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Site specific osteoarthritis and the index to ring finger length ratio

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Summary

Objective: To quantify the relationship between the index to ring finger length ratio second digit:fourth digit(2D:4D) and radiographic osteoarthritis (OA) of the knee.

Methods: Data from the Clearwater Osteoarthritis Study (COS) were analyzed. We selected a random sample of 236 subjects with knee OA (Kellgren–Lawrence scores ≥2) and compared their finger length ratio pattern with a random sample of 242 controls. Finger length measurements were recorded from digitized hand radiographs. Subjects were classified into three groups: type 1 (index finger longer than ring finger), type 2 (fingers of equal length) and type 3 (index finger shorter than ring finger). Using a case-control design, we calculated odds ratios (OR).

Results: The type 3 finger pattern was significantly associated with knee OA (OR 2.59, 95% confidence interval (CI) 1.54–4.37). Women demonstrated a stronger association of visual type 3 finger pattern and knee OA (OR 4.40, 95% CI 2.62–7.38) compared to men (OR 2.59, 95% CI 1.34–5.00).

Conclusions: The type 3 finger length pattern is associated, to a statistically significant degree, with OA of the knee. The type 3 finger length pattern (ring finger longer than index finger) appears to be an indicator of OA predisposition. Consideration of this pattern in clinical assessments may be an added aid as clinicians screen patients for OA risk.

Key words: Digit ratio, Osteoarthritis.

Introduction

Osteoarthritis (OA) is a common complex disorder with multiple risk factors[1]. Clinically determined markers of risk could prove useful for identifying people for appropriate targeting of primary prevention measures. The ratio of the lengths of the second digit (2D), or index finger, to the fourth digit (4D), or ring finger, is a sexually dimorphic trait such that males tend to have a lower mean 2D:4D ratio than females[2]. In other words, in males the index finger is usually shorter than the ring finger. The index to ring finger length ratio has been associated with a wide variety of behavioral and physiological traits. For example, the 2D:4D ratio has been hypothesized to be an indicator of prenatal exposure and adult levels of testosterone and estrogen[2–5], congenital adrenal hyperplasia[6], coronary heart disease[7], age at myocardial infarction[8], athletic ability[9,10] and academic performance[11,12]. A recent publication by Zhang, *et al.*[13] provided compelling evidence that the index to ring finger length ratio is also associated with the risk of developing knee OA. The findings by Zhang *et al.* led us to test the same hypothesis tapping into the database from the Clearwater Osteoarthritis Study (COS).

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Subjects and methods

Data collected from volunteer subjects enrolled in the COS were used. In 1988, The Arthritis Research Institute of America (ARIA) initiated the COS. It is an on-going community-based longitudinal cohort study designed to identify the major risk factors for the development and progression of radiographic OA. Currently in its twenty-first year, the 25 year longitudinal study follows individuals 40 years of age and older, collecting demographic, historical, clinical, and radiological data. The COS Study is a dynamic entry cohort with on-going enrollment. To date, more than 3700 enrollees have been recruited and examined. The COS houses one of the largest repositories of sequential radiographic OA data. All study visits are conducted at the institute's sole location in Clearwater, Florida. The study has been fully funded by individuals' private donations. There is no cost, nor compensation, to the study subjects. Subjects are motivated to participate, and continue, by their desire to advance medical knowledge and having the satisfaction of helping others. ARIA is located in Pinellas County, Florida drawing upon a population with a large percentage of residents 65 years and older. The study sample of this older community is comprised of subjects who are recruited by various methods. These include: invitational letters, television and radio announcements, newspaper articles publicizing the COS study, articles posted in community organizations' bulletins, as well as seminars held at community clubs and organizations. In efforts to include younger subjects who are more likely to be free of OA, concerted recruitment efforts were used to encourage participation by employees of the Pinellas County School System and the City of Clearwater. Research was conducted in compliance with the Helsinki Declaration. The COS was approved by the Institutional Review Board of ARIA. Many COS details have been reported elsewhere[14–17] and are available on the Institute's website, www.preventarthritis.org. Study characteristics of the case and control subjects, by OA site, are shown in Table I.

CASES AND CONTROLS

The COS knee radiographs are graded for OA status using the ordinal Kellgren–Lawrence scale[18]. Cases of radiographic knee OA were defined as having a score of grade 2 or higher on the Kellgren–Lawrence scale. Radiographic knee OA assessment was restricted to tibio-femoral OA alone.

Table I
Characteristics of the study sample, by radiographic knee OA status

	Knee OA status		P-value
	Yes ($n = 236$)	No ($n = 242$)	
No. Men/Women	88/148	65/177	0.02
Age, mean (SD)	69 (9)	57 (9)	<0.001
BMI, mean (SD)	29.8 (5.9)	25.6 (4.7)	<0.001
Visual finger pattern			<0.001*
1	34	56	
2	78	131	
3	124	55	
2D:4D phalangeal ratio, mean (SD)	0.91 (0.07)	0.92 (0.09)	0.10
2D:4D combined ratio, mean (SD)	1.02 (0.05)	1.03 (0.06)	0.08

*OA cases were rated by knee OA of score 2+ on the Kellgren–Lawrence scale. 2D:4D = index to ring finger ratio.

At the time the COS data were pulled for the purpose of this current study, there were 626 cases of radiographic knee OA. Our primary hypothesis was: "Type 3 finger pattern is positively associated with an elevated risk of radiographic knee OA". A random sample of 274 knee OA cases was generated. Study controls were defined as COS subjects who exhibited no evidence of OA, by either radiograph or self-reported pain status. From the 1453 subjects who met these criteria, a random sample of 274 controls was generated. The simple randomization without replacement method was used to select the cases and the controls.

RADIOGRAPHIC CLASSIFICATION OF OA

Radiographic classification of OA was assessed as previously described[17]. Briefly, serial X-rays were taken at study baseline and subsequently at 2-year intervals. A case was defined when radiographic structural evidence of disease was found. Each radiograph was graded 0–4 for OA by the criteria of Kellgren–Lawrence[18]: 0, absent; 1, questionable osteophytes and no joint space narrowing; 2, definite osteophytes with possible joint space narrowing; 3, definite joint space narrowing with moderate multiple osteophytes and some sclerosis; 4, severe joint space narrowing with cysts, osteophytes and sclerosis present. The weight-bearing, anterior–posterior knee radiographs were taken by a licensed X-ray technician using standard exposure techniques. The control group (free of knee OA) was also free of OA at the hand, foot, and cervical spine. Hand OA was defined as evidence of disease in one, or more, of the following bilateral joints: second distal interphalangeal joint (DIP), third proximal interphalangeal joint (PIP), and first carpo-metacarpal (CMC). Diagnosis of foot OA was based on radiological evidence (weight-bearing) of disease in the first metatarsophalangeal joints. Cervical spine OA cases were defined as those subjects with grades 2 or higher for degenerative changes in any of the cervical facet joints. The cervical spine radiograph view was lateral. Radiographs were interpreted by a board-certified radiologist. To assess inter-reader validity, every tenth subject's assembled films were independently interpreted by a nonaffiliated radiologist who was blinded to the results of the first reading. The study radiologist, as well as the independent radiologist, was blinded to information about the individual study participants.

FINGER LENGTH RATIO CLASSIFICATION

Both visual classification and physical measurement of the 2D:4D ratios were completed in a blinded fashion using hand radiographs from the COS's digitized films. Digital Jacket software (DesAcc, Inc.) was used. When possible the assessments were completed from the subjects' baseline radiograph. The right hand was used for both visual classification and physical measurement of the 2D:4D ratio. Previous studies determined that the 2D:4D ratio is symmetrical between left and right hands and does not relate to hand dominance[19]. Visual classification consisted of classifying the hand as index finger longer than ring finger (type 1), equal to the ring finger (type 2), or shorter than the ring finger (type 3). The measured 2D:4D ratio was determined by measuring the length (in pixels) of the metacarpals and phalanges of both the index and ring fingers. The length of the metacarpals was determined by measuring from the midpoint of the base to the midpoint of the tip. The length of the phalanges was determined by measuring from the midpoint of the base of the proximal phalanx to the midpoint of the tip of the distal phalanx. The ratio for the combined length of the metacarpals and phalanges was determined by adding the individual lengths. The sum of the combined lengths was then divided to determine the combined ratio. (To date, the COS study has been able to fund a limited number of finger length ratio interpretations. Future funding will expand our current ability to explore hypotheses related to OA and the 2D:4D ratio, including OA at non-knee sites).

STATISTICAL ANALYSES

The reproducibility of both the visually assessed and physically measured 2D:4D was determined in a random sample of 53 study subjects after completion of the 2D:4D measurements. The random sample of radiographs was read in a blinded fashion for both visual classification and physical 2D:4D measurements. The intraclass correlation coefficient (ICC) and weighted kappa were used to determine agreement for both continuous and ordinal data, respectively.

Several comparisons were made between cases and controls and descriptive statistics were determined. Prevalence of visual type 3 2D:4D ratio was calculated. The data were organized into tertiles for the metacarpal, phalangeal, and combined ratios in which tertile 1 had the smallest 2D:4D ratio. Thus, tertile 1 contained the subjects with longer ring fingers, compared to index fingers, or 2D:4D type 3. For each case-control comparison, a Student's t-test was used for continuous data and a Chi-square test was used for dichotomous data. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated to estimate the risk of radiographic knee OA associated with type 3 2D:4D ratio. The adjusted ORs were determined using a logistic regression model to control for age, body mass index (BMI) and gender.

Results

In the random sample of 274 knee OA cases and controls, 2D:4D ratio measurements could not be completed for 38 cases and 32 controls due to incomplete data on the subjects, unreadable X-ray films, or because of other complications such as digit amputation. Thus, our final sample was comprised of 236 cases of knee OA and 242 persons who were free of radiographic knee OA. Compared to controls, cases with knee OA were older, tended to be female, and had a slightly higher BMI (Table I).

The visual classification, as well as the measurement of the finger length ratio, was highly reproducible. For visual classification the weighted kappa was 0.81. The ICC for measurement of metacarpals on the index finger was 0.98 (95% CI 0.96–0.98, $P < 0.0001$) and on the ring finger was 0.97 (95% CI 0.94–0.98, $P < 0.0001$). The ICC for the measurement of the phalanges on the index finger was 0.99 (95% CI 0.99–0.99, $P < 0.0001$) and on the ring finger was 0.96 (95% CI 0.93–0.96, $P < 0.0001$).

Compared to visual finger pattern types 1 and 2, type 3 finger pattern was associated with the presence of knee OA (Table II). The adjusted OR radiographic knee OA was statistically significant (OR 2.59, 95% CI 1.54–4.37).

Table II
Association of visual type 3 2D:4D ratio pattern and knee OA

Frequency of type 3 finger pattern		OR (95% CI)		Adjusted P-value
Cases	Controls	Crude	Adjusted	
124/112	55/187	3.76 (2.53–5.89)	2.59 (1.54–4.37)	0.001

Adjusted for age, gender and BMI.

Table III
Association of visual type 3 2D:4D ratio pattern and knee OA, by gender OR (95% CI)

Men	Women
2.59 (1.34–5.00)	4.40 (2.62–7.38)

Adjusted for age and BMI.

Table III displays gender-stratified ORs showing a stronger association of visual type 3 finger pattern and knee OA in women (OR 4.40, 95% CI 2.62–7.38) than in men (OR 2.59, 95% CI 1.34–5.00).

We quantified the dose response relationship between the number of sites affected with OA and a visual type 3 finger pattern (Table IV). Compared to controls, the highest adjusted OR was found for those persons with 4 affected sites (OR 3.55, 95% CI 1.72–5.32). While a Chi-square test for the trend for the adjusted ORs was not statistically significant ($P = 0.22$), the data in Table IV suggest that visual type 3 finger pattern is positively associated with an increased risk of OA at multiple sites. A significant dose response relationship was found for both the phalangeal and combined (metacarpal length + phalangeal length) 2D:4D ratios (Tables V and VI).

Discussion

Zhang, *et al.*[13], were the first researchers to note the relationship between the 2D:4D finger length ratio and OA. They found an association with knee OA but not with hip OA. We compared the 2D:4D finger length ratio in those with knee OA (Kellgren–Lawrence scores ≥ 2) with those cohort subjects who were completely OA free. We found a strong association of this same ratio with knee OA for both men and women. The association is stronger in women than men, concurring with the Zhang group finding.

The Zhang *et al.*[13] study demonstrated a dose response relationship between the risk of knee OA and increasing metacarpal and phalangeal 2D:4D ratio. In our study sample, we did not observe an association between knee OA and the metacarpal 2D:4D ratio. The study by Zhang *et al.*[13] also demonstrated a positive association between knee OA and a higher 2D:4D metacarpal ratio. In our study sample, we did not observe an association between knee OA and the metacarpal 2D:4D ratio (data not shown). Zhang, *et al.*[13] further demonstrated there was a dose response relationship between the risk of knee OA and increasing metacarpal and phalangeal 2D:4D ratio.

These findings are intriguing and we believe that our results, in addition to the findings from the previously published earlier study[13], show that the type 3 finger length pattern is a significant marker for knee OA. The biology of this phenomenon is complex. It is possible that there is a genetic linkage which may result in a predisposition to both the type 3 pattern and the development of OA later in life. Several studies conducted in both human subjects and laboratory animals have proposed that the 2D:4D ratio is influenced by prenatal testosterone exposure[2–4,8,20–22]. Further, it has been proposed that the homeobox (*Hox*) genes, specifically those of the *Hox A* and *Hox D* groups, which are involved in the growth of bone, cartilage, and soft tissue of appendages, may be the underlying genetic determinants of the 2D:4D ratio[23]. The increasing literature concerning the type 3 finger ratio pattern leads to other speculation as well. Persons with this pattern may well engage in more physically risky behaviors, which in turn, could lead to joint trauma and eventually OA[24]. Because of the strong associations noted, we are planning to conduct an extensive expansion of this investigation. We intend to classify all COS cohort subjects' 2D:4D ratios for this purpose.

It should be noted that we did not include the variable "OA at other sites" in our adjusted analyses. We did account for the most universally accepted confounding variables, age and BMI. We also produced gender-specific analyses. As previous studies have suggested, we speculate about the strong possibility of an underlying genetic component to this phenomenon. That is, whatever is contributing to the propensity to possess a type 3 finger length ratio (ring finger longer than index finger) may well contribute to a predisposition to have OA at multiple joints. If that is true, then adjusting for OA at other sites would attenuate the estimated risk at the site of study. In other words, the effect may well be in the causal pathway for most OA sites and it would not be appropriate to adjust for such a variable.

A consideration for interpreting the results from this study is the choice of the OA definition, Kellgren–Lawrence grade 2+. It has been suggested that criteria such as Kellgren–Lawrence grade 3+ (definite narrowing, definite osteophytes) could have produced different results. We suggest that if there is an association between OA and the 2D:4D ratio (as noted by these data), the selection of subjects with more severe OA would produce higher ORs. There is some controversy about OA diagnoses (e.g., symptomatic, radiographic, weight-bearing status, etc.). With the Kellgren–Lawrence scale, we chose a fairly common approach with films read blindly in a standardize manner. Additionally, although future analyses with the 2D:4D ratio will better clarify, the

Table IV
Association of visual type 3 2D:4D ratio and knee OA, by total number of sites with OA

# of OA sites	#	Crude OR	Adjusted OR
0	242	1.0 (reference)	1.0 (reference)
Knee only	22	2.35 (0.96–5.80)	2.09 (0.79–5.51)
2	55	4.08 (2.22–7.51)	2.74 (1.37–5.48)
3	95	3.19 (1.93–5.28)	2.23 (1.20–4.15)
4	64	5.30 (2.95–9.52)	3.55 (1.72–5.32)

Radiographic OA status was determined for the following sites: knee, hand, foot and cervical spine. Adjusted for age, gender and BMI.

Table V
Association of phalangeal 2D:4D ratio and knee OA, by 2D:4D ratio tertile

Adjusted OR (95% CI)			
Tertile 3*	Tertile 2	Tertile 1	*P* for trend
1.00	1.09 (0.61–1.97)	1.69 (0.93–3.09)	0.009

*Reference group.

Table VI
Association of combined metacarpal and phalanges 2D:4D ratio and knee OA, by 2D:4D ratio tertile

Adjusted OR (95% CI)			
Tertile 3*	Tertile 2	Tertile 1	*P* for trend
1.00	0.74 (0.41–1.34)	1.43 (0.78–2.62)	0.002

*Reference group.

cross-sectional design may have been a study limitation. If the presence of OA in the finger joints impacted the measurement of the 2D:4D ratio, this could influence the outcome. In our experience, we do not feel that this occurred. However, a prospective cohort study design (using subjects free of hand OA) would eliminate that potential measurement error, thus limiting study bias. The researcher interpreting the hand films for the 2D:4D ratio was not a physician and had no basic knowledge of the Kellgren–Lawrence scale or in reading films for evidence of OA. Rather the researcher, blinded to the subjects' OA status, was focused solely on the 2D:4D ratio measurements. Although one cannot rule out this potential bias, the practical manifestation of it seems unlikely.

The first group to report this association, Zhang, *et al.* acknowledged that the rationale behind the OA and 2D:4D ratio relationship is unknown. At first, one might be inclined to assign it to genetic factors. However, the issue seems to be much more complex. Studies have shown the 2D:4D ratio to be associated with athletic abilities which, of course, could lead to exposure to well-known injury risks for OA. Obviously, such an intermediate variable could still be attributed to an underlying genetic predisposition for both a larger 2D:4D ratio, as well as increased OA risk. A full understanding will need to be clarified in further investigations. Regardless of causal mechanisms, it seems clear that this ratio is indeed a strong indicator of OA risk and, where possible, should be taken into account in any overall OA risk assessment.

In summary, we have duplicated the initial findings of Zhang, *et al.,*[13], by showing a strong relationship between a type 3 finger length ratio pattern and OA of the knee. Because replication is at the heart of epidemiology, we anticipate that other researchers will evaluate this association in different populations. Despite current progress, the exact biological underpinnings involved in this relationship remain elusive. However, we believe that the type 3 finger length pattern (ring finger clearly longer than the index finger) is an indicator of OA predisposition which should not be overlooked in clinical assessments. We plan further investigations of this marker using the COS's library of serial radiographs.

Conflict of interest

The authors have no conflict of interest.

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