Alternative Digit Ratios and Their Relationship to Prostate Cancer

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Abstract

Alternative finger measurements and their association with prostate cancer parameters were explored in 452 patients, with an emphasis on finding a stronger correlation than seen in previous digit ratio studies. Strong racial differences were observed in alternative digit ratios, whereas the clinical relationships involving prostate cancer need to be viewed heuristically.

Background: The ratio of the second to the fourth digits (2D:4D) has been linked to prenatal androgen exposure and prostate cancer (PCa). The use of alternative finger ratios has been shown to be a greater indicator of sexual dimorphism when compared with the traditional 2D:4D ratio. This study aimed to assess the relationship between alternative digit ratios, racial demographics, and clinical/pathologic parameters associated with PCa. **Materials and Methods:** Digital finger length measurements were made from scanned images of hands from patients with PCa. Race, age, family history, history of metastasis, and Gleason score at diagnosis were assessed in a cross-sectional clinic-based study. Demographic and clinical parameters were analyzed with respect to various alternative finger length ratios. **Results:** Hand measurements were obtained in 354 white and 98 African-American patients with PCa. African-American men were more likely to have a smaller 2D:3D ($P < .0001$) and 2D:4D digit ratio ($P < .0001$) in both hands. Larger right (R)3D:5D ($P = .0005$), R4D:5D ($P = .0014$), and R2T:2D ($P = .0501$) digit ratios were present in African-Americans compared with whites. In exploratory analyses, African-American men with a smaller left (L)2T:2D ratio were younger at the time of PCa diagnosis ($P = .0125$). No relationship was found between the various digit ratios and Gleason score, the presence of metastatic disease, or family history. **Conclusion:** Various alternative finger length ratios show strong differences between African-American and white men in this study. The potential relationship between the 2T:2D ratio and age at diagnosis in African-Americans needs additional verification.

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Introduction

As a noninvasive retrospective view into the prenatal environment, the use of digit ratios may provide potential biometric predictors of physiologic and pathologic changes. Digit ratios have been used with increasing frequency in a wide range of studies in disease, psychological disorders, physical behavior, and sexual orientation. Because many diseases like prostate cancer (PCa) typically present much later in life, the ability to use digit ratios as a biomarker to predict future disease could be of potential utility in a risk-based screening stratification.

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During gestation, the development of the prostate is dependent on a functional androgen receptor and the presence of androgens.[1] The levels of these androgens have been shown to vary across ethnicities.[2] Prenatal androgen exposure and its relationship to PCa has never been fully evaluated given the long duration required for such studies. Studies differ on whether a definitive relationship exists between serum/plasma sex hormones and PCa risk in the adult population,[3-5] despite androgens being implicated in PCa growth and androgen deprivation being a key component of PCa treatment.[6]

Sex differences between finger lengths have been documented since the late 19th century.[7,8] Prenatal androgen levels are implicated in these differences in several studies.[9,10] Animal studies demonstrate evidence of androgens affecting digit length in utero.[11] The ratio between finger lengths, specifically the second digit (2D) and the fourth digit (4D), have clearly been shown to be a sexually dimorphic trait.[12] Increasing levels of prenatal androgens are associated with a reduced 2D:4D ratio; decreasing androgen levels

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correlate with an increased 2D:4D ratio.[13] This 2D:4D ratio also varies between different ethnicities; African-Americans have smaller 2D:4D ratios when compared with whites.[14]

Although the use of the 2D:4D ratio has been widespread, alternative digit ratios have been reported to have a stronger correlation across sex differences when compared with the traditional 2D:4D ratio.[15,16] Ratios involving the 2D:5D have a greater difference between sex compared with 2D:4D.[15] In addition, the distal extent of the second digit relative to finger length (2T:2D) has been shown in another study to be a stronger sexually dimorphic trait than finger length alone.[17] Thus sexual dimorphism for alternative digit ratios is clear.

The use of the 2D:4D digit ratio has been explored as an early noninvasive predictor of PCa risk[18,19] and severity[20] in recent studies, but findings are inconsistent. Although the 2D:4D ratio has already been used to evaluate a connection with PCa, the use of alternative digit ratios has yet to be explored. We hypothesize that the use of alternative digit ratios will show a stronger and more consistent correlation to PCa characteristics than traditional 2D:4D ratios.

Materials and Methods

Participants were recruited from a large university clinic specializing in PCa, and all had a histologic diagnosis of PCa. Thus, this was a clinic-based cross-sectional study that involved 452 patients. Institutional review board approval was obtained, and each patient consented to have a digital hand scan taken of both hands. The length of the second, third, fourth, and fifth digits was measured directly from scanned images, from the bottom crease at the center of the finger to the fingertip. The distal extent of the second digit was also measured directly from scanned images, from the bottom crease at the center of the distal phalanx to the fingertip. Using Quartz PCI, version 8.0 (Quartz Imaging, Vancouver, BC, Canada), each digit was measured electronically. Participants with injuries to the digits or scans in which hand creases were not present were not evaluated. Self-reported family history and self-reported race were documented at the time of the scan. Patients were queried about first-degree relatives (father or brothers, or both) with a known diagnosis of PCa, which if present was documented as a positive family history. Only first-degree relatives were assessed. If no first-degree relatives had a history of PCa, the family was annotated as having a negative family history. The patient's age at diagnosis was accessed through hospital records. Gleason score was determined by review of pathology reports derived from prostate tissue. Gleason scores were not centrally graded. The presence or absence of metastases was updated at each visit to ensure that the history of metastatic disease was current to the best extent possible.

Statistical Analysis

Given that African-Americans and whites have known differences in 2D:4D ratios, all analyses herein stratified the population as either African-American or white. Other racial groups were excluded from the analysis because of small sample size. Descriptive statistics for tabulation purposes only were calculated using mean and standard deviation for age at diagnosis, median and range for finger length ratios, Gleason score (< 7, 7, > 7), and frequency for categorical variables including race, family history (yes/no), and metastasis (yes/no). All data were assessed for normality using the Kolmogorov-Smirnov test statistic to determine normality of distributions. Finger length ratios were treated as a continuous variable and compared between racial groups using analysis of variance. Categorical covariates (family history, metastasis) and continuous covariates (age at diagnosis, Gleason score) were compared by digit ratio for each racial group using analysis of covariance. Tukey-Kramer honestly significant difference post hoc analysis was performed to assess pairwise contrasts and adjusted for multiple comparisons. All tests were 2-sided and P values $\leq .05$ were considered statistically significant. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Characteristics of the study population are listed in Table 1. Hand scans were conducted and measured digitally in 452 patients with PCa, who included 98 African-Americans (21.7%) and 354 whites (78.3%). For patients whose metastatic disease status (yes/no) was known (60.2% of African-Americans and 59.0% of whites), a substantial proportion were positive for metastatic disease (50.8% of African-Americans and 49.3% of whites). For patients with a documented Gleason score (70.4% of African-Americans and 81.1% of whites), a noteworthy number were considered high (≥ 8) for both African-American (42.0%) and white (38.0%) men. Age at diagnosis was consistent between the races (62.2 and 62.5 years for African-Americans and whites, respectively) in this data set.

Overall, there were various statistical differences between African-American men and white men using both the traditional 2D:4D and various alternative digit ratios in both the right hand (Table 2)

Table 1 Characteristics of Study Population (n = 452)

Race, n (%)	
African-American	98 (21.7)
White	354 (78.3)
Family History, N (%)	
African-American	38 (40.0)
White	98 (28.8)
Gleason Score, n (%)	
African-American	
High (≥8)	29 (42.0)
Medium (7)	26 (37.7)
Low (≤6)	14 (20.3)
White	
High (≥8)	109 (38.0)
Medium (7)	102 (35.5)
Low (≤6)	76 (26.5)
Metastasis, n (%)	
African-American	30 (50.8)
White	103 (49.3)
Age at Diagnosis, mean (SD)	
African-American	62.2 (7.6)
White	62.5 (7.9)

Abbreviation: SD = standard deviation.