Original Article

RELATIONSHIP BETWEEN THE RATIO OF THE LENGTH OF THE 2ND DIGIT TO THE 4TH DIGIT (2D:4D RATIO) AND PROSTATE CANCER

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ABSTRACT

Background: The ratio of the length of the second digit or index finger (2D) to the fourth digit or ring finger(4D) is a marker for prenatal androgen exposure. A low 2D:4D ratio suggests a high intrauterine androgen exposure. There is evidence that intrauterine androgen exposure plays a role in the aetiology of malignancies, including prostate cancer. Prostate cancer is known to be androgen-dependent. **Objective**: This study aims to determine the relationship between prostate cancer and the ratio of the index length to the ring finger. (2D:4D ratio) **Methodology:** This is a comparative descriptive cross-sectional study between patients with prostate cancer (PCa) and benign prostatic enlargement (BPE) that serve as the control. Investigation results such as prostate-specific antigen (PSA) levels, ultrasound scan, histology results of the prostate biopsy were obtained for both the PCa and BPE groups. All the patients in the PCa group had histologically diagnosed prostate cancer. The patient in the BPE (Control) had clinically or histologically diagnosed BPE. The length of their second (2D) and fourth fingers (4D) were measured. **Result**s: Forty patients participated in the study: twenty PCa and twenty with BPE (Control). Their age range was between 39-93years, with a mean age of the PCa group being 71.50 ± 7.59years, while the BPE group had a mean of 70.55 ± 13.82years. The mean PSA of the PCa group was significantly higher (116.57 ± 164.5ng/ml) than the BPE group (10.64 ± 18.65ng/ml; p=0.0070). Patients with PCa had a higher mean 2D:4D ratio than the BPE group. There was a statistically significant weak positive relationship between prostate cancer and 2d:4d ratio, indicating that men with a high 2D:4D ratio had a significantly moderately greater risk of developing prostate cancer. (p=0.035, r=0.236). **Conclusion**: Our study indicated that prostate cancer patients had higher 2D:4D ratios and higher serum PSA compared to the control patients with BPH. The relationship between 2D:4D ratio requires more investigation.

KEYWORDS: Index finger, ring finger, 2D:4D ratio, Prostate cancer, BPE.

INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous malignancy in men.[1] It accounts for a significant percentage of urological clinic and emergency consults.[2] One in seven men may have prostate cancer in their lifetime, and 1 in 38 men will die of prostate cancer.[3] The incidence of prostate cancer has been noted to be higher in Africans and African Americans. The aetiology of PCa is still generally unknown. Still, some factors have been found to increase the risk of developing PCa, which include: family history of PCa, age, ethnicity, diet and prenatal androgen exposure.[4] The ratio of the length of the second digit or index finger (2D) to the fourth digit or ring finger(4D) is a marker for prenatal androgen exposure. A low 2D:4D ratio suggests a high intrauterine androgen exposure.[5,6] There is evidence that intrauterine androgen exposure plays a role in the aetiology of malignancies.[7] Men with low androgen levels, such as men with congenital adrenal hyperplasia, have been noted to have a shorter digit ratio.[8] PCa is a hormone-dependent malignancy; however, the hormone exposure required to cause PCa in adults is still undetermined.[9] The genetic controls for finger ratio have been implicated in some cancers such as breast, gastric and especially PCa. In these cancers, the 2D:4D ratio has shown a strong positive correlation.[10,11]

In this study, we aim to determine the relationship between prostate cancer and the ratio of the length of the index (2D) to the ring (4d) finger.(2D:4D ratio)

METHODS

This is a comparative descriptive cross-sectional study between patients with prostate cancer and with a benign prostatic enlargement (BPE) that serve as the control. They were consecutively selected at presentation at the Urology Division, University of Port Harcourt Teaching Hospital Rivers State. Informed consent was obtained. Their records, such as biodata, history and digital rectal examination findings, were noted. Investigation results such as prostate-specific antigen (PSA) levels, ultrasound scan, histology results of the prostate biopsy were also obtained for both the PCa and BPE groups. All the patients in the PCa group had histologically diagnosed prostate cancer. Patients without PSA or histology reports were excluded. The patient in the BPE (Control) had clinically or histologically diagnosed BPE. The length of their second (2D) and fourth fingers (4D) of their left hand were measured with a measuring tape from the metacarpophalangeal joint to the tip of the finger, excluding their nails.

RESULTS

Demographics

Forty patients participated in the study: twenty PCa and twenty with BPE (Control). Their age range was between 39-93years, with a mean age of the PCa group being 71.50±7.59years, while the BPE group had a mean of 70.55±13.82years.

Prostate-Specific Antigen
The mean PSA of the PCa group was significantly higher (116.57±164.5ng/ml) than the BPE group (10.64±18.65ng/ml; p=0.0070). The correlation between PSA and PCa was robust, positive and statistically significant. There was also a positive relationship between PSA and 2d:4D ratio that was not statistically significant.

2D:4D ratio
Patients with PCa had a higher mean 2D:4D ratio than the BPE group (Table 3). There was a statistically significant weak positive relationship between prostate cancer and 2d:4d ratio, indicating that men with a high 2D:4D ratio had a significantly moderately greater risk of developing prostate cancer. (p=0.035, r=0.236).

Table 1: Age characteristic of prostate cancer and benign prostatic enlargement (Control) patients.

N	40
Mean	71.02
Median	72.00
Std. Deviation	11.05
Range	57.00
Minimum	39.00
Maximum	96.00

Table 2: Age distribution of Prostate Cancer and Control patients with a benign prostatic enlargement (BPE) and Prostate cancer.

	Group				Chi-square	p-value
	BPH		PCa			
	n	(%)	n	(%)		
Age group						
<50	2	(10.0)	0	(0.0)		
50-59	2	(10.0)	1	(5.0)	4.54	0.478
60-69	4	(20.0)	7	(35.0)		
70-79	7	(35.0)	9	(45.0)		
80-89	4	(20.0)	3	(15.0)		
>90	1	(5.0)	0	(0.0)		
Total	**20**	**(100.0)**	**20**	**(100.0)**		

Table 3: Mean age, PSA, and 2D:4D ratio of patients with benign prostatic enlargement and prostate cancer.

	N=20			N=20		
	Benign Prostatic Enlargement (Control)			Prostate Cancer		
	Mean age (years)	Mean PSA ng/ml	Mean 2D:4D	Mean Age	Mean PSA ng/ml	Mean 2D:4D
Mean	70	10.64	0.76	71.50	116.50	0.93
Median	72	3.06+-	0.91	72..0	66.00	0.94
Standard deviation	13.82	18.64	0.34	7.59	164.50	0.05
Minimum	39	0.34	0.09	50	2.20	0.80
Maximum	96	76	1.02	84	719.62	1.07

Table 4: Relationship of Prostate Cancer and Benign Prostatic Enlargement with Age, PSA And 2d:4d Ratio.

	Group				t-test	p-value
	BPH (n=10)		PCa (n=10)			
	Mean±SD	Median(range)	Mean±SD	Median(range)		
Age(years)	70.55±13.82	72.0(39.0 -96.0)	71.50±7.59	72.0(50.0 -84.0)	-0.27	0.789
PSA (ng/ml)	10.64±18.65	3.06(0.34 - 76.90)	116.57±164.5	66.09(2.20 - 719.62)	-2.86	0.007*
2D:4D RATIO	0.76±0.35	0.91(0.09 - 1.02)	0.93±0.06	0.95(0.80 - 1.07)	-2.18	0.035*

Table 5: Spearman's Rank correlation shows the relationships between Age 2D:4D ratio and PSA.

		Group	2D:4D RATIO
Group	r	1.000	0.334
	p-value	.	0.035*
	N	40	40
2D4DRATIO	r	0.334	1.000
	p-value	0.035*	.
	N	40	40
Age	r	0.002	0.342
	p-value	0.989	0.031*
	N	40	40
PSA ng/ml	r	0.745	0.236
	p-value	0.0001*	0.142
	N	40	40

DISCUSSION

The prospect of determining the risk of prostate cancer from the length of the fingers and measurement of the 2D:4D ratio is very "tantalizing", and the potential benefit is immense.[11-13] The basis for the relationship is due to the simultaneous activation of genes such as androgen receptor (AR) and Homeobox (HOX) gene during fetal development. Both of these genes are involved in finger ratio and PCa development.[10] The combined expression of these genes occurs naturally during embryogenesis. The HOX gene regulates the process of cell differentiation and embryogenesis and is dysregulated in many cancers.[14,15] Also, early hormonal exposure plays a role in the aetiology of many cancers.[7] The mean age of all the respondents in this study was 71.02±11.05years. The mean age for those in the PCa group and BPE group was similar, with no statistically significant difference between the two groups (p=0.789). This is an indication that the two groups were adequately age-matched.

In our study, the PSA of the PCa and BPE groups were 116.57±164.5ng/ml and 10.64±18.65ng/ml, respectively. We found a statistically significant strong relationship between the 2D:4D ratio and PSA (p=0.0001, r=0.745), suggesting that patients with higher 2D:4D ratios are likely to present with higher PSA levels. (Table 3&4) An elevated PSA is associated with an increased risk of cancer. The mean PSA of 110.6ng/ml suggests that the majority of the patients presented with advanced diseases. This is the most frequent presentation of prostate cancer in Nigeria.[16] On the contrary, Jung et al.,[11] in their study, found a weak inverse correlation between PSA and 2D:4D ratio of both hands in their study of 366 men aged 40years and above. This implies

patients with a low 2D:4D ratio have a higher risk of developing PCa. Similar research in Korea found that a 2D:4D ratio of <0.95 was associated with increased risk of PCa[11,17] Other studies also had similar inverse relationships between PSA and 2D:4D and PCa.[6,13,18]

However, as shown in Tables 3&4, we observed that the mean 2D:4D ratio of 0.93±0.06 in our PCa patients was statistically significantly higher than those with BPE. [0.76±0.35; p=0.007] Unlike the findings of many other researchers, our patients with PCa had a higher 2D:4D ratio and was statistically significant. (p=0.035). This is similar to one study in Spain[19] that showed a 2D:4D ratio of >0.95 increased the risk of PCa. The variations in the relationships between the 2D:4D ratio and prostate cancer in these various studies buttress the finding of inter-racial and intra-racial heterogeneity of 2D:4D ratio among the different populations and could mitigate its use for risk evaluation of prostate cancer patients as observed by Water et al.[20]

Muller et al.[13] found no association between the 2D:4D ratio and PCa. They, however, stated that they could not conclude that there was no mild relationship. In their study, Water et al.[20] noted that the 2D:4D ratio varied among different races and did not correlate with the severity of PCa in men diagnosed before 60year.

The intricate interplay of the AR and HOX genes that are synchronously co-activated in the development of the digit still suggest a relationship with prostate cancer carcinogenesis.[11] The fourth finger has been shown to have more AR activity than the second finger.[21] It is a fact that PCa is androgen-dependent, and changes in the AR gene may lead to PCa androgen insensitivity.[11,21]

Additional studies are required to qualify and quantify any observed association and correlation between the 2D:4D ratio and prostate cancer risk. Our study population is small; more extensive studies are needed to determine the presence and validation of the relationship researchers have noted.

Finally, other factors that could impact the standardized metric application of 2D:4D ratio in prostate cancer evaluation include nutritional deficiencies and genetic and racial factors in musculoskeletal growth and development. A study in Nigeria[22] also showed significant inherent inter-ethnic and intra-ethnic diversity in the 2D:4D ratio.[13,18] The is an additional confounder in our study.

CONCLUSION

Our study's patients with prostate cancer had higher 2D:4D ratios and higher serum PSA compared to the control with BPH. Prostate cancer is a global health problem, and identifying risk factors, and early commencement of screening in the at-risk groups will aid in prompt diagnosis, treatment and improve disease-free survival. The 2D:4D ratio is a potentially objective, non-invasive, easily administered modality for evaluating the risk of developing the disease. Further Multi-Centred studies are needed to clarify any existing relationship.

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