

ORIGINAL ARTICLE

Right hand digit ratio (2D:4D) is associated with prostate cancer: Findings of an admixed population study

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Abstract

Objective: Digit ratios are considered putative markers for prenatal hormone exposure, as well as the action of HOX and AR genes. Such genes have been connected to carcinogenesis and digit ratio could help to identify patients that bear such predisposition. The purpose of this study was to investigate the possible correlations between digit ratio, prostate cancer (PCA) - the most common cancer in men – and benign prostate hyperplasia (BPH) in a multiethnic sample of men between 50 and 80 years, the main risk group for this disease.

Methods: Digital images of the right hands of patients diagnosed with PCA (n=40), BPH (n=40) and age-matched controls (n=40) were obtained. Fingers were measured using Adobe Photoshop 7.0® and the mean ratios between the 2nd and 4th digits were compared. Data were analyzed by Student's t test and regression models ($\alpha=0.05$). Risk factors (dietary factors, tobacco consumption, age and familial history) were similar among the three study groups.

Results: Males in the PCA group presented significantly lower digit ratio ($P=0.04$) in comparison with males without prostatic lesions.

Conclusions: Males with the lower digit ratio seem to be more prone to undergo malignization of prostatic lesions. Similar risk factors for the three groups allows us to infer that digit ratio could add to the research of etiological factors and be a putative marker for the screening of patients', especially in a admixed population.

Key words

Digit ratio, 2D:4D, Prostate cancer, Benign prostatic hyperplasia

Introduction

Human hands present different lengths of index and ring fingers for males and females, a difference first attributed to prenatal hormone exposure - high digit ratio meaning higher estrogen exposure and low digit ratio pointing to higher testosterone exposure^[1]. The ratio between these fingers, known as 2D:4D or digit ratio is considered a putative marker for prenatal hormone exposure as well as HOX and AR gene expression^[1-3]. Finger length ratio has since been correlated to medical, behavioral and psychological conditions, particularly those influenced by prenatal hormone exposure.

Proposition of digit ratio as a predictive marker of the susceptibility to some types of cancer, especially those that show sex differences in their occurrence, progression, and/or prognosis has gained strength ^[4-7].

Prostate cancer (PCA) is the most common cancer in men and the commonest overall, with a reported incidence of 165.8 per 100.000 ^[8]. Although its exact etiology is currently unknown, it has been correlated to factors such as age, race, familial history and hormone exposure ^[9]. This lesion is thought to arise from premalignant conditions such as Benign Prostatic Hyperplasia (BPH) and about 83% of all prostate cancers develop in preexistent sites of BPH. Currently, there are only two studies that addressed correlations between 2D:4D and prostate cancer, and those have been performed in populations that have relatively few ethnic differences ^[6,7]. Prostate cancer developments could be influenced by in-utero testosterone overexposure, which would reflect in lower digit ratios for individuals that develop this disease. This study investigated this possible correlation between Prostate Cancer, BPH and 2D:4D in a multi-ethnic population.

Patients and Methods

The local institutional review committee approved this research. Males between 50 and 80 years were invited to participate in this study, and responded to a questionnaire regarding habits, medical personal and familial history. Subjects with right index or ring finger fracture history and/or hormonal disorders were excluded. All subjects were diagnosed by clinical and histological analysis and were currently under treatment follow-up.

Individuals had their right hand palm photographed by a digital camera (Canon Powershot A550, Canon, USA) attached to a standardizing device, forming a 90° angle with the base. Photographs were under the same camera configuration to avoid discrepancies between images. Individuals kept their wrist, back of hands and fingers extended and placed in the base throughout the capturing process. Image analysis was made using Adobe Photoshop 7.0® (Adobe Systems, USA) measuring tool, using 100% zoom.

Measurements of right hand index and ring fingers were performed in linear fashion from the middle point of the most proximal crease up to the tip of the finger and repeated 3 times, two days apart. Index finger length was divided by ring finger length, originating the 2D:4D ratio. The analyzed ratio was the mean of the three measurements performed.

After the measurement, individuals were assigned to their respective groups; (a) NOL group – patients without present or past malignant or premalignant prostatic lesions; (b) PCA group - patients diagnosed with prostate cancer; (c) BPH group - patients diagnosed with BPH, present or past. Individuals were age-matched between groups. Data were analyzed by Student's t test and logistic regression ($\alpha = 5\%$).

Results

Populational characteristics of the study are described in Table 1. Overall, 120 individuals were selected for this study. In a largely admixed population such as Brazilian, it is hard to attest ancestry of the individuals. Thus, there was no possibility to divide the participants into ethnic groups such as African descendants, Caucasians, Asians or Indians, among other ethnic groups.

Table 1. Characteristics of the study subjects

Group	Age	2D:4D ratio	TC / (Cigarettes/Day)	EC	FH
PCA (n=40)	70.4 ± 5.4	0.9498 ± 0.0417	72.5% (24.0)	75.0%	57.5%
BPH (n=40)	64.5 ± 7.5	0.9638 ± 0.0550	75.0% (20.0)	72.5%	47.5%
NOL (n=40)	59.2 ± 11.3	0.9665 ± 0.0395	60.0% (22.7)	87.5%	52.5%

Abbreviations: PCA–prostate cancer; BPH–benign prostatic hyperplasia; NOL–no lesion; EC–Regular ethanol consumption; FH–Familial history of malignant neoplasia. TC–Tobacco consumption

Familial history of malignant neoplasia and alcohol and tobacco consumption were frequently reported. The mean alcohol and cigarette consumption were not significantly different among all groups ($P=0.57$). Hormone therapy was not reported. Familial history of prostate cancer was similar among the groups.

Repeated measurements presented intra-class correlation coefficient (ICCS) of 0.95 for the test 1 against 2, 0.94 for test 2 against 3 and 0.97 for test 3 against 1, indicating reproducibility of the method.

Digit ratios for the PCA group were 0.9498 ± 0.0417 and 22 individuals presented low 2D:4D (lower than 0.9500); BPH group had mean 2D:4D of 0.9638 ± 0.0550 with 14 individuals having low 2D:4D; NOL group had mean finger-length of 0.9665 ± 0.0395 with 12 individuals below the 0.9500 mark. Digit ratios were not significantly different between NOL and HPB groups and HPB versus CA group ($P=0.40$ and 0.18 respectively; $OR=1.08$ and 1.25 respectively), but they were significant for the CA versus NOL group ($P=0.04$; $OR=1.36$; $95\% CI = 1.11 - 1.61$).

Discussion

Since 1998, more than 500 published articles have addressed the correlation of digit ratios to a plethora of gender-linked traits and pathologies, such as physical and verbal aggressiveness, decision-making processes^[10]; and medical conditions such as cervix cancer, atherosclerotic plaque development and delayed menarche^[11-13].

Many genetic conditions can influence digit ratios, in particular the action of HOX and androgen receptor (AR) genes. HOX gene family controls the differentiation of fingers and gonads as well as the urogenital system development^[6]. Digit ratios could reflect the action of these genes, acting as a putative marker for susceptibility to diseases they are thought to influence^[14]. Low digit ratios were proposed as proxy markers for short CAG-triplet repeat lengths on the AR, predisposing patients for cancer development^[2]. Positive correlations between 2D:4D and the amount of CAG triplets on the AR gene were reported^[3] and thus, low digit ratios could predispose patients to carcinogenesis and short CAG sequences would contribute for disease prognosis.

Although recent publications have associated PCA to varied aetiologies, its main risk factors are considered increased age, ethnicity and familial history of prostate cancer^[15]. Given these main risk factors, the individuals selected for this study presented similar characteristics. Alcohol consumption, which could act as a dietary factor, did not significantly differ among groups. This selection diminished the influence of etiological factors on the analysis, focusing on the influence of 2D:4D, adding to the explanation of why some patients evolve for BPH malignization while others remain with indolent lesions or even unaffected.

Previous studies have investigated correlations between digit ratios and prostate cancer in Korean patients - an expected genetically homogeneous and less susceptible population - and patients from the United Kingdom, a far less admixed sample^[6, 7]. It is difficult to establish race correlations on multiethnic populations such as Brazilian, and thus ethnic influences seem to play smaller roles than hormonal influences on prostate cancer.

It was suggested that indirect measurements could weaken the results of digit ratio studies^[16]. In fact, every measurement methodology has inherent discrepancies and thus, distortions on the relative lengths may occur. The two other studies regarding digit ratios and prostate cancer used direct measurements and self-reports^[6, 7]. A standardized method of image capturing was suggested for this study and, if distortions occurred, they were similar for all images. Results from ICCS also pointed to method reproducibility. This study corroborates previous findings from the British and Korean studies. However, larger multi-ethnic epidemiological as well as genetic and hormonal studies are necessary to investigate the strength of correlations between prostate cancer and digit ratios.

Males diagnosed with PCA in our study presented more masculinized digit ratios, especially when compared to males that presented no prostatic lesion at all. This finding corroborates previous reports and endorses the complex etiology of PCA carcinogenesis. This study adds to the discussion about the etiology of prostate cancer and reinforces the correlations found elsewhere, with the special characteristic of being performed in an admixed population. Digit ratios could provide a possible putative marker for the screening of patients in risk to develop prostatic malignancies, if and when correlations are confirmed by larger studies. It also points to the necessity of further investigation of the relations between PCA and genetic and hormonal factors that could be represented by digit ratios.

Conflict of interest

The author declares that there is no conflict of interest statement.

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