Temas em Saúde
Volume 20, Número 3
ISSN 2447-2131
João Pessoa, 2020

Artigo

ASSOCIATION BETWEEN HAND DIGIT RATIO (2D:4D) AND ORAL SQUAMOUS CELL CARCINOMA

ASSOCIAÇÃO ENTRE A RAZÃO DIGITAL (2D:4D) E O CARCINOMA DE CÉLULAS ESCAMOSA ORAL

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ABSTRACT - **Objective:** Digit ratio (2D:4D) has been suggested as a biomarker for prenatal hormone activity and has been linked to several types of neoplasms. This study aimed to investigate the possible correlation between 2D:4D ratios and oral squamous cell carcinoma. **Material and methods:** A case-control study was performed with brazilian subjects. Direct measurements of the lengths of index and ring fingers of both hands of patients with oral cancer (n=30) and controls matched by age, gender, and tobacco and alcohol habits (n=30) were obtained using a digital vernier callipers. Mean ratios among the second and fourth digits were compared. The data were analysed using a Student's *t*-test with a significance level of 5%. **Results:** Men with oral squamous cell

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carcinoma presented right 2D:4D higher than healthy men (0.9807 and 0.9598, *p*=0.047, respectively). **Conclusions:** This study reinforces the relationship, built upon previous studies, between 2D:4D as a likely biomarker associated with oral squamous cell carcinoma, suggesting that intrauterine exposure to foetal oestrogens could be a likely risk factor for this multifactorial disease.

Keywords: Finger ratio; Gonadal steroid hormones; Oral cancer.

RESUMO - Objetivo: A razão digital (2D:4D) tem sido sugerida como um biomarcador da atividade hormonal pré-natal e está sendo associada a vários tipos de neoplasias. Este estudo teve como objetivo investigar a possível correlação entre as razões 2D:4D e carcinoma de células escamosas oral. **Material e Métodos:** Um estudo de caso-controle foi realizado com sujeitos brasileiros. A medida dos comprimentos dos dedos indicador e anelar de ambas as mãos dos pacientes com câncer bucal (n = 30) e controles pareados por idade, sexo e hábitos tabagistas e etilistas (n = 30) foram obtidas com um paquímetro digital. As razões médias entre o segundo e o quarto dígito foram comparadas. Os dados foram analisados usando um teste t de Student com um nível de significância de 5%. **Resultados**: Homens com carcinoma espinocelular oral apresentaram 2D:4D superior aos homens saudáveis (0,9807 e 0,9598, p = 0,047, respectivamente). **Conclusão:** Este estudo reforça a relação, baseada em estudos anteriores, entre 2D:4D como provável biomarcador associado ao carcinoma células escamosas oral, sugerindo que a exposição intrauterina a estrogênios fetais poderia ser um provável fator de risco para esta doença multifatorial.

Palavras-chave: Razão digital; Hormônios esteroides gonadais; Câncer bucal.

INTRODUCTION

The ratio of the length of the second (index) finger to the fourth (ring) finger (known as digit ratio or the 2D:4D ratio) represents an individual difference variable putatively related to prenatal hormonal exposure – a high digit ratio means higher oestrogen exposure and a low digit ratio suggests higher testosterone exposure (MANNING *et al*., 1998; MANNING *et al.,* 2002; MANNING *et al*., 2003).

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The 2D:4D ratio has been used as a marker in studies of behavioural and psychological characteristics and has even been used to determine an individual's propensity to a range of diseases, especially those diseases that show sex differences in their occurrence, progression and/or prognosis (SWADDLE *et al*., 2002).

Approximately 19 genes have been correlated to the formation and differentiation of digit ratios and some of them have been correlated to carcinogenesis, making 2D:4D a marker for the action of these genes and predictive of the susceptibility to several types of cancer, such as oral cancer, prostate cancer, breast cancer , gastric cancer and colorectal cancer (SWADDLE *et al*., 2002; SARODE *et al*., 2014; MENDES *et al*., 2016; GONÇALVES *et al*., 2017; FERREIRA FILHO *et al.,* 2015).

Thus, the plausibility of the correlation between 2D:4D and oral cancer refers to the simultaneous action of genes, especially Homeobox (*HOX*), androgen receptor genes (*AR*), and *LIN28B* in differentiation of the digits, as well as in oral carcinogenesis. *HOX* genes play an important role in the formation of the fingers, especially *HOXA* and *HOXD* notably, other studies reinforce the role of *HOX* family genes in the onset of oral squamous cell carcinoma (OSCC) with a greater expression of *HOXB7* (MANNING *et al*., 2003; COLETTA et al., 2009). With respect to *AR* genes, it has been postulated that these are essential for the differentiation of fingers, with *AR* activity higher in digit 4 than in digit 2. This result is decisive for establishing the 2D:4D ratio (ZHENG *et al*., 2011). Studies have established a correlation between a lower number of polyglutamine (CAG) sequences in this gene and a higher incidence of head and neck cancer, as well as a correlation between short polyglutamine sequences and a worse prognosis for these carcinomas (ROSA *et al.,* 2007). Medland et al. (2010), identified a variant of the *LIN28B* gene, rs314277, which was robustly associated with 2D:4D, while other evidence indicates that *LIN28B* is critically involved in initiation, progression, and overexpression in human OSCC (MEDLAND *et al.,* 2010; CHI *et al.,* 2015; WANG *et al.,* 2015; WU et al., 2017).

The 2D:4D ratio is a marker for the activity of these genes and it is possible that digital length is also a predictor for the development of oral cancer; this suggests that such a condition might be related to effects of intrauterine exposure to sex hormones (SWADDLE *et al*., 2002; SARODE *et al*., 2014).

OSCC is the most common malignancy of the head and neck (excluding non-melanoma skin cancer) and accounts for approximately 90% of all oral and oropharyngeal malignancies (CHI *et al.,* 2015). In Brazil, 11,180 new cases of oral cavity cancer in men and 4,010 in women were estimated in 2020-2022. These values correspond to an

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estimated risk of 10,69 new cases per 100,000 men and 3,71 per 100,000 women (Brazil, 2019).

Considering the multifactorial aetiology of OSCC and that some individuals manifest the disease without presenting the main risk factors, it is necessary to carry out studies that seek to elucidate other risk factors, primarily those related to the prevention and early identification of the disease. Thus, the aim of this study is to investigate whether 2D:4D is a marker for OSCC in a Brazilian population by comparing 2D:4D ratios among individuals with and without oral cancer.

MATERIALS AND METHODS

Samples

A case-control study was performed between October 2016 and June 2017 with a total of 30 patients with OSCC and 30 healthy controls. Patients with OSCC were recruited from the oncology centres of Minas Gerais State, Brazil, and met the following inclusion criteria: having a histopathological diagnosis of OSCC and undergoing treatment at the institutions. Exclusion criteria of both groups involved hormonal changes (data obtained from patient reports and medical records), a history of fractures on fingers of either hand, and, for the OSCC group, cases of lip cancer.

After identifying the cases, controls were selected to include patients who were assisted by primary care physicians in smoking cessation programmes conducted by public health services. The controls were given an oral evaluation and were matched by gender, age (range of ±2 years), and history of smoking and alcohol habits in relation to the OSCC group. All subjects enrolled in this study resided in the same geographical area (northern region of Minas Gerais State). Thus, healthy controls presented similar demographic, ethnic, and sociocultural characteristics compared with the OSCC group. Furthermore, individuals from both groups primarily used the public health services, a fact that ensures equivalent health assistance and screening practices.

2D:4D ratio

The lengths of the second (index) and fourth (ring) fingers were measured using digital vernier callipers with a resolution of 0.01 mm. Measurements were taken from the

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tip of the finger to the basal crease and were repeated two times, with a 30-minute interval between measurements. The second measurement was blind compared with the first. When two creases were visible at the base of the digit, the crease proximal to the palm was chosen. The length of the index finger was divided by the length of the ring finger to obtain the 2D:4D ratio. The analysed ratio was the mean of the two measurements performed. The right hand minus the left hand 2D:4D (DR-L) was calculated as the difference between the right and left 2D:4D (MULLER *et al*., 2012)

The measurements were undertaken by a team of three trained researchers. Intra-class correlation coefficients (ICC) were calculated to check intra- and inter-observer reliability of the 2D and 4D measurements (VORACEK *et al*., 2006). Written informed consent was obtained from each subject and the study was carried out with the approval of the Human Research Ethics Committee of the University (311.756/2013), following the recommendations of the Helsinki Declaration.

Statistical analysis

Sample size was calculated according to a specific formula using averages of independent groups (ARANGO, 2009). The size adopted a significance level of 5% and power of 80%. The mean values and standard deviations used in the sample formula were based on the results of Sarode; Sarode; Anand (2014) which compared average 2D:4D among individuals with and without the disease (0.98 [±0.02] and 0.96 [±0.02]), respectively). Thus, this study required at least 16 individuals in each group.

For the analysis of the results, initially, a descriptive statistical analysis was carried out. Next, a Shapiro-Wilk test was used to check the distribution of the sample and revealed that right and left 2D:4D and DR-L followed a normal distribution. Finally, a Student's *t*-test for unpaired samples was performed to compare means of 2D:4D ratios among groups. The effect size, which consists of a measure of standardized magnitude that represents the importance of association in practical terms, was also calculated, measured by Pearson correlation (coefficient r) (FIELD, 2009). All analyses were done in SPSS® 19.0 for Windows® (IBM SPSS, Armonk, NY USA) with a significance level of 5%.

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RESULTS

Intra-class correlation coefficients (ICC) were calculated to check intra- and inter-observer reliability of the 2D and 4D measurements. Intra-observer reliability was high for all measurements, with ICC greater than 0.98. ICC for inter-observer reliability were lower, but still adequate (lower value of 0.92). This suggests that the observed variability in digit ratio is due to individual differences rather than measurement error.

The sample comprised 60 individuals divided into two groups matched by gender and age. Of the 30 individuals of both groups, 25 (83%) were males and 5 (17%) women. The age of the individuals in the OSCC group ranged from 42 to 92 years (mean 61.17 ± 10.48), while in the control group the age ranged from 40 to 95 years (mean 61.00 ± 10.41). Characteristics of the study population are shown in Table 1. Note that features such as tobacco and alcohol consumption were matched between groups.

Table 1. Comparison of characteristics such as tobacco and alcohol consumption between groups.

Characteristics	OSCC Group	Control Group
Age [mean (SD)]	61.17 (10.48)	61.00 (10.41)
TC* (n)		
Never	2	2
Ex-smokers	12	12
Smokers	16	16
AC* (n)		
Never	4	4
Ex-drinkers	10	10
Drinkers	16	16

Regarding the location of oral cancer in the OSCC Group, 15 (25%) patients presented in the tongue, 8 (13.3%) in the floor of the mouth, 5 (8.3%) in the soft palate, 1 (1.7%) in the hard palate, and 1 (1.7%) in the retromolar trigone. Clinical features of the OSCC group at diagnosis are shown in Table 2. Table 3 summarizes the difference of 2D:4D between the OSCC and control groups for the whole sample, and for distribution by gender.

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Table 2. Clinical features of patients with oral cancer at moment of diagnosis.

	Mean (SD)	**Median (range)**
Age (years)	60.57 (10.2)	58.5 (41–92)
	n	**(%)**
Clinical stage		
I	6	20
II	2	6.66
III	13	43.33
IV	9	30
Regional metastasis		
Yes	18	60
No	12	40
Distant metastasis		
Yes	04	13.33
No	15	50
Not determined	11	36.66

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Table 3. Comparison of right hand digit ratio (R2D:4D), left hand digit ratio (L2D:4D), and right hand minus left hand digit ratio (DR-L) between patients with oral cancer (OSCC) and control group and distribution by gender.

	OSCC Group Mean (SD)	**CI95%**	**Control Group Mean (SD)**	**CI95%**	***p* value**	***effect size***
All subject 30						
R2D:4D	0.9752 (0.0387)	(0.9607–0.9896)	0.9572 (0.0377)	(0.9431–0.9713)	0.074[a]	r = 0.23
L2D:4D	0.9754 (0.0321)	(0.9634–0.9874)	0.9701 (0.0393)	(0.9554–0.9848)	0.568[a]	r = 0.07
DR-L	−0.0002 (0.0313)	(−0.0119–0.0114)	−0.0012 (0.0360)	(−0.0263–0.0052)	0.152[a]	r = 0.18
By gender, *Men, 25*						
R2D:4D	0.9807 (0.0342)	(0.9666-0.9949)	0.9598 (0.0382)	(0.9440-0.9756)	0.047[a]	r = 0.28
L2D:4D	0.9793 (0.0315)	(0.9663-0.9923)	0.9727 (0.0362)	(0.9577-0.9877)	0.492[a]	r = 0.09
DR-L	0.0014 (0.0320)	(-0.0118-0.0146)	-0.0128 (0.0382)	(-0.0286-0.0029)	0.159[a]	r = 0.20
Women, 5						
R2D:4D	0.9472 (0.0518)	(0.8829-1.0115)	0.9439 (0.0355)	(0.8998-0.9880)	0.910[a]	r = 0.04
L2D:4D	0.9559 (0.0314)	(0.9169-0.9949)	0.9572 (0.0554)	(0.8884-1.0260)	0.966[a]	r = 0.01
DR-L	-0.0087 (0.0291)	(-0.0449-0.0274)	-0.0132 (0.0250)	(-0.0444-0.0178)	0.798[a]	r = 0.09

[a] Student's *t*-test for unpaired samples.

Right hand digit ratios (R2D:4D), left hand digit ratios (L2D:4D), and DR-L were higher in the OSCC group than in the control group, especially in the right hand; however, these did not present statistically significant differences. When looking at each gender,

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men with oral cancer presented higher R2D:4D than men without the disease, with a significant difference ($p<0.05$). Figure 1 shows the distribution variability of the right hand 2D:4D (R2D:4D) means between men with oral cancer and men of the control group. Figure 2 presents the mean difference between R2D:4D of male cases and their respective controls (0.0209; 95% CI: 0.0003–0.0416).

Figure 1. Distribution variability of the right hand 2D:4D (R2D:4D) means between men with oral cancer and men of control group.

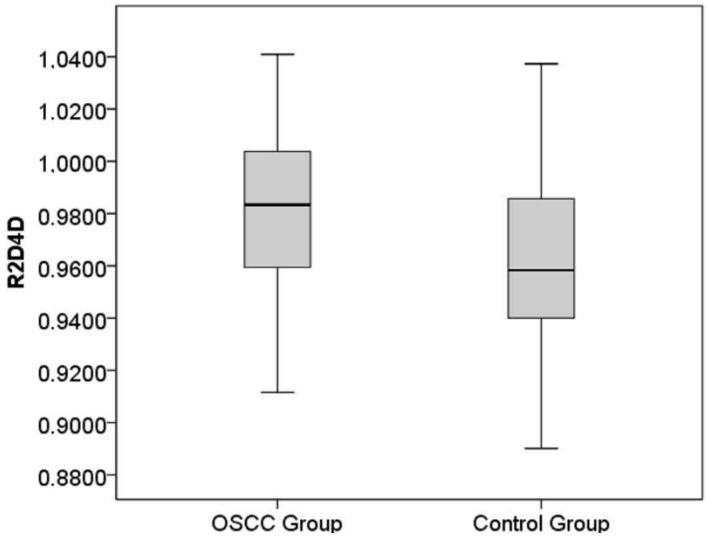

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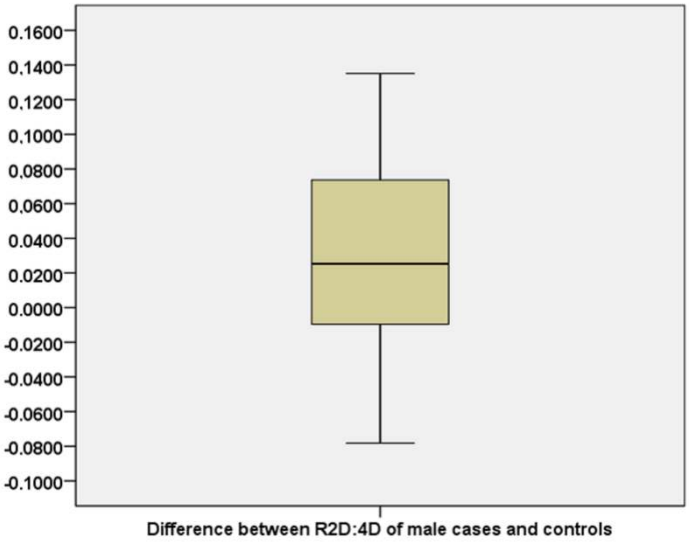
Figure 2. Mean difference between R2D:4D of male cases and their respective controls.



DISCUSSION

Sex hormone environment during early development is associated with cancer risk later in life. Thus, studies exploring the link between intrauterine hormone environment and cancer risk are encouraged (BUNEVICIUS *et al*., 2018). The concurrent action of the *HOX*, *AR*, and *LIN28b* genes in the differentiation of fingers, as well as in oral carcinogenesis, has shown that the 2D:4D ratio can be a putative marker which links these two situations.

In the present study, we verified that men of the OSCC group had significantly higher R2D:4D than men without the disease. These findings corroborate two studies previously conducted that compared 2D:4D in OSCC patients with healthy subjects.
The first study was a Brazilian research study that correlated 2D:4D of 25 patients with OSCC – 25 individuals with oral premalignant lesions and 25 controls. Individuals in the OSCC group presented with significantly higher 2D:4D (0.9700 ± 0.0551) in comparison with subjects with oral premalignant lesions (0.9625 ± 0.0512) and individuals without oral lesions (0.9643 ± 0.0365). It was concluded that individuals with higher 2D:4D seem

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to be more prone to malignant transformation of lesions in the oral cavity (HOPP *et al*., 2011).

The other study was performed by Sarode et al. (2014), which included 26 male patients with OSCC and 26 males without the disease. They observed that 2D:4D was significantly higher in the OSCC group (0.9855 ± 0.0262) as compared with the control group (0.9605 ± 0.0216). In Sarode; Sarode; Anand' study, only individuals without a history of tobacco and alcohol consumption were included, resulting in a more specific correlation of genetic aspects of OSCC and 2D:4D.

In the present study, we matched exposure to main risk factors for cancer among individuals in both groups to reduce the influence of these factors in the analysis. Thus, for each subject in the OSCC group, a control of the same gender was selected, close to the same age (range of ±2 years), and similar smoking and alcohol habits. It was difficult for researchers to achieve this pairing. A solution was to include in the control group individuals who had participated in smoking cessation programmes.

It is noteworthy that this study observed a higher digit ratio primarily in the right hand in the OSCC group as compared with the control group, as well as a significant difference in the right hand between men in both groups. Several studies evaluated the right hand only [6-9,30,31], a decision that was supported by meta-analysis which showed that the right hand might be a better indicator of prenatal androgenisation than the left hand (HÖNEKOPP *et al*., 2010). However, other studies that linked 2D:4D and cancer found significant associations with the left hand, which reinforces the importance of evaluating both hands in studies regarding this association (MULLER *et al*., 2012; HOPP *et al*., 2013; FERREIRA FILHO *et al*., 2015)

2D:4D ratio displays differences between races and ethnic groups (MANNING *et al*., 2003). The ethnic variation in 2D:4D is of methodological importance, as it implies that ethnicity needs to be assessed and controlled in 2D:4D studies; participants should be carefully matched for ethnicity or ethnically homogeneous samples should be used for the study. Mendes et al. (2016), state that, within this context, it is important to make some remarks about the Brazilian population's race and this should be considered when comparing the brazilian people with other populations in studies involving 2D:4D ratio. The brazilian population was derived from three different ancestral roots: Amerindians, Europeans, and Africans. This has resulted in a great variability of skin pigmentation, with no discontinuities between black and white skin colour (PENA *et al*., 2011).

Thus, the race of Brazilian individuals cannot be determined by skin colour. The ideal method is to genetically identify the contribution of components of ancestry to

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characterize the race of the study population. A study concluded that European ancestry is the major contributor to the genetic background of Brazilians (MOURA *et al*., 2015).

Several techniques are used to evaluate the 2D:4D ratio. We chose the direct technique for measuring the length of fingers using vernier callipers because of its significant reproducibility, low cost, and practicality. Furthermore, the direct technique is more suitable for studies involving small samples (RIBEIRO *et al*., 2016). Despite the appropriate sample calculation, the limitation of this study derives from the use of a small sample, not exceeding the samples of studies already published. Nonetheless, our results, built upon previous studies, reinforce a relationship, between 2D:4D as a likely putative biomarker associated with OSCC, showing that high 2D:4D could be associated with higher intrauterine exposure to oestrogens, which in turn could increase the risk of oral cancer.

The elucidation of a new risk factor for this disease contributes to the investigation of its multifactorial aetiology and the identification of a physical and easily accessible marker; it could contribute to the screening of patients at risk of developing this malignance. Speight et al. (2017), ratify the importance of performing screening tests for oral cancer as a public health measure, applied to people who are free of disease as a strategy for early identification of lesions or conditions that favour the development of the disease.

For oral cancer, the association with 2D:4D is still incipient in view of the low number of published studies. Further research is needed in different populations, with larger samples and control of the risk factors for the disease, in order to confirm this correlation.

Acknowledgment

The Minas Gerais State Research Foundation (FAPEMIG, Minas Gerais, Brazil), the National Council for Scientific and Technological Development (CNPq, Brazil), and the Coordination of Training of Higher Education Graduate Foundation (CAPES, Brasilia, Brazil).

For the Surgeons' Doctors of head and neck Cláudio Marcelo Cardoso and Francis Balduino Guimarães Santos, for support during data collection.

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DOI: 10.29327/213319.20.3-15
Páginas 256 a 271

Temas em Saúde
Volume 20, Número 3
ISSN 2447-2131
João Pessoa, 2020

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