From Palmistry to Anthropometry: Can 2nd to 4th Digit Length (2D:4D) Predict the Risk of Prostate Cancer?

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Abstract

Objective: The 2nd to 4th digit length (2D:4D) is inversely related to androgen exposure during the fetal period, which may represent a risk factor for several steroid-related diseases. We aimed to evaluate the relationship between 2D:4D ratio and the risk of developing prostate cancer (PCa). **Subjects and Methods:** We assessed the 2D:4D ratio of 474 men >40 years old, stratified into three groups: group 1 (n = 222) patients with PCa, group 2 (n = 82) subjects with high risk of PCa, and group 3 (n = 170) men with low risk of PCa. Subjects were submitted to a digital picture of the ventral surface of the right hand and 2nd and 4th fingers measurements were determined by the distance from the proximal crease to the tip using computer-assisted analysis. **Results:** The mean serum prostate-specific antigen level was 7.5 ng/ml in the high-risk group and 0.92 ng/ml in the low-risk group (p < 0.05). The mean 2D:4D ratios were 0.96 ± 0.04, 0.97 ± 0.04 and 0.96 ± 0.04 for the PCa, high-risk and low-risk groups, respectively, and no difference was found among the three groups (p = 0.12). **Conclusion:** Anthropometry of the hand using the 2D:4D ratio is not a predictor of PCa.

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Introduction

Prostate cancer (PCa) is the second most common cause of cancer-related death in men, representing an important public health problem [1]. PCa screening with prostate-specific antigen (PSA) and digital rectal examination (DRE) has been recommended in the vast majority of countries, despite recent concerns regarding the effectiveness of these assessments in the reduction of PCa mortality [2]. In order to optimize the screening and determine men with high risk of PCa, research focusing on new biomarkers, genetic patterns and identification of individual physical characteristics possibly related to PCa has been performed [3–6].

Sexual hormones plays a key role in PCa, but the exact mechanisms in the cancer induction process are not totally understood. Long-term fetal exposure to elevated levels of estrogen against a normal androgen background induced a high incidence of PCa in animal models [7]. It is known that amniotic fluid testing is the best method of early fetal hormone exposure assessment, however it is not used in routine practice due to its invasive character, ethical concerns and fetal risk. The ratio of 2nd to 4th digit length (2D:4D) in the right hand has been described as the best non-invasive method for evaluation of fetal androgen exposition [8, 9].

Finger development is under control of the family of Hox genes as well as differentiation of the urogenital sys-

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Table 1. Characteristics of the study population

	PCa group	High-risk group	Low-risk group	p
Number of subjects	222	82	170	
Median age, years (range)	72 (46–90)	62 (46–80)	61 (41–85)	<0.05*
Mean 2D:4D ± SD	0.96±0.04	0.97±0.04	0.96±0.04	0.12
Median Gleason score	7	NA	NA	
Mean PSA ± SD, ng/ml	NA	7.50±3.77	0.92±0.56	<0.05

NA = Not assessed. * Statistically significant.

tem [10]. The 2D:4D ratio in the right hand is negatively correlated with prenatal testosterone levels and positively correlated with prenatal estrogen levels [11]. Furthermore, the 2D:4D ratio is established early in utero, presents sexual dimorphism (lower in males) and is maintained along the whole lifespan [12–15].

Recently, an association of the 2D:4D ratio with several diseases has been investigated, including disorders due to sexual hormones exposure such as congenital adrenal hyperplasia, abnormal penile size and breast cancer [16–19]. Moreover, the digit ratio is interesting not only to biomedical researchers, but it is also attracting the attention of the lay media [20].

To our knowledge, studies evaluating the relationship between the 2D:4D ratio and PCa are scarce, and all of them used different methodology and presented conflicting results [21–23]. Thus, new research is necessary to determine the real role of the 2D:4D ratio as a predictor of PCa.

Fig. 1. Equipment used to evaluate the 2D:4D ratio.

Subjects and Methods

This is a case-control study approved by the local ethical committee; all subjects signed an informed consent form.

We assessed the 2D:4D ratio of 474 men >40 years old during routine medical visits to our urology clinic. The subjects were categorized into three groups. Group 1 (PCa group) was composed of patients with histologically confirmed PCa. Group 2 (high-risk group) was composed of subjects with a serum PSA level >2.5 ng/ml or abnormal DRE, who were submitted to one prostate biopsy negative for cancer. Group 3 (low-risk group) was composed of men with a serum PSA level <1.5 ng/ml and normal DRE [24, 25]. Deformities in the right hand were considered exclusion criteria. Table 1 describes the characteristics of the study population.

The subjects lightly pressed their stretched ventral surface of right hand against a scaled glass, which was perpendicularly mounted on a table top. A digital camera was placed 15 cm from the glass and digital photographs were taken, using auto focus, without flashlight and with a white background (fig. 1) [26, 27]. A computer-assisted image analysis software (GNU Image Manipulation Program, GIMP, version 2.6.11) was used and the measurements of the 2nd and the 4th fingers were determined by the distance from the proximal crease to the tip (fig. 2) [28]. In order to verify the inter-individual variation of the assessment method, the first 100 hands were measured by two blinded independent investigators and the mean 2D:4D ratio was compared (r = 0.886; p < 0.001).

Statistical analyses were performed by using one-way analysis of variance, t test and Pearson's correlation. A p value <0.05 was considered significant.

Results

We analyzed 222 men with PCa, 82 with high risk of PCa and 170 with low risk, with a median age of 72 years (46–90), 62 years (46–80) and 61 years (41–85), respectively. Subjects with PCa were the oldest (p < 0.05).

The PCa group had a median Gleason score of 7. Mean PSA was 7.5 and 0.92 ng/ml for the high- and low-risk

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groups, respectively, and this difference was statistically significant (table 1).

The mean 2D:4D ratios were 0.96 ± 0.04, 0.97 ± 0.04 and 0.96 ± 0.04 for the PCa, high-risk and low-risk groups, respectively, and no statistical difference was found among the three groups (fig. 3).

Discussion

To our knowledge, six studies aimed to correlate the 2D:4D ratio with PCa and presented conflicting results. The Korean Cohort study was the first publication addressing this issue and assessed the 2D:4D ratio directly with a vernier caliper in 366 men who complained of lower urinary tract symptoms [21]. The authors showed that a ratio <0.95 as a cut-off point is a predictor of PCa. However, their PCa sample represented only 8% (n = 28) of the total, and this could potentially have compromised their conclusion.

A British case-control study evaluated a large sample of men using self-reporting questionnaires that were previously posted to the patients, containing different pictures of right-hand patterns [23]. Men with 2nd finger longer than 4th finger showed low PCa risk. The lack of objective measurements of the 2D:4D ratio implies that their conclusion must be considered with caution.

The Melbourne Collaborative Cohort Study analyzed 6,258 digit ratios from photocopies and did not observe an association between 2D:4D ratio and PCa risk [22]. Although the 2D:4D ratio can be measured by several methods, some concerns on photocopies regarding the level of intra- and inter-observer reliability are described [28].

More recently, three studies have evaluated 2D:4D ratio and PCa diagnosis and severity [29–31]. A Spanish group found that patients with a left 2D:4D ratio >0.95 had a 4-fold risk of PCa diagnosis in biopsy [29]. This finding was just the opposite of an Korean group study, which found an increased PCa detection in patients with a lower 2D:4D ratio in right hand [30]. An American group study did not find an association between 2D:4D ratio and PCa severity [31].

The different methodologies among these six studies and the different ethnical aspects of British, Korean, Australian, Spanish and American people can partially explain the contradictory results. Despite the possible impact of ethnical aspects, we did not use any racial questionnaires because the vast majority of our population consisted of a mix of Afro-Brazilians, Caucasians and
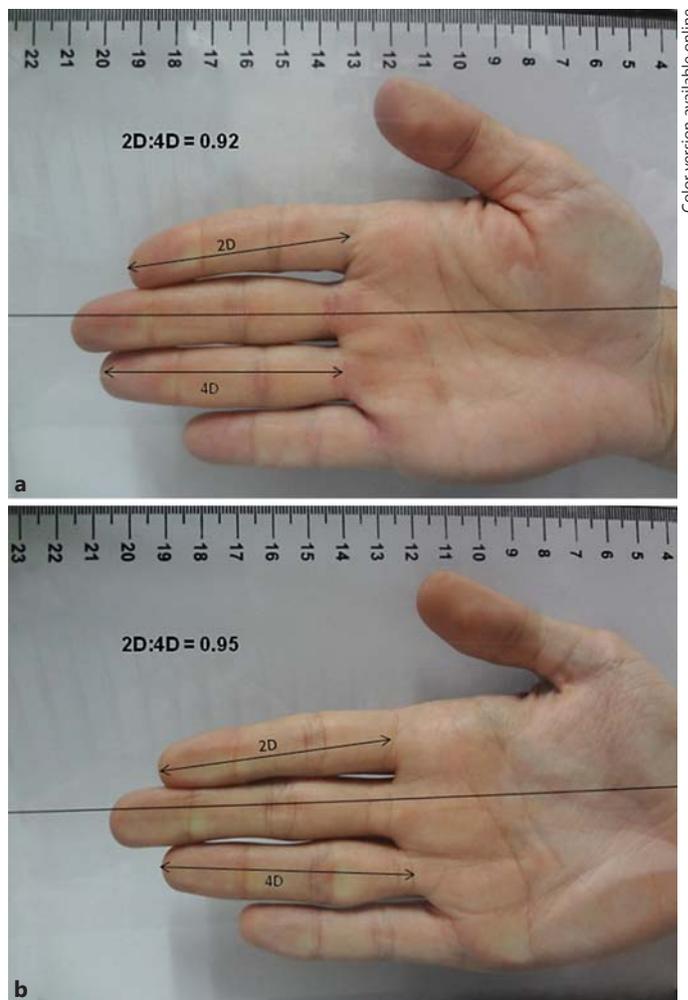

Fig. 2. Measurement from the proximal crease to the tip of the finger by computer-assisted image analysis software. **a** Visual 2nd finger shorter than 4th finger with 2D:4D = 0.92. **b** 2nd and 4th finger appear to be equal, but 2D:4D = 0.95.
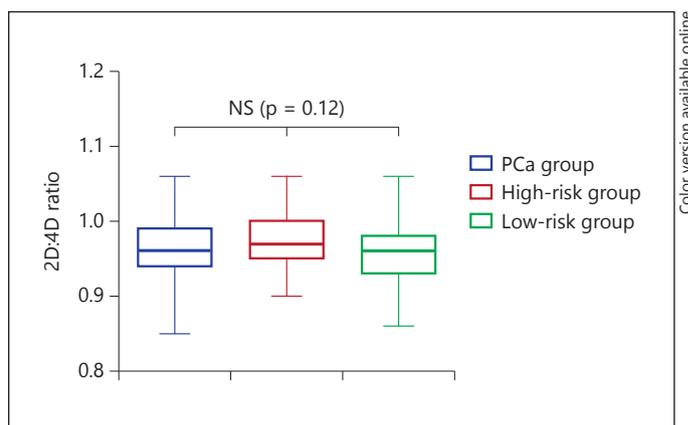

Fig. 3. Mean 2D:4D ratio in the three groups. NS = Not significant.

Indians, to different degrees, so this kind of evaluation becomes very subjective. Thus, to verify the exact role of 2D:4D ratio as a predictor of PCa, we established two control groups and used an accurate biometric method. Digital picture followed by computer-assisted analysis is the most consistent way for 2D:4D ratio measurement [27, 28].

In our study, the age difference between the PCa and control groups was expected due to major prevalence of PCa in older men, but this cannot be considered a bias because the 2D:4D ratio suffers no changes along the lifespan [15].

To establish the ideal control group to oppose a PCa group in a case-control study is complicated due to the low specificity of the current screening methods, such as PSA and DRE. Thus, if a man does not have suspicious prostate exams or even has a negative prostate biopsy at the moment of screening assessment, this does not guarantee that he is or will be free from PCa in the future.

We addressed efforts toward minimizing confounding factors in the control groups. Thus, we included in the low-risk group only men with a serum PSA level <1.5 ng/ml and normal DRE. According to the data from the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer, these men have a significantly lower risk of PCa diagnosis than patients with a PSA >1.5 ng/ml [25].

We also evaluated a group at high risk of PCa to verify whether the 2D:4D ratio could be useful as a predictor of additional prostate biopsies in a second-round screening. The PSA difference between these two control groups (PSA was higher in the high-risk group) was statistically significant and corroborates the risk pattern of each group. The serum PSA level was not recorded in the PCa group because the endpoint was the presence of neoplasm, and thus assessment of PSA levels in this group made no sense. Herein, we did not find significant difference of 2D:4D ratio among the three groups, so efforts to correlate this ratio with others characteristics of prostate cancer, as Gleason score, PSA level and staging seems to be unnecessary. These findings are in agreement with the Melbourne Cohort results and support that 2D:4D ratio plays no role as a predictor for prostate cancer.

Conclusion

Anthropometry of the right hand using the ratio 2D:4D is not a predictor for PCa.

Disclosure Statement

The authors have no conflict of interest. There was no funding source.

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