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Second to fourth digit ratio: its relationship with core cancer volume and Gleason score in prostate biopsy

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ABSTRACT

Objective: To investigate the relationships between 2nd to 4th digit ratio (digit ratio) and prostate cancer detection rate and biopsy findings, including Gleason score.

Materials and Methods: In 770 consecutive men aged 40 years or older that presented with lower urinary tract symptoms (LUTS), right hand 2nd and 4th digit lengths were measured prior to PSA determinations, DRE and transrectal ultrasonography (TRUS). Among these, 166 men with a prostate specific antigen (PSA) level ≥ 3 ng/mL or abnormal digit rectal examination (DRE) prospectively underwent prostate biopsies. The relationship between digit ratio and prostate cancer detection rate and biopsy findings was investigated.

Results: The study subjects were allocated to two groups by digit ratio (group A: digit ratio < 0.95; n = 420; group B: digit ratio ≥ 0.95; n = 350). Despite similar biopsy rates (22.4% vs. 20.6%, p = 0.544), group A had higher cancer detection rate (46.8% (44/94) vs. 23.6% (17/72), p = 0.002; OR = 2.847, 95% CI = 1.445-5.610). When we analyzed 408 positive biopsy cores (group A: digit ratio < 0.95, n = 282; group B: digit ratio ≥ 0.95, n = 126), group A had higher percentage of core cancer volume (46.7% vs. 37.1%, p = 0.005) and more biopsy cores with high Gleason score (sum of Gleason score ≥ 9: 18/282 (6.4%) vs. 1/126 (0.8%), p = 0.010; primary Gleason score = 5: 12/282 (4.3%) vs. 0/126 (0.0%), p = 0.021).

Conclusions: A lower digit ratio is related to an increased detection rate of prostate cancer, a high percentage of core cancer volume and a high Gleason score.

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INTRODUCTION

The ratio of the 2nd to 4th digit length (digit ratio) of the right hand is known to be fixed in utero (1-3), and is sexually dimorphic and lower in men than in women (4-6). The digit ratio is negatively related to prenatal testosterone and positively related to prenatal estrogen concentrations (7).

The digit ratio of the right hand is related to the activity of the androgen receptor (AR) (8). Manning and colleagues demonstrated that the digit ratio of the right-hand is positively correlated with the CAG repeat number of the AR gene, and that individuals with a low digit ratio possess AR alleles with low CAG repeat numbers (8). It has been well established that a low AR CAG repeat number increases the risks of prostate cancer (9,10).

It has recently been suggested that the digit ratio is related to prostate specific antigen (PSA) level and the prostate cancer risk (11).

Based on the above-mentioned evidence, we thought that if digit ratio is related to the prostate cancer risk, digit ratio might be related to the detection rate of prostate biopsies and the

biopsy findings including the indices of tumor volume (i.e., the number of cores involved and the percentage of cores involved) and Gleason score. We investigated the relationship between digit ratio and prostate cancer detection rate and biopsy findings.

MATERIALS AND METHODS

Among the men that presented with lower urinary tract symptoms (LUTS) at a single tertiary academic center, 770 consecutive men aged 40 years or older were prospectively enrolled. All patients in the present study come from a same ethnic Korean group.

Right hand 2nd and 4th digit lengths were measured by an investigator prior to the PSA determinations and digit rectal examination (DRE) and transrectal ultrasonography (TRUS). The digit lengths were measured directly on the ventral surface of the fingers using a digital vernier calliper (6); this measurement has been previously reported to provide a high degree of repeatability (12,13). To minimize measurement errors, the mean values of duplicate measurements were used in the analysis.

Among 770 men, 166 men with a PSA level ≥ 3 ng/mL or abnormal DRE findings underwent a 12 core prostate biopsy as an initial biopsy. Biopsies were performed transrectally using an 18-gauge biopsy needle and a biopsy gun under TRUS guidance to provide the 17 mm long tissue cores.

The study subjects were allocated into two groups by digit ratio. As noted in previous study (11), we chose 0.95 as the cut-off value because the mean and median values of digit ratio of all patients (n = 770) were 0.948 and 0.946.

The cancer detection rates and biopsy findings were analyzed according to digit ratio. Student's t-test and Chi-square test were used to compare the variables of the two study groups, which were divided by digit ratio. To identify the independent predictive factors influencing prostate cancer detection, univariate and multivariate analysis were performed using logistic regression model. The analysis was performed using SPSS 12.0 (SPSS, Chicago, IL), and differences were considered statistically significant when the P values were less than 0.05.

RESULTS

The patients' characteristics are summarized in Table-1. The mean patients' age, testosterone level, prostate volume, PSA level and prostate specific antigen density (PSAD) were 61.4 ± 10.4 yrs (mean ± SD), 453.64 ± 167.45 ng/dL, 34.70 ± 18.04 cc, 3.96 ± 11.98 ng/mL and 0.101 ± 0.312 ng/mL/cc, respectively. The mean 2nd and 4th digit lengths and the mean digit ratio were 7.223 ± 0.467 cm, 7.625 ± 0.483 cm and 0.948 ± 0.043, respectively. Among 770 men, only five men (0.6%) had a family history of prostate cancer (first-degree relative) and 41 men (5.3%) had abnormal DRE findings. Among 770 men, 166 men (21.6%) underwent prostate biopsies and 61 men (7.9%) were found to have

Table 1 - Characteristics of the studied population.

	Mean ± SD
Age (years)	61.4 ± 10.4
2nd digit length (cm)	7.223 ± 0.467
4th digit length (cm)	7.625 ± 0.483
Digit ratio	0.948 ± 0.043
PV (cc)	34.70 ± 18.04
PSA (ng/mL)	3.96 ± 11.98
PSAD (ng/mL/cc)	0.101 ± 0.312
Testosterone (ng/dL)	453.64 ± 167.45
Family history (%)	0.6% (5/770)
Abnormal DRE (%)	5.3% (41/770)
Biopsy (%)	21.6% (166/770)
Cancer (%)	7.9% (61/770)
Cancer detection rate (%)	36.7% (61/166)

Digit ratio = 2nd digit length / 4th digit length; **PV =** prostate volume; **PSA =** prostate specific antigen; **PSAD =** prostate specific antigen density; **DRE =** digital rectal examination.

prostate cancer. Cancer detection rate of prostate biopsy was 36.7% (61/166).

Besides age, PSA and DRE, univariate and multivariate analysis showed that digit ratio was also an independent predictor of prostate cancer detection (Table-2).

Table 2 - Univariate and multivariate analysis using logistic regression model in biopsied patients (N = 166).

		Ca	Non Ca	OR (95% CI)	Univariate p-value	Multivariate p-value
Age (yrs)	≥ 65	51	67	2.893 (1.318-6.348)	0.007	0.013
	< 65	10	38			
PSA (ng/mL)	≥ 6	46	45	4.089 (2.032-8.228)	0.000	0.009
	< 6	15	60			
PV (cc)	≥35	41	74	0.859 (0.435-1.694)	0.660	
	< 35	20	31			
DRE	Abnormal	29	12	7.023 (3.208-15.376)	0.000	0.000
	Normal	32	93			
Digit ratio	< 0.95	44	50	2.847 (1.445-5.610)	0.002	0.003
	≥ 0.95	17	55			

Ca = cancer; **PSA =** prostate specific antigen; **PV =** prostate volume; **DRE =** digital rectal examination; **Digit ratio** = 2nd digit length / 4th digit length

The study subjects were allocated into two groups by digit ratio (group A: digit ratio < 0.95, n = 420; group B: digit ratio ≥ 0.95, n = 350). Despite similar biopsy rates (22.4% vs. 20.6%, p = 0.544), group A had a higher cancer detection rate (46.8% vs. 23.6%, p = 0.002; OR = 2.847, 95% CI = 1.445-5.610). However, no intergroup difference was found for age, serum testosterone level, prostate volume, PSA, DRE findings, biopsy findings and clinical stage (Tables 3 and 4).

We analyzed the 408 positive biopsy cores (group A: digit ratio < 0.95, n = 282; group B: digit ratio ≥ 0.95, n = 126). Table 5 shows the relationships between digit ratio and biopsy findings. Group A had a higher percentage of core cancer volume (46.69 ± 31.73% vs. 37.07 ± 29.43%, p = 0.005) (Table-5). The distributions of the primary Gleason scores of the positive cores were different between the two groups (Table-5). Furthermore, in group A, a significantly greater proportion of cores were found to have Gleason scores ≥ 9 (18/282 (6.4%) vs. 1/126 (0.8%), p = 0.010) and primary Gleason score = 5 (12/282 (4.3%) vs. 0/126 (0.0%), p = 0.021) (Table-5).

When we analyzed the 266 positive biopsy cores with the sum of Gleason scores ≥ 7, the distributions of sum of Gleason scores as well as primary Gleason score were different between the two groups (Table-6).

Table 3 - Comparison of the study variables between the two studied groups.

	Digit ratio < 0.95	Digit ratio ≥ 0.95	p-value
No of total patients	**420**	**350**	
Age (years)	61.7 ± 10.2	61.0 ± 10.6	0.371
Digit ratio	0.919 ± 0.024	0.983 ± 0.033	0.000
PV (cc)	34.45 ± 17.77	34.99 ± 18.37	0.681
PSA (ng/mL)	4.41 ± 12.78	3.41 ± 10.95	0.248
Abnormal DRE	24/420 (5.7%)	17/350 (4.9%)	0.598
Biopsy rate (%)	94/420 (22.4%)	72/350 (20.6%)	0.544
No of biopsy patients	**94**	**72**	
Age (yrs)	68.3 ± 7.9	69.2 ± 9.0	0.492
Digit ratio	0.918 ± 0.024	0.980 ± 0.025	0.000
PV (cc)	48.80 ± 22.51	51.23 ± 26.16	0.522
PSA (ng/mL)	16.34 ± 23.42	12.81 ± 21.80	0.323
Abnormal DRE	24/94 (25.5%)	17/72 (23.6%)	0.778
Cancer detection rate (%)	44/94 (46.8%)	17/72 (23.6%)	0.002

Digit ratio = 2nd digit length / 4th digit length; **PV =** prostate volume; **PSA =** prostate specific antigen; **DRE =** digital rectal examination.

DISCUSSION

In humans, the growth and pattern of digits and the differentiation of gonads are controlled by the homeobox genes HOXA and HOXD (2,13,14). Therefore, gonadal fetal products such as testosterone may influence finger morphology (6,15,16). For example, a high concentration of testosterone, indicating high prenatal testicular activity leads to low digit ratio (17). Recently, Lutchmaya et al. (7) showed that digit ratio is negatively associated with prenatal testosterone levels and it is positively associated with prenatal estrogen levels.

It is well known that testosterone and androgen receptors (AR) play central roles in prostate growth and the development of prostate cancer. The short CAG repeat length of the androgen receptor gene (AR) has been reported to be associated with the aetiologies of prostate cancer (9,10). Manning et al. (8) showed that the right-hand digit ratio is positively correlated with the CAG repeat number of AR.

Recently, Rahman et al. (18) reported that digit ratio is a reasonable marker for evaluation of prostate cancer risk. In their large case-control study, a higher digit ratio is related to more protective effect on prostate cancer risk, in particular, patients with age under 60 years. Considering these studies, it is highly suggestive that digit ratio may be related to prostate cancer.

In other study of the relationship between digit ratio and prostate cancer, Jung et al. (11) proposed that the 2nd to 4th digit ratio (digit ratio) of the right hand is related to PSA

Table 4 - Comparison of the study variables between the two studied groups.

	Digit ratio < 0.95	Digit ratio ≥ 0.95	p-value
No of cancer patients	**44**	**17**	
Age (yrs)	70.4 ± 6.9	72.7 ± 8.6	0.273
Digit ratio	0.921 ± 0.021	0.979 ± 0.018	0.000
PV (cc)	45.32 ± 22.38	46.99 ± 19.62	0.787
PSA (ng/mL)	26.84 ± 30.63	30.75 ± 38.56	0.679
No of positive cores	6.5 ± 3.8	7.4 ± 3.6	0.420
Max core cancer vol (%)	56.83 ± 34.08	59.29 ± 31.92	0.815
Max Sum of GS	7.1 ± 1.0	7.1 ± 1.0	0.849
Max Primary GS	3.6 ± 0.5	3.6 ± 0.5	0.867
Max Secondary GS	3.5 ± 0.7	3.5 ± 0.7	0.880
Clinical stage			
cT1	15	2	0.293
cT2	15	6	
cT3	10	6	
cT4	4	3	

Digit ratio = 2nd digit length / 4th digit length; **PV =** prostate volume; **PSA =** prostate specific antigen; **PSAD =** prostate specific antigen density; **GS =** Gleason score.

level and the presence of prostate cancer. They showed the significant negative relationships between digit ratio and PSA level and the presence of prostate cancer. However, Jung et al. (11) did not find that the prostate biopsy findings were correlated to digit ratio because the number of prostate cancer patients in their study was not sufficient to reveal the relationship of digit ratio to the biopsy findings.

The histologic grade is the most important piece of information obtained from the needle biopsy. The Gleason grading system is the most commonly used classification scheme for the histologic grading of prostate cancer (19,20). Gleason grade has been shown to correlate with the pathologic extent of disease (21-25). The presence of a Gleason pattern 4 or greater or a Gleason sum of 7 or greater is particularly predictive of a poorer prognosis. Numerous multivariate analyses support the assertion that Gleason sum is a strong predictor of the extent of prostate disease (22,23,26-28).

According to our data, only five patients had family history of prostate cancer (first-degree relative). At present, the screening of prostate cancer in Korea is not as widespread as in Western countries (29). Furthermore, among Korean men, prostate cancer accounts for 2.4% and 1.5% of the total cancer cases and deaths, respectively (30,31). Also, age-adjusted incidence and mortality rates of prostate cancer in Korea are much lower than those in most Western nations (32). Therefore, it is unusual that the prostate biopsy patients have family history of prostate cancer.

In the present study, besides age, PSA and DRE, univariate and multivariate analysis using logistic regression model showed that digit ratio is also an independent predictor of prostate can-

Table 5 - Comparison of the positive cores between the two studied groups.

		Digit ratio < 0.95	Digit ratio ≥ 0.95	p-value	OR (95% CI)
No of positive cores		282	126		
% core cancer vol		46.69 ± 31.73	37.07 ± 29.43	0.005	
No of cores	4	8	1	0.140	
with sum of GS	5	3	2		
	6	86	42		
	7	111	55		
	8	56	25		
	9	18	1		
	≤ 8	264	125	0.010	8.523 (1.125-64.562)
	≥ 9	18	1		
No of cores with primary GS	2	8	1	0.042	
	3	153	67		
	4	109	58		
	5	12	0		
	≤ 4	270	126	0.021	1.044 (1.019-1.070)
	5	12	0		
No of cores with secondary GS	2	11	3	0.150	
	3	135	74		
	4	128	48		
	5	8	1		

% = percentage; **Digit ratio =** 2nd digit length / 4th digit length; **GS =** Gleason score.

cer detection (Table-2). Therefore, it can be suggested that digit ratio is associated with prostate cancer risk.

One of the novel findings of this study was that digit ratio is related to the cancer detection rate and the aggressiveness (high percentage of core cancer volume and high Gleason score) of prostate cancer.

To date, only three studies have investigated the relationship between digit ratio and prostate cancer risk (11,18,33). Two studies have reported a strong association between 2D:4D and risk of prostate cancer (11,18). In the other study, although it is weak, an inverse association was observed between 2D:4D and risk of prostate cancer for patients aged < 60 (33). However, these studies did

Table 6 - Comparison of the positive cores with GS ≥ 7 between the two studied groups.

		Digit ratio < 0.95	Digit ratio ≥ 0.95	p-value
No of positive cores		185	81	
% core cancer vol.		57.57 ± 30.24	40.27 ± 29.95	0.000
Sum of GS		7.5 ± 0.7	7.3 ± 0.5	0.028
Primary GS		3.7 ± 0.6	3.7 ± 0.5	0.965
Secondary GS		3.8 ± 0.5	3.6 ± 0.5	0.020
No of cores with sum of GS	7	111	55	0.044
	8	56	25	
	9	18	1	
No of cores with Primary GS	3	64	23	0.025
	4	109	58	
	5	12	0	

% = percentage; Digit ratio = 2nd digit length / 4th digit length; GS = Gleason score.

not reveal the relationship between digit ratio and cancer detection rate and cancer aggressiveness.

In our study, despite similar biopsy rates (22.4% vs. 20.6%, p = 0.544), lower digit ratio group had a higher cancer detection rate than higher digit ratio group (46.8% vs. 23.6%, p = 0.002; OR = 2.847, 95% CI = 1.445-5.610) (Table-3).

Furthermore, when we analyzed the 408 positive biopsy cores (group A: digit ratio < 0.95, n = 282; group B: digit ratio ≥ 0.95, n = 126), lower digit ratio group had a higher percentage of core cancer volume than higher digit ratio group (46.69 ± 31.73% vs. 37.07 ± 29.43%, p = 0.005) (Table-5). Also, a significantly greater proportion of cores were found to have sum of Gleason score ≥ 9 (18/282 (6.4%) vs. 1/126 (0.8%), p = 0.010) and primary Gleason score = 5 (12/282 (4.3%) vs. 0/126 (0.0%), p = 0.021) in lower digit ratio group (Table-5).

In other words, most of the positive cores with sum of Gleason score ≥ 9 or all the positive cores with primary Gleason score = 5 were found in the group with a lower digit ratio rather than in the group with a higher digit ratio. These results suggest that digit ratio may predict the histologic grade as well as the cancer detection rate on prostate biopsy. We think that this is very important and it can be highly suggestive of the relationship between digit ratio and cancer aggressiveness.

According to our data, we have found that the prostate biopsy findings of each cancer patient were not related to digit ratio (Table-4). Actually, the total number of patients who had prostate cancer was 61. So, we think that the number of prostate cancer patients was not sufficient to reveal the relationship of digit ratio to the biopsy findings of the patients. However, when we considered the prostate biopsy findings of each positive core, the prostate biopsy findings of the positive cores were related to digit ratio (Tables 5 and 6). Since the total number of positive cores was 408, we think that this number is sufficient to reveal the relationship of digit ratio to the biopsy findings.

Our results show that the positive cores of the patients with a lower digit ratio have a higher percentage of core cancer volume and that a significantly greater proportion of cores with a lower digit ratio have a high Gleason score. Concluding,

digit ratio may be related to the histologic grading of prostate cancer and the extent of disease.

Digit ratio is reflective of prenatal androgen exposure and the in utero milieu. Our results show that digit ratio is related to prostate cancer, like was shown by the study of Jung et al. (11). This can be one of the evidences that prenatal androgen exposure (the in utero milieu) may be related to the later development of prostate cancer, which was already proposed by Henderson et al. (34) in 1988.

CONCLUSIONS

Our results showed that a lower digit ratio is related to an increasing probability of detection of prostate cancer, a high percentage of core cancer volume and a high Gleason score. These findings mean that patients with a lower digit ratio have a higher chance of developing prostate cancer and they might have more aggressive prostate cancer.

CONFLICT OF INTEREST

None declared.

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