatter plots were assessed for visual differences using the first four PCA directions and the DWD direction[13]. Next, a series of naïve 2-sample Student's t-tests were performed on each set of PCA projection scores with Bonferroni correction for multiple ($n = 4$) comparisons to determine the statistical significance of each. Then, the potentially significant difference between the two distributions in the DWD direction was investigated using the DiProPerm test[12]. Finally, the femur shape variation was plotted to give anatomical insights into the direction and type of variation between the cases and controls. Receiver operating characteristic (ROC) curves were employed to compare directly the discriminative ability of these two methods. Sensitivity analyses were employed to investigate adjustment for covariates (age, BMI, and KLG) and for non-independent observations.

Results

The analysis included 382 hips from 342 individuals (39% men, 18% African Americans, mean age 62 years, mean baseline body mass index 29 kg/m^2), with 190 case and 192 control hips. Of the 382 hips, 185 were from white women, 132 from white men, 49 from African American women, and 16 from African American men (Table I).

Figure 1 demonstrates the shape distributions of case and control proximal femurs by four sex and race subgroups, showing potential differences in the mean femur shape among cases and controls, particularly for African Americans.

Therefore, we were interested in further exploring potential differences between cases and controls for hip shape among African American women, a small subset of the overall sample (49/382). First, following standard methodology, the scatter plots generated by the projection of the first 4 principal components (PCs; together explaining 76% of the total variance) are shown in Supplemental Fig. (A). A 2-sample t-test was applied to each of the four principal directions with a Bonferroni correction such that each P-value of the standard t-test was multiplied by 4, the number of tested variables (of note, P-values > 1 are censored at 1). As can be seen from Supplemental Fig. (A), the corrected P-value for the t-test on the 3rd PC was 0.052, which is nearly statistically significant.

To compare this to our novel methodology, the scatter plots of the projections in the DWD direction and the orthogonal principal directions are shown in Supplemental Fig. (B). As expected, the projections on the DWD direction showed a more evident distinction between the incident RHOA cases and controls than any individual PC in Supplemental Fig. (A). The potentially statistically significant difference between the distributions of the incident RHOA cases and controls among African American women was confirmed using the DiProPerm test, which quantified the inferential uncertainty with a P-value of 0.033, as shown in Fig. 2.

The left panel of Fig. 2 [replicated from the upper left element in Supplemental Fig. (B)] displays the visual difference between the