UNIVERSIDADE ESTADUAL DE CAMPINAS

FACULDADE DE ODONTOLOGIA DE PIRACICABA

RENATO NICOLÁS HOPP

CORRELAÇÃO ENTRE A PROPORÇÃO 2D:4D E O DESEMPENHO ACADÊMICO EM ALUNOS DE ODONTOLOGIA

Tese de Doutorado apresentada à Faculdade de Odontologia de Piracicaba, da UNICAMP para obtenção do título de Doutor em Estomatopatologia, na Área de Patologia

Orientador: Prof. Dr. Jacks Jorge Júnior

Este exemplar corresponde à versão final da Tese defendida pelo aluno e orientada pelo Prof. Dr. Jacks Jorge Júnior

_____
Assinatura do Orientador

PIRACICABA, 2012

i

UNIVERSIDADE ESTADUAL DE CAMPINAS
Faculdade de Odontologia de Piracicaba

A Comissão Julgadora dos trabalhos de Defesa de Tese de Doutorado, em sessão pública realizada em 29 de Março de 2012, considerou o candidato RENATO NICOLÁS HOPP aprovado.

_____
Prof. Dr. JACKS JORGE JUNIOR

_____
Profa. Dra. KARINA GOTTARDELLO ZECCHIN

_____
Profa. Dra. DANIELA ATILI BRANDINI

_____
Profa. Dra. VANESSA ROCHA LIMA SHCAIRA

_____
Prof. Dr. MARCO ANTONIO CARVALHO

DEDICATÓRIA

Aos meus pais Antonio Jacó Hopp e Maria Aparecida Nicolás Lopes Hopp, sempre presentes em todas as lutas conquistas e passos, mesmo os mais ilógicos. A eles, o meu muito obrigado, e a minha eterna gratidão.

Ao meu tio, João Rodolfo Hopp, por ser exemplo de perseverança, caráter e luta. Por me apoiar na carreira universitária e, por estar presente sempre com importantes conselhos, direcionamento e muito carinho. A você dedico este trabalho.

AGRADECIMENTOS

À Faculdade de Odontologia de Piracicaba, na pessoa de seu Diretor Jacks Jorge Júnior, pela oportunidade e infra-estrutura para a realização deste trabalho e pela chance deste crescimento profissional.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES, pela bolsa de estudos concedida para a realização deste curso, tanto no país como no exterior

Ao meu orientador, Prof. Jacks Jorge, por mostrar-me o caminho profissional, mas, também, por mostrar-me que devemos ser profissionais e humanos, pois sendo humanos nos tornaremos melhores profissionais. Grato por abrir o escopo de meu trabalho e meu pensamento, e, por dar-me exemplo de pensamento amplo e irrestrito.

Ao Prof. Márcio Ajudarte Lopes, pelas lições ensinadas no Orocentro.

Ao Prof. Pablo Agustin Vargas, pela paciência, compreensão conhecimento, cultura e profissionalismo.

Ao Prof. Edgard Graner, exemplo de sabedoria e humildade.

Ao Prof. Oslei Paes de Almeida, pessoa de sabedoria e experiência incalculáveis, porém, acima de tudo exemplo do bom uso destas duas qualidades.

Ao Dr. Marcelo Brum Corrêa, exemplo de humildade, conhecimento e didática.

AGRADECIMENTOS ESPECIAIS

Deus, ó grande Amigo. Tens sido tão bom com este Teu filho durante todos estes anos. Tens sido especialmente generoso dando a mim a oportunidade de trabalhar e a saúde e perseverança para prosseguir, colocando sempre as pessoas mais apropiadas em cada momento em meu caminho.. A Ti Senhor, meu muito obrigado.

Cheguei a Piracicaba em dezembro de 2007 para o curso de Mestrado enviado por dois "pais" de coração e que continuam presentes e sendo grande fonte de inspiração, conhecimento e admiração; Eloi Dezan Júnior, o qual interveio diretamente em minha decisão de tentar esta mudança, além de dar-me conselhos sábios e verdadeiros, sendo sempre um grande professor e amigo e João Eduardo Gomes Filho, que me adotou mais como filho ou irmão do que como orientado, dando-me a chance de ingressar na vida acadêmica, provendo palavras de apoio e correção nos momentos chave e de suporte e reconhecimento quando apropriado.

Deixei uma família em Araçatuba, uma família construída ao longo dos vários anos de graduação e de estágio na Universidade Estadual Paulista. Agradeço aos amigos Eduardo Katsuragawa Louzada, Flávio Augusto Martins Gabas, Rafael Gonzales Camargo, Vinícius Marcato Fernandes Martins e Marcel Oliveira de Lima e a todos os colegas de turma. Tiago Augusto Becker, Aguinaldo Cândido da Silva Facundo, Diego Valentim, André Luis de Sousa, Adriano Takashi Kian, Claudiel Batista de Oliveira e Felipe Lino de Oliveira pelo apoio em todas as horas, mas especialmente na hora mais difícil de toda a minha estada em Araçatuba. Cabe aqui um agradecimento especial ao Professor Alvimar Lima de Castro, pelo mesmo motivo. Agradecimentos ainda a Maria Cecília Querido de Oliveira, Marília Mesquita Cury, Alexandre Rodrigues Freire, grandes amigos conquistados nesta jornada.

Aos grandes professores Roberto Holland, Valdir de Souza, Mauro Juvenal Nery, José Arlindo Otoboni Filho, Pedro Felício Estrada Bernabé, Ana Maria Pires Soubhia, Eduardo Passos Rocha, Cícero Eleutério da Silva Filho e Daniela Atili Brandini que souberam entender-me e guiar-me sempre na melhor das direções. Aos funcionários Neuza, Nelci, Ermelinda, Sueli Murata, Magda e Isabel pela convivência.

Aos bons amigos e pessoas importantes conquistados durante esta caminhada, Jonatas Henrique Vasconcelos, Lucas Alves Moura, Juliana Pucci de Moraes, Alessandra Cury Machado, Simone Watanabe, Natália Marlena Cancian, Henrique Schultz Lacerda Guimarães, Filipe Trotta, Tânia Knapp da Silva, André Luis de Oliveira Bressan, Frederico Di Bruno da Fonseca, Telmo Oliveira Bittar, Karen Mendes Graner, Nádia Cristina Fávaro Moreira. Obrigado pela convivência e pelas lições ensinadas no caminho.

Aos amigos do período de Doutorado Sanduíche, que contribuíram de maneira incalculável à minha adaptação e produção durante todo o período e quetornaram-se grandes amigos, Thom Wilcockson, Edwin Burns, Paul Boyce, JJ Tomash, Andreas Larsson, Lee White, Maria Katisfaraki, Shakeila Davies, James Greville, Charlie Finn, Liam Kilduff.

Ao Professor John Manning, meu agradecimento especial pelo apoio e por ter confiado em mim, me ensinando sobre a pesquisa, a metodologia de trabalho, a vida e conhecimentos gerais sobre culturas, povos e costumes ao redor do mundo.

À querida Catherine Kennedy, meu mais sincero agradecimento e meu mais sincero sentimento, por ajudar-me em todas as horas e ser fonte de inspiração para conquistas e desafios.

"E que a fria luz da razão não cale o azul da aura que me veste."

(Vander Lee)

"A living thing is distinguished from a dead thing by the multiplicity of the changes at any moment taking place in it."

(Herbert Spencer)

"Ef sy'n ceisio dod o hyd gweddill diflastod. Ef sy'n ceisio gwaith yn canfod gweddill."

(Aquele que procura descanso encontra o tédio, aquele que procura trabalho, encontra descanso)

(Dylan Thomas)

RESUMO

Estudos sugerem que a exposição pré-natal à testosterona (PT) está relacionada à inteligência ou à capacidade de aprendizado. A proporção entre os dedos indicador e anelar (proporção digital ou 2D:4D) correlaciona-se negativamente à exposição pré-natal à testosterona. Este estudo avaliou as correlações entre o 2D:4D e o sucesso acadêmico em disciplinas teóricas e práticas no currículo do curso de Odontologia da Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas, Brasil. Ao todo, 80 indivíduos (40 homens e 40 mulheres) com idade entre 18 e 22 anos (média 19,5 ± 1,1 anos para os homens e 19,7 ± 1,2 para mulheres), alunos do 2º ao 4º ano de graduação tiveram sua mão direita fotografada por meio de câmera digital acoplada a dispositivo padronizador perpendicular à superfície. As imagens foram transferidas ao *software* Adobe Photoshop® e os dedos indicador e anelar foram medidos de forma linear, da depressão mais caudal ao ponto mais rostral da ponta do dedo. Os dados foram analisados usando os *softwares* Microsoft Excel, SPSS 16 e Statview. A proporção digital média foi de 0,980 ± 0,038 para homens e 0,991 ± 0,025 para mulheres. Correlacionou-se então esta proporção às notas teóricas e práticas obtidas pelos estudantes durante os primeiros quatro semestres letivos do curso. As notas teóricas e práticas foram negativamente correlacionadas à proporção digital em homens (especialmente após a remoção da influência das horas de estudo domésticas; p = 0,02 e 0,004, respectivamente), mas não em mulheres (p = 0,89 e 0,77, respectivamente). Este achado apóia a correlação entre a influência da testosterona pré-natal e o desenvolvimento da inteligência em homens. A falta de correlação entre a testosterona pré-natal e o sucesso acadêmico em mulheres sugere que a inteligência no sexo feminino deve ser influenciada por fatores alheios à testosterona pré-natal.

Palavras-chave: Proporção 2D:4D, Estudantes, Odontologia, Inteligência, Testosterona pré-natal.

ABSTRACT

It has been suggested that prenatal testosterone (PT) is positively related to intelligence or learning-ability skills. Digit ratio (2D:4D) is a negative correlate of PT. This study considered the correlations between 2D:4D and academic success in practical and theoretical disciplines in the Dental School curriculum of the Piracicaba Dental School, State University of Campinas, Brazil. Overall, 80 subjects (40 males and 40 females) aged between 18 and 22 years (means 19.5 ± 1.1 and 19.7 ± 1.2, respectively) had their right hand palm photographed by a digital camera attached to a standardising device, perpendicular to the surface. The images were transferred to a computer and the index and ring fingers were measured from the ventralmost crease up to the tip of the finger using Adobe Photoshop. Data were analyzed using Microsoft Excel and SPSS 16. Mean digit ratio was 0.980 ± 0.038 for males and 0.991 ± 0.025 for females. Digit ratio was correlated to the grades obtained by the students through their first four semesters. Theoretical and practical grades were significantly negatively correlated to digit ratio in males (and this was particularly so after the influence of age and hours of study were removed, $p = 0.02$ and 0.004, respectively), but not in females ($p = 0.89$ and 0.77, respectively). This finding supports a link between high PT and intelligence in males. The lack of relationship between 2D:4D and examination marks in female students, suggests that intelligence in females may be influenced by factors other than prenatal testosterone.

Keywords: Digit ratio, Students, Dentistry, Intelligence, Prenatal testosterone.

SUMÁRIO

1- INTRODUÇÃO

Da susceptibilidade a doenças (Manning & Bundred, 2003) ao sucesso na bolsa de valores (Coates *et al.*, 2008), da influência no desenvolvimento de cânceres (Brabin *et al*., 2008) ao sucesso nos esportes (Voracek *et al.*, 2006), pesquisadores têm investigado um marcador putativo para avaliar características comportamentais, psicológicas e até mesmo doenças influenciadas pelo gênero masculino e pelo gênero feminino – a proporção entre os dedos anelar e indicador, também chamada 2D:4D, ou proporção digital (*digit ratio).*

Este marcador putativo tem sido correlacionado a condições ligadas à atividade dos hormônios sexuais - testosterona, estrógeno e hormônio luteinizante (Manning *et al.*, 1998). Correlações têm sido encontradas nos campos da psicologia (Nelson & Shultz, 2009) e medicina (Voracek, 2008), associando o 2D:4D a diversos traços de personalidade (Bailey & Hurd, 2005), orientação sexual (Hiraishi *et al*, 2012) e ao aparecimento de doenças nos sistemas reprodutivo (Brabin *et al*., 2008), circulatório (Ozdogmus *et al.*, 2009), locomotor (Manning, 2002), bem como ao desenvolvimento de neoplasias (Brabin *et al.,* 2008; Rahman *et al.,* 2011; Hopp e Jorge, 2011; Hopp e Jorge, 2012).

Os primeiros estudos sobre a proporção 2D:4D datam do século XIX. Naquele momento, pesquisadores acreditavam que este fosse um traço predominantemente hereditário (Phelps, 1952). Sabe-se hoje que a proporção entre estes dois dedos é estabelecida ainda no útero (Manning *et al.*, 2003) e sofre pouca ou nenhuma alteração após o nascimento (Manning & Bundred, 2000). Estudo recente em animais (Zheng e Cohn., 2011) confirmou que a proporção digital é estabelecida pelo equilíbrio entre exposição e sensibilidade aos hormônios estrógeno e testosterona, fatores estes comandados pela atividade de 19 genes (Em ordem alfabética, *Bmp6, Col4a2, Col5a1, Col6a2, Col10a1, Col12a1, Col14a1, Fgf3, FgfR2, Igfbp2, Igfbp5, Ihh, Itgam, Mmp9, Msx1, Runx2, Smad3, Sox9, Wnt5a*). Estes genes

influenciam principalmente a sensibilidade dos receptores celulares de andrógenos (AR) e estrógeno (ER), de modo a aumentar sua expressão (*Ihh, FgfR2, Sox9, Col10a1, Col4a2,* e *Col12a1* no caso dos AR e *Fgf3, Msx1, Igfbp2,* e *Igfbp5* para os ER) ou diminuí-la (*Bmp6, Smad3, Wnt5a, Igfbp2, Igfbp5, Runx2, Mmp9,* e *Itgam* para os AR e *Ihh, Col4a2, Col5a1, Col6a2,* e *Col14a1* para os ER).

O equilíbrio entre a exposição aos dois hormônios sexuais e a sensibilidade a estes (influenciada geneticamente), gera diferenças na proporção entre os dedos anelar e indicador, correlacionada negativamente à exposição à testosterona e positivamente à expressão ao estrógeno. Quanto maior for a exposição ao estrógeno, menor será o dedo anelar e maior será o dedo indicador, aumentando a proporção digital. O contrário é verdadeiro quando da maior exposição à testosterona, isto é, o dedo anelar é alongado e o dedo indicador encurtado, diminuindo a proporção digital. A influência do estrógeno e da testosterona é maior sob o dedo anelar, principalmente sobre as falanges proximal e média. Devido a esta influência, homens tendem a apresentar baixa proporção 2D:4D (dedo indicador menor do que o dedo anelar) e mulheres tendem a apresentar proporção aproximadamente igual entre os dois dedos. Os valores normais para a população caucasiana são 0,98 para os homens e 1,00 para as mulheres (Manning *et al.,* 1998).

Acredita-se que o comprimento digital seja também influenciado pelos genes da família *HOX* (Manning *et al.*, 2003), que é responsável pelo desenvolvimento e diferenciação dos dedos e do sistema urogenital (Kondo *et al.*, 1997). Também se postula que esta proporção aja como marcador putativo para a atividade do gene receptor de andrógenos (Manning *et al.*, 2002). Todos esses fatores agem na organização e diferenciação de diversas áreas do corpo humano e podem influenciar a inteligência ou capacidade de aprendizado, além de aumentar ou diminuir a chance de desenvolver doenças em um algum momento da vida (Hopp e Jorge, 2011; Hopp e Jorge, 2012)

O método de estudo baseado na obtenção de medidas desses dois dedos para estudar os efeitos da exposição pré-natal à testosterona, primeiramente proposto e realizado por Manning et al em 1998, tornou-se amplamente utilizado, uma vez que outros métodos como a coleta sanguínea de fetos *in utero* , líquido amniótico, sangue do cordão umbilical ou ainda sangue materno, são difíceis de realizar, pouco significativos, ainda não foram testados, ou são pouco promissores (McIntyre, 2006). O estudo dessa proporção, bem como de sua correlação a diferentes traços, tanto de personalidade quanto de susceptibilidade a variadas condições dos dois gêneros, levou a diversos estudos nos últimos 14 anos, incluindo a correlação entre a proporção digital e características psicológicas e a prevalência de determinadas doenças (Voracek & Loibl, 2009)

A avaliação da proporção 2D:4D é feita hoje por meio de paquímetros convencionais e digitais, réguas milimetradas ou tubos escalonados diretamente nas mãos dos voluntários, medição de fotocópias ou escaneamentos digitais das mãos, auto-medições e fotografias digitais das mãos dos voluntários por meio de dispositivos padronizadores. Não há método universalmente aceito para a medição dos dedos e sabe-se que existem diferenças entre a medição direta e a medição indireta (Voracek *et al.,* 2007). O método de fotografia digital difere dos outros métodos de digitalização por fotografar as mãos em posição supina, sendo o mais próximo à medição direta.

Há ainda vasto campo a ser explorado pelas pesquisas envolvendo a proporção 2D:4D. Os estudos que investigam características psicológicas em relação à proporção digital são numerosos na literatura, porém, há poucos e incompletos estudos investigando a proporção digital em relação à inteligência e/ou à capacidade de aprendizado. Estes muitas vezes investigam apenas um gênero (Coco *et al*, 2011), apenas atividades teóricas ou exames entre especialidades (Brosnan *et al.,* 2006). Além disso, o estudo da Odontologia pode ser visto como singular entre as carreiras, pois envolve

disciplinas práticas que requerem destreza manual, aliadas ao conhecimento teórico adquirido em aula, além da capacidade de executar tarefas no menor tempo possível, muitas vezes envolvendo otimização das atividades, disciplina e avaliação de riscos operatórios durante o próprio ato cirúrgico (Chambers, 2001). Tendo em vista estes fatores, este estudo objetivou correlacionar a proporção 2D:4D ao desempenho acadêmico de alunos de Odontologia, por meio da análise de fotografias digitais da mão direita comparadas a escores acadêmicos em disciplinas teóricas e práticas.

2 – CAPÍTULO ÚNICO

2.1 – Digit ratio and academic performance in dentistry students

Digit Ratio and Academic Performance in Dentistry Students

Renato Nicolás Hopp, MsC. Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas, Piracicaba, São Paulo, Brasil.

Juliana Pucci de Moraes, Undergraduate Student. Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas, Piracicaba, São Paulo, Brasil.

Jacks Jorge, PhD. Associate Professor. Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas, Piracicaba, São Paulo, Brasil.

Corresponding Author

Renato Nicolás Hopp, Avenida Limeira, 901, Piracicaba, São Paulo, Brasil, 13414-903 Phone +551921065267, Fax: +551921065320 renhopp@gmail.com

Highlights

First study to correlate digit ratios and learning abilities in academic males and females

Significant correlation between prenatal testosterone and intelligence in males, but not in females

First study to consider both practical and theoretical learning abilities and their relations to digit ratios, prenatal testosterone and estrogen

Abstract

It has been suggested that prenatal testosterone (PT) is positively related to intelligence or learning-ability skills. Digit ratio (2D:4D) is a negative correlate of PT. This study considered the correlations between 2D:4D and success in practical and theoretical examinations in the Dental School curriculum of a Brazilian University. Overall, 80 subjects (40 males) had their right hand palm photographed by a digital camera attached to a standardizing device. The index and ring fingers were measured using Adobe Photoshop. Digit ratio was correlated to the grades obtained by the students through four semesters. Theoretical and Practical grades were significantly negatively correlated to digit ratio in males (and this was particularly so after the influence of age and hours of study were removed, p=0.02 and p=0.004 respectively), but not in females (p=0.89 and 0.77, respectively). This finding supports a link between high PT and intelligence in males. Our finding of no relationship

between 2D:4D and examination marks in female students, suggests that PT may not influence intelligence in females.

Keywords: Digit ratio, Students, Dentistry, Intelligence, Prenatal Testosterone, Prenatal Estrogen

1 - Introduction

Prenatal testosterone (PT) has been proposed to directly influence intelligence or learning-ability skills by modulating the developmental processes of neuronal proliferation, migration, differentiation, and apoptosis. This is thought to increase the density of neuronal networks in certain areas of the brain (Mrazik and Dombrowski, 2010). In addition, high PT at the end of the first trimester is thought to increase the probability of autism and Asperger's Syndrome (Manning, Baron-Cohen, Wheelwright and Sanders, 2001), traits that are often associated with 'islets' of giftedness.

Here we consider the possibility that digit ratio (2D:4D), as a putative marker for prenatal testosterone (Manning, Scutt, Wilson and Lewis-Jones, 1998; Manning, Bundred and Flanagan, 2002), could reflect these alterations, and be a marker for learning ability. Previous studies have correlated digit ratio (and by implication PT) to autism and Aspergers' Syndrome, concluding that autistic children had the lowest digit ratio (which could be translated as an excess in PT), while Aspergers' children, who have communication impairments similar to autistic children but are thought to have normal or high IQ (Soulières, Dawson, Gernsbacher, Mottron, 2011) have higher-thanautistic but lower-than-normal 2D:4D (Manning et al, 2001).

Human hands can present index and ring fingers of relatively different lengths for males and females, a difference first attributed to prenatal hormone exposure—high digit ratio indicating low PT relative to prenatal oestrogen and low digit ratio pointing to high PT relative to prenatal oestrogen (Manning et al., 1998; Manning, in press). There is correlational evidence that 2D:4D is negatively related to 2D:4D (Breedlove, 2010), and experimental evidence that 2D:4D is related to the relative amounts of PT and prenatal oestrogen (Zheng & Cohn, 2011). Differences in prenatal hormone exposure can lead to different traits in personality, aggression, behavior and ability to perform tasks such as playing sports, driving carefully, investing money or doing manual labor. Low 2D:4D has been correlated to success and profitability in financial trading (Coates, Gurnell and Rustichini, 2009) and success in sports such as rugby, sprinting and running (Bennett, Manning, Cook and Kilduff, 2010; Manning and Hill, 2009; Manning, Morris and Caswell, 2007). In addition, low 2D:4D has been correlated with numeric capabilities and ability to understand information communication technology (Brosnan, 2006; Brosnan, Gallop, Iftikhar and Keogh, 2011), and is also thought to correlate with learning in manual labour tasks (Rosler, 1957). Digit ratio, and therefore PT, can influence cognitive skills and analysis of situations in order to develop better solutions to a given problem (Coates, Gurnell and Rustichini, 2009). Earlier reports have shown that individuals with higher cognitive skills are more patient and

have a greater ability to plan and persevere, as well as a greater perception of situations (Burks, Carpenter, Goette and Rustichini, 2009).

Previous research has successfully negatively correlated 2D:4D to success in written admission tests for a medical school, but failed to replicate such a correlation to written exams taken throughout the six years of the course (Coco et al., 2011). Within the framework of this background, the present study aimed to consider the hypothesis that 2D:4D could be negatively correlated to success in practical and theoretical examinations in the Dental School curriculum. Our hypothesis was that individuals with low 2D:4D (high PT relative to prenatal oestrogen) would score higher marks than individuals with high 2D:4D in both theoretical and practical (manual) activities.

2 - Methods

This work was carried out in accordance with The Code of Ethics of the World Medical Association for experiments involving humans, and approved by the local Institutional Review Board. Students from the Piracicaba Dental School, Piracicaba, São Paulo, Brazil, were invited to participate in this study. Digit ratio is known to vary with ethnicity (Manning, 2002). Therefore, we restricted recruitment to White participants. Those with a history of fractures in the fingers of the right hand or hormonal disease were excluded. Only students that had completed more than 4 semesters or the equivalent to two levels were selected, in order to give a range of theoretical and practical grades that could be used. Students that had failed one class and retaken the same class had their grade from the first examination recorded. The participants were asked to complete a questionnaire regarding age, gender, the performance of manual activities at home, and hours of home study in theoretical aspects of their subject. After answering the questionnaire, the participants had the ventral surface of their right hand photographed using a digital camera (Canon Powershot A550, Canon, USA) attached to a standardizing device, forming a 90° angle with the base, a technique previously described by Hopp and Jorge (2011). We chose to measure the right hand 2D:4D because there is evidence that sex differences in right 2D:4D are greater than sexual dimorphism in left 2D:4D (Honekopp and Watson, 2010). All photographs were made using the same camera configuration. Image analysis was performed using Adobe Photoshop 7.0® (Adobe Systems, USA) measuring tool, at 100% zoom. Right hand index and ring fingers were measured twice (second measurement blind to first) in linear fashion from the middle point of the most proximal crease up to the tip of the finger (Manning et al, 1998). Mean grades were calculated from theoretical (MT) and practical (MP) examinations, in addition we calculated the ratio between practical and theoretical (MP:MT) grades to give an indication of whether a given student was more likely to do well in the theoretical or practical part of the course. Data are presented as means (± standard deviations). Statistical analysis used Student's t test for male versus female digit ratio comparison, and Pearson's correlation coefficient and linear multiple regression for 2D:4D versus grades relationships.

7

3 - Results

After exclusion criteria, 80 individuals were selected to participate in the study (Males n=40). The mean age for the participants was 19.5 ± 1.1 years for males and 19.7 ± 1.2 for females (range 18-22).

A comparison of 2D:4D from the first and second measurements showed a high intraclass correlation (ICC = 0.94, F = 31.6, p = 0.0001). This meant that the differences in 2D:4D between-individuals were much greater than measurement error. Therefore, we calculated mean 2D:4D from our first and second measurements and used the mean 2D:4D in all subsequent analyses.

Mean 2D:4D for males was 0.980 ± 0.038 and for females 0.991 ± 0.025 with an effect size (Cohen's d) of 0.34. This sex difference in 2D:4D was in the expected direction but the sexual dimorphism was significant (t = 1.47, p = 0.15). However, the effect size of the sex difference was within the expected range for 2D:4D (Manning, 2002). With regard to sex differences in the marks for theoretical and practical examinations, males and females did not differ in their theory marks (males 7.55±0.90, females 7.79±1.04, t = 1.07, p = 0.29), but females scored significantly higher practical marks than males (males 8.01±0.59, females 8.38±0.54, t = 2.90, p = 0.005).

With regard to relationships between 2D:4D and examination marks for males we found these to be significant for both theory and practical. With regard to theory, there was a significant negative correlation between 2D:4D and mean theory mark (r = -0.32, p =0.04) (Figure1). Multiple regression analysis showed that the relationship between 2D:4D and theory marks remained significant after the influence of age and hours of study were removed (2D:4D b = -0.42, t = 0.02; age b = -0.18, t = 1.10, p = 0.27; hours study b = 0.04, t = 0.27, p = 0.79). A similar association was found for 2D:4D and practical marks (r = -0.317, p = 0.046). This remained significant after controlling for age and hours of study. However, in this instance age was also significantly related to practical marks in that young males scored higher than older males (2D:4D b = -0.47, t = 3.07, p = 0.004; age b = -0.38, t = 2.50, p = 0.02; hours study b = - 0.001, t = 0.008, p = 0.99). It is to be noted that the correlations between 2D:4D and theory and practical marks are of similar strength, and this was confirmed by an examination of the correlation between 2D:4D and the ratio between practical and theory marks (r = 0.18, p = 0.26).

With regard to females, there was no significant correlation between 2D:4D and theory (r = -0.02, p = 0.89) or practical marks (r = –0.05, p = 0.77). Multiple regression analyses showed 2D:4D and hours of study were not related to examination marks, but age tended to be negatively associated with both theory (significant) and practical (marginally significant). For theory marks, 2D:4D b = 0.04, t = 0.26, p = 0.79, age b = - 0.41, t = 2.46, p = 0.02, hours study b = -0.12, t = 0.74, p = 0.46. For practical marks, 2D:4D b =-0.06, t = 0.40, p = 0.69, age b = -0.32, t = 1.96, p = 0.06, hours study b = 0.20, t =

1.21, p = 0.24. As with males the correlation between 2D:4D and the ratio between practical and theory marks was not significant (r = 0.05, p = 0.75).

4 - Discussion

We have found that right hand 2D:4D is negatively related to theory and practical marks in male dental students. The effect size for these correlations is similar and 2D:4D is not predictive of the ratio between practical and theory marks. This finding suggests that 2D:4D is a proxy for ability in theory and practical dental examinations. There is correlational evidence that 2D:4D is negatively associated with PT and the ratio between PT and prenatal oestrogen (Manning et al, 1998; Manning, 2002, Manning and Fink, 2008; Lutchmaya, Baron-Cohen, Raggatt, Knickmeyer and Manning, 2004; Breedlove, 2010). In addition, experimental manipulation (including loss of androgen and oestrogen receptors and addition of androgen and oestrogen blockers and testosterone and estradiol) of sex steroids in the mouse has shown that 2D:4D is dependent on the ratio of prenatal testosterone and prenatal oestrogen (Zheng and Cohn, 2011). That is, when PT is high and prenatal oestrogen is low then 2D:4D is low. Therefore, our findings suggest that males with high PT and low prenatal oestrogen tend to have high intelligence. These findings were strengthened when the influence of age and hours of study was removed. We suggest that this supports the hypothesis of Mrazik and Dombrowski (2010), who have suggested that high intelligence is linked to high PT through the latter's influence on neuronal proliferation, migration, differentiation, and apoptosis. However, we have not found a correlation between 2D:4D and theory and practical marks in female dental students. This may be because the effect of PT on intelligence differs between the sexes and/or the link between PT and intelligence is particularly strong when PT is high (as it is in males).

Prenatal testosterone exposure may directly influence intelligence, by altering neuronal migration, leading to greater right-hemisphere development (Geschwind and Behan, 1982), as well as greater coordination within and between the hemispheres (Alexander, O'Boyle and Benbow, 1996, Anderson and Harvey, 1996). This could lead to dense neuronal networks in areas related to cognition, learning and memory, either by decreasing apoptosis of brain cells during development, or increasing migration of cells to one of those areas (Mrazik and Dombrowski, 2010). As 2D:4D is considered a marker for prenatal testosterone exposure, these traits may be negatively correlated with 2D:4D.

The dentistry undergraduate course curriculum is composed of theoretical classes and written exams as well as a number of practical activities that accounts for the biggest portion of the course. In the practical branch of the course, students are required to perform dental procedures on dummy models before they start to perform them in real patients. All procedures demand the students to be capable to perform tasks in the shortest time possible, but with no significant loss in work quality.

The demand for low-time versus high quality in inexperienced students creates a need for intensified vigilance, as well as quickened reaction times, as well as risk taking. This trait has been correlated to

low digit ratio (Coates et al, 2009; Millet, 2009). Our results pointed to a negative correlation between 2D:4D and practical success in practical disciplines, especially in males, where the results were significant. In females, the results were much weaker, pointing to a marked sex-difference between males and females regarding the process of performing manual labor, and the prenatal testosterone influence over it. A earlier report that considered 192 students regarding math tests concluded that there was an influence of gender over risk perception rather than intelligence or mathematical abilities (Brañas-Garza, Guillen, del Paso, 2008).

Theoretical examinations are taken once every two months and are composed of cumulative tasks, i.e. on the second test the subjects of the first test also take part. These examinations evaluate the ability of the student not only to memorize, but to connect to the knowledge previously acquired in order to solve problems or diagnose a patient's condition. As a general rule, the students have around 1 hour to complete the exam, which is often composed of 10 questions with problems or diagnoses. These exams demand not only the ability of memorizing the classes, but, more importantly, connecting the information and deciding, as quickly as possible, the diagnosis on a patient's condition and guiding the treatment.

The results of this study pointed to a negative correlation between 2D:4D and theoretical grades as well as practical grades. This could be due to the nature of the examinations, which demands quick decisions in order to complete 10 questions – which gives about 6 minutes to formulate a response and write it – which could be interpreted as a risky situation that requires quick decisions. Although tests and examinations per se must not be considered as a risk taking situation by educators, students are always confronted with doubts about questions and possibilities, especially when deciding between right and wrong diagnoses or answers. This is particularly so when, as in most examinations, there is a time element in the assessment. Therefore, there may be links between cognitive abilities and risk taking. A earlier study with 1,000 trainees concluded that individuals with better cognitive skills are more patient and perceive high-pressure situations more calmly, being able to think through and elaborate better solutions for a given problem (Burks et al, 2009).

It is thought that PT at the end of the first trimester may correlate with developmental disorders such as autism and Aspergers' syndrome (Manning et al, 2001). In comparison to population norms, autistic individuals have been found to be gifted in identifying recurrent patterns, processing perceptual information, and often have exceptional memories and are less likely to misremember data (Mottron, 2011). These are characteristics that are useful in order to perform well in practical and theoretical examinations.

Coco et al (2011) evaluated a group of 48 male students, and found a significant correlation between 2D:4D and success in admission tests for a medical school in Italy. The study, however, failed to replicate this correlation when analyzing grades throughout the medical school course. The exams

taken by the students in the present study may resemble the admission tests taken by the students in the previous study, as they require quick decisions in order to obtain a successful result. In that light, the present study replicates previous results (Coco et al., 2011). The present study is also the first to consider practical grades, which have not been analyzed in previous studies. Indeed, evaluating practical activities through grades is less complicated in dentistry than in medicine, as well as the immersion of the students in the activities, which takes place earlier in the former course.

5 - Conclusion

We have found that low 2D:4D (a correlate of high PT and low prenatal oestrogen) is related to practical and theory examination marks in Brazilian dental students. We suggest that this finding supports a theoretical link between high PT and high intelligence. The lack of a relationship between 2D:4D and examination marks in female dental students indicates that PT does not influence female intelligence in the same manner as that in males.

References

Alexander JE, O'Boyle MW and Benbow, CP. (1996). Developmentally advanced EEG alpha power in gifted male and female adolescents. International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 23, 25 - 31.

Anderson B and Harvey T. (1996). Alterations in cortical thickness and neuronal density in the frontal cortex of Albert Einstein. Neuroscience Letters, 153, 98 - 102.

Bennett M, Manning JT, Cook CJ and Kilduff LP. (2010). Digit ratio (2D:4D) and performance in elite rugby players. Journal of Sports Sciences, 28, 1415 - 1421.

Brañas-Garza P, Guillen P and del Paso RL. (2008). Math Skills and Risk Attitudes. Economics Letters 99, 332 - 336

Breedlove SM. (2010). Minireview: Organizational hypothesis: instances of the fingerpost. Endocrinology, 151, 4116 - 4122.

Brosnan MJ, Gallop V, Iftikhar N and Keogh E. (2011). Digit ratio (2D:4D), academic performance in computer science and computer-related anxiety. Personality and Individual Differences, 51, 371-375.

Brosnan MJ. (2006). Digit ratio and faculty membership: implications for the relationship between prenatal testosterone and academia. British Journal of Psychology, 97, 455 - 466.

Burks SV, Carpenter JP, Goette L and Rustichini A. (2009). Cognitive skills affect economic preferences, strategic behavior, and job attachment. Proceedings of the National Academy of Sciences U S A, 106, 7745 - 50.

Coates JM, Gurnell M and Rustichini A. (2009). Second-to-fourth digit ratio predicts success among high-frequency financial traders. Proceedings of the National Academy of Sciences U S A, 106, 623 - 628.

Coco M, Perciavalle V, Maci T, Nicoletti F, Di Corrado D and Perciavalle V. (2011). The second-to-fourth digit ratio correlates with the rate of academic performance in medical school students. Molecular Medicine Reports, 4, 471 – 476.

Geschwind N and Behan P. (1982). Lefthandedness: Association with immune disease, migraine, and developmental learning disorder. Proceedings of the National Academy of Sciences, 79, 5097–5100.

Hönekopp J and Watson S. (2010). Meta-analysis of digit ratio 2D:4D shows greater sex difference in the right hand. American Journal of Human Biology, 22, 619 - 630.

Hopp RN and Jorge J. (2011). Right hand digit ratio (2D:4D) is associated with oral cancer. American Journal of Human Biology, 23, 423 - 425.

Lutchmaya S, Baron-Cohen S, Raggatt P, Knickmeyer R and Manning JT. (2004). 2nd to 4th digit ratios, fetal testosterone and estradiol. Early Human Development, 77, 23 - 28.

Manning JT and Fink B. (2008). Digit ratio (2D:4D), dominance, reproductive success, asymmetry, and sociosexuality in the BBC Internet Study. American Journal of Human Biology, 20, 451 - 461.

Manning JT and Hill MR. (2009) Digit ratio (2D:4D) and sprinting speed in boys. American Journal of Human Biology, 21, 210 - 213.

Manning JT, Baron-Cohen S, Wheelwright S and Sanders G. (2001). The 2nd to 4th digit ratio and autism. Developmental Medicine and Child Neurology,43, 160 - 4.

Manning JT, Bundred PE and Flanagan BF. (2002). The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene? Medical Hypotheses, 59, 334 - 336.

Manning JT, Morris L and Caswell N. (2007). Endurance running and digit ratio (2D:4D): implications for fetal testosterone effects on running speed and vascular health. American Journal of Human Biology,19, 416 - 421.

Manning JT, Scutt D, Wilson J and Lewis-Jones DI. (1998). The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Human Reproduction, 13, 3000 - 3004.

Manning JT. (2002). Digit ratio: a pointer to fertility, behavior, and health. New Brunswick, NJ: Rutgers University Press. 192 p.

Manning JT. (2011). Resolving the role of prenatal sex steroids in the development of digit ratio. Proceedings of the National Academy of Sciences U S A, 108, 16143 - 4.

Millet K. (2009). Low second-to-fourth-digit ratio might predict success among highfrequency financial traders because of a higher need for achievement. Proceedings of the National Academy of Sciences U S A, 106, E30

Mottron L. (2011). Changing perceptions: The power of autism. Nature, 479, 33 - 5. Mrazik M and Dombrowski SC. (2010). The Neurobiological Foundations of Giftedness. Roeper Review, 32, 224–234.

Rosler HD. (1957). Finger length proportion and manual labor. Internationale Zeitschrift für angewandte Physiologie, einschliesslich Arbeitsphysiologie, 16, 434 - 452.

Soulières I, Dawson M, Gernsbacher MA and Mottron L. (2011), The level and nature of autistic intelligence II: what about Asperger syndrome? PLoS One. 6, e25372.

Zheng Z and Cohn MJ. (2011). Developmental basis of sexually dimorphic digit ratios. Proceedings of the National Academy of Sciences U S A, 108, 16289 - 94.
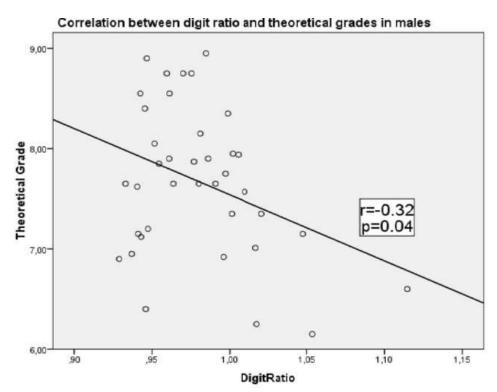
Figure 1 - Correlation between digit ratio and theoretical grades in males.

Correlation between digit ratio and theoretical grades in males

3 – CONSIDERAÇÕES GERAIS

A proporção 2D:4D é hoje alvo de diferentes estudos ao redor do mundo, nas mais variadas temáticas e aplicações. O futuro das pesquisas envolvendo esta metodologia é bastante promissor e o escopo de estudos possíveis é bastante amplo.

Entre os assuntos passíveis de investigação está a correlação entre a proporção 2D:4D e a inteligência em diversas etnias, Quociente de Inteligência (Q.I.), sucesso escolar em nível pré-universitário, habilidade linguística e testes psicotécnicos. Estudos têm sido feitos em diversos países em populações de diferentes idades e etnias. Comparar diferentes populações valendo-se de análise curricular ou mesmo notas acadêmicas não é tarefa simples, e estudos multicêntricos necessitariam padronizações que talvez fizessem perder-se dados que seriam significativos se analisados separadamente. Condições que dificultam o aprendizado como a dislexia, a síndrome de Asperger e o autismo necessitam também novos estudos para que se verifique sua possível conexão à proporção digital. Outro campo ainda não explorado totalmente é o dos traços comportamentais como medo, comportamento social e dominância social.

Esta linha de pesquisa é bastante promissora também no que diz respeito à sua correlação a doenças, principalmente as influenciadas pelos genes descritos por Zheng e Cohen (2011). Entre estas doenças encontram-se as neoplasias de pulmão, estômago, mama, esôfago, pâncreas, rim, cólon, leucemias, linfomas, síndrome da fissura lábio-palatina, neoplasias ósseas, mielomas múltiplos, síndrome de Ehlers-Danlos, tumores cerebrais, condrossarcomas, degeneração macular, melanoma, infarto hemorrágico, partos prematuros e defeitos cardíacos congênitos.

Novas pesquisas tendem a aprofundar o conhecimento de como a proporção 2D:4D, isto é, a exposição pré-natal aos hormônios sexuais influencia a produção de hormônios sexuais na vida adulta, não só em

organismos saudáveis, como também em organismos que perderam seu equilíbrio devido a situações de estresse ou doença. A averiguação do comportamento da testosterona frente a alterações nos sistemas imunológico, simpático, parassimpático e límbico é passo importante a ser investigado, podendo trazer resultados promissores até mesmo para o tratamento e prognóstico das afecções destes sistemas.

Pesquisa na base de dados PubMed pelos termos *digit ratio, 2d4d* ou *finger length* aponta 388 trabalhos publicados. O cruzamento com o termo *intelligence* aponta sete trabalhos publicados. Porém, o cruzamento com o termo *psychology* aponta 127 estudos. Correlacionando-se estes termos à palavra *disease*, obtém-se 25 trabalhos publicados. Finalmente, correlacionar os termos supracitados ao termo *cancer* retorna 17 estudos. Portanto, são variadas as possibilidades de avaliação de correlações possíveis entre este marcador de exposição e sensibilidade pré-natal à testosterona e ao estrógeno, assim como é vasto o campo de pesquisa disponível para a proporção 2D:4D.

4 – CONCLUSÕES

Baseados nos resultados deste trabalho, podemos concluir que:

(a) O método de estudo 2D:4D envolvendo a análise de fotografias digitais é de fácil utilização, apresenta alta reprodutibilidade, baixo custo e alta capacidade de visualização das imagens para identificação dos pontos de medição.

(b) A proporção 2D:4D foi significativamente diferente entre homens e mulheres, com efeito Cohen na direção esperada, o que significa que homens jovens na população avaliada parecem ter o 2D:4D mais baixo do que mulheres jovens da mesma população.

(c) Homens com proporções 2D:4D menores tiveram maior sucesso acadêmico em disciplinas teóricas e práticas, resultado este inversamente correlacionado ao valor da proporção 2D:4D. A inteligência e/ou capacidade de aprendizado parece ser influenciada em homens, seja pela capacidade de adaptação dos circuitos cerebrais, seja pela densidade neuronal aumentada pela exposição à testosterona, seja devido à ação de genes descritos na literatura que influenciam tanto a organização cerebral, quanto a proporção 2D:4D

(d) São necessários estudos complementares para correlacionar a proporção 2D:4D a marcadores de inteligência e aprendizado.

REFERÊNCIAS*

Bailey AA, Hurd PL. Finger length ratio (2D:4D) correlates with physical aggression in men but not in women. Biol Psychol. 2005; 68:215-22.

Brabin L, Roberts SA, Farzaneh F, Fairbrother E, Kitchener HC. The second to fourth digit ratio (2D:4D) in women with and without human papillomavirus and cervical dysplasia. Am J Hum Biol. 2008; 20:337-41.

Chambers DW. Preliminary evidence for a general competency hypothesis. J Dent Educ. 2001; 65:1243-52.

Coates JM, Gurnell M, Rustichini A. Second-to-fourth digit ratio predicts success among high-frequency financial traders. Proc Natl Acad Sci U S A. 2009; 106:623-8.

Hiraishi K, Sasaki S, Shikishima C, Ando J. The Second to Fourth Digit Ratio (2D:4D) in a Japanese Twin Sample: Heritability, Prenatal Hormone Transfer, and Association with Sexual Orientation. Arch Sex Behav. 2012. [Epub ahead of print]

Hopp RN, Jorge J. Right hand digit ratio (2D:4D) is associated with oral cancer. Am J Hum Biol. 2011; 23:423-5.

Hopp RN, Jorge J. Right hand digit ratio (2D:4D) is associated with prostate cancer: Findings of an admixed population study. J Solid Tumours. 2012; 2: 22-5

Kondo T, Zákány J, Innis JW, Duboule D. Of fingers, toes and penises. Nature. 1997; 390:29.

Manning JT, Bundred PE, Flanagan BF. The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene? Med Hypotheses. 2002; 59:334-6.

Manning JT, Bundred PE, Flanagan BF. The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene? Med Hypotheses. 2002; 59:334-6.

Manning JT, Henzi P, Venkatramana P, Martin S, Singh D. Second to fourth digit ratio: ethnic differences and family size in English, Indian and South African populations. Ann Hum Biol. 2003; 30:579-88.

Manning JT, Scutt D, Wilson J, Lewis-Jones DI. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum Reprod. 1998; 13:3000-4.

Manning JT. The ratio of 2nd to 4th digit length and performance in skiing. J Sports Med Phys Fitness. 2002; 42:446-50.

McIntyre MH, Lipson SF, Ellison PT. Effects of developmental and adult androgens on male abdominal adiposity. Am J Hum Biol. 2003; 15(5):662-6.

Nelson E, Shultz S. Finger length ratios (2D:4D) in anthropoids implicate reduced prenatal androgens in social bonding. Am J Phys Anthropol. 2010; 141:395-405.

Ozdogmus O, Cakmak YO, Coskun M, Verimli U, Cavdar S, Uzun I. The high 2D:4D finger length ratio effects on atherosclerotic plaque development. Cen Eur Neurosurg. 2009; 70:36-8.

Phelps VR. Relative index finger length as a sex-influenced trait in man. Am J Hum Genet. 1952; 4:72-89.

Rahman AA, Lophatananon A, Stewart-Brown S, Harriss D, Anderson J, Parker T *et al.* Hand pattern indicates prostate cancer risk. Br J Cancer. 2011; 104:175-7.

Voracek M, Loibl LM. Scientometric analysis and bibliography of digit ratio (2d:4d) research, 1998–2008. Psychol Rep. 2009; 104:922-56

Voracek M, Manning JT, Dressler SG. Repeatability and Interobserver Error of Digit Ratio (2D:4D) Measurements Made by Experts. Am J Hum Biol. 2007; 19:142–146.

Voracek M, Reimer B, Ertl C, Dressler SG. Digit ratio (2D:4D), lateral preferences, and performance in fencing. Percept Mot Skills. 2006; 103:427-46.

Voracek M. Digit ratio (2D:4D), ABO blood type, and the Rhesus factor. Percept Mot Skills. 2008; 107:737-46.

Zheng Z, Cohn MJ. Developmental basis of sexually dimorphic digit ratios. Proc Natl Acad Sci U S A. 2011; 108:16289-94.

ANEXOS

Anexo 1 – Questionário

Questionário

Idade_____anos Gênero (   )M   (   )F   ( ) Destro   (   )Canhoto

1 – Você sofreu alguma fratura nos dedos anular ou indicador?

(   )Sim   (   )Não

2 – Você costuma estudar as matérias da odontologia em casa?

( ) Sim   ( ) Não – Se sim, qual(is)? _____

3 – Quanto tempo você costuma estudar em casa as matérias da Odontologia?

(   )Horas/Dia   (   )Horas/Semana   (   )Não costumo estudar

4 – Você estuda as matérias práticas e teóricas em casada mesma forma e com a mesma carga horária?

(   )Sim, estudo matérias teóricas e práticas da mesma maneira e com a mesma intensidade

(   )Não, estudo mais as matérias teóricas

(   )Não, estudo mais as matérias práticas

(   )Não estudo as matérias além da sala de aula.

5 – Você costuma praticar alguma atividade que necessite de habilidade manual?

(   )Sim   Tipo_____

(   )Não

COMITÊ DE ÉTICA EM PESQUISA
FACULDADE DE ODONTOLOGIA DE PIRACICABA
UNIVERSIDADE ESTADUAL DE CAMPINAS

CERTIFICADO

O Comitê de Ética em Pesquisa da FOP-UNICAMP certifica que o projeto de pesquisa **"Avaliação da correlação entre desempenho acadêmico e a proporção 2D:4D"**, protocolo nº 146/2009, dos pesquisadores Renato Nicolás Hopp, Jacks Jorge Junior e Juliana Pucci de Moraes, satisfaz as exigências do Conselho Nacional de Saúde - Ministério da Saúde para as pesquisas em seres humanos e foi aprovado por este comitê em 12/11/2009.

The Ethics Committee in Research of the School of Dentistry of Piracicaba - State University of Campinas, certify that the project **"2D:4D ratio and academic performance"**, register number 146/2009, of Renato Nicolás Hopp, Jacks Jorge Junior and Juliana Pucci de Moraes, comply with the recommendations of the National Health Council - Ministry of Health of Brazil for research in human subjects and therefore was approved by this committee at 11/12/2009.

Prof. Dr. Pablo Agustin Vargas
Secretário
CEP/FOP/UNICAMP

Prof. Dr. Jacks Jorge Junior
Coordenador
CEP/FOP/UNICAMP

Nota: O título do protocolo aparece como fornecido pelos pesquisadores, sem qualquer edição.
Notice: The title of the project appears as provided by the authors, without editing.

Anexo 3 – Artigo: Right Hand Digit Ratio (2D:4D) is Associated with Oral Cancer

Short Report

Right Hand Digit Ratio (2D:4D) is Associated with Oral Cancer

RENATO NICOLÁS HOPP* AND JACKS JORGE
Piracicaba Dental School, Department of Oral Diagnosis, Piracicaba, São Paulo, Brazil 13414-903

ABSTRACT   Finger length ratio has been proposed as a putative marker for prenatal hormone exposure, as well as the action of HOX, AR, and a variant of the LIN28b genes. These genes have been recently connected to carcinogenesis and digit ratio could help to identify patients with this predisposition.

Objectives: The purpose of this study was to investigate the possible correlations between digit ratio, oral squamous cell carcinoma (OSCC)—the most common oral cancer—and oral premalignant lesions (OPLs) in tobacco-consuming males, the main risk group for this disease.

Methods: Digital images of the right hands of patients diagnosed with OSCC ($n = 25$), OPLs ($n = 25$), and age-matched controls ($n = 25$) were obtained. Fingers were measured using Adobe Photoshop® and the mean ratios between the 2nd and 4th digits were compared. Data were analyzed by ANOVA ($\alpha = 0.05$).

Results: Risk factors (alcohol and tobacco consumption, familial history) were similar between the three study groups. Males in the OSCC group presented significantly higher digit ratio ($P = 0.03$) in comparison with males with OPLs and individuals without oral lesions.

Conclusions: According to the results, males with the higher digit ratio seem to be more prone to undergo malignization of lesions in the oral cavity. Similar deleterious habits 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' susceptibility to develop oral squamous cell carcinoma. Am. J. Hum. Biol. 23:423–425, 2011.   © 2011 Wiley-Liss, Inc.

The ratio between the second and fourth digits, also known as 2D:4D or digit ratio has been proposed as a putative marker for prenatal hormone exposure as well as HOX and AR gene expression (Manning et al., 1998, 2002, 2003b). Human hands can present index and ring fingers of different lengths 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 (Manning et al., 1998). Digit ratio has since been correlated to medical, behavioral, and psychological traits as well as factors beyond prenatal hormone exposure, such as the action of HOX gene family, androgen receptor gene (AR), and a variant of LIN28B gene (Medland et al., 2010). These genes have been correlated to carcinogenesis and, if 2D:4D is a putative marker for the action of these genes, it might be linked to carcinogenic events. Evidence was also set out that 2D:4D may be predictive of susceptibility to some types of cancer and that this may be particularly true for cancers that show sex differences in their occurrence, progression, and/or prognosis (Manning, 2002).

More than 80% of all oral cancers correspond to oral squamous cell carcinoma (OSCC), a lesion that is much more common in men than in women—16.0 versus 6.1 per 100,000, respectively (Edwards et al., 2010). Tobacco and alcohol consumption are the main etiological factors, but OSCC has been correlated to HPV, nutrition, oral hygiene and p53, HOX and AR gene deregulations (Hassan et al., 2006; Santos et al., 2004; Scully and Bagan, 2009). OSCC is often preceded by oral premalignant lesions (OPLs), the most prevalent being leukoplakia and erithroplakia (Wang et al., 2009).

This study investigated the possible correlation of OSCC and OPLs to 2D:4D in alcohol and tobacco consuming men, the main risk group for the development of these diseases.

METHODS

Males between 40 and 80 years participated in this study. Research was approved by the local institutional review committee. Subjects responded to a questionnaire regarding tobacco and alcohol consumption, medical personal and familial history. Individuals with history of tobacco consumption were selected for this study. Those with right index or ring finger fracture history and/or hormonal disorders were excluded. All subjects underwent oral clinical examination to detect recurrences on already diagnosed patients, as well as identifying the presence of lesions on newly examined patients.

After the oral examination, subjects 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. All 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 through the capturing process. Image analysis was made by Adobe Photoshop 7.0® (Adobe Systems, USA) measuring tool, using 100% zoom.

Right hand index and ring fingers were measured in linear fashion from the middle point of the most proximal crease up to the tip of the finger. Measurements were repeated three times, 2 days apart. Index finger length was divided by ring finger length, originating the 2D:4D

TABLE 1. *Characteristics of the study subjects*

Group	Age	2D:4D ratio	Cigarettes/day	EC	FH
SCC ($n = 25$)	60.3 ± 4.1	0.9700 ± 0.0551	30.6	88%	56%
PML ($n = 25$)	62 ± 11.7	0.9625 ± 0.0512	22.6	92%	56%
NOR ($n = 25$)	57.9 ± 12.5	0.9643 ± 0.0365	22.0	96%	56%

SCC—squamous cell carcinoma; PML—premalignant lesion; NOR—no lesion; EC—Regular ethanol consumption; FH—Familial history of malignant neoplasia.

ratio. The analyzed ratio was the mean of the three measurements performed.

After the measurement, individuals were assigned to their respective groups; (a) NOR group—patients without present or past oral malignant or premalignant lesions; (b) SCC group—patients diagnosed with OSCC, independent of subsite; (c) OPL group—patients diagnosed with OPLs, present or past, independent of type and subsite. Individuals were age-matched between groups. Data were analyzed by repeated measures one-way ANOVA and Student's t test using Microsoft Excel ($\alpha = 5\%$).

RESULTS

General characteristics of the population are described in Table 1. Overall, 75 tobacco-consuming individuals were selected for this study. Alcohol consumption and familial history of malignant neoplasia were frequently reported. The mean cigarette consumption was slightly higher on the SCC group, being similar between NOR and PML groups, however, the difference among groups was not significant ($P = 0.10$). Ethanol consumption was also similar between the groups. Hormone therapy was not reported.

SCC group had mean 2D:4D of 0.9700 ± 0.0551 and 18 individuals presented high 2D:4D (higher than 0.9500); PML group had mean 2D:4D of 0.9625 ± 0.0512 with 14 individuals having high 2D:4D; NOR group had mean 2D:4D of 0.9643 ± 0.0365 with 18 individuals above the 0.9500 mark. The mean digit ratio between the three groups presented statistically significant difference ($P = 0.03$). Repeated measurements presented ICCS of 0.94 for the Test 1 against 2, 0.96 for Test 2 against 3 and 0.96 for Test 3 against 1, indicating reproducibility of the method.

DISCUSSION

Finger-length ratio has been correlated to many gender-linked traits and pathologies, comprising 200-plus published articles in recent years regarding behavioral treats such as physical and verbal aggressiveness, decision-making processes (Coates et al., 2009); and medical conditions such as cervix cancer and delayed menarche (Brabin et al., 2008; Matchock, 2008).

Digit ratios could be influenced by many genetic conditions—action of HOX, AR, and a variant of the LIN28b genes. HOX gene family controls the urogenital system development, as well as the differentiation of fingers and gonads (Jung et al., 2010). HOX function could reflect in 2nd to 4th digit ratio and this could be used as a putative marker for susceptibility to diseases influenced by such genes (Manning et al., 2003b). Previous research proposed that low 2D:4D could be a proxy marker for short CAG-triplet repeat lengths on the AR, predisposing patients for can-

cer development (Manning et al., 2002). Manning et al. (2003a) correlated high 2D:4D on the right hand to high numbers of CAG triplets in the AR gene, but this high ratio could also stand for a partial inactivation of this gene (Berenbaum et al., 2009), contributing for disease prognosis. Recently, correlations between high 2D:4D and a variant in the LIN28B gene were reported (Medland et al., 2010).

HOX genes *a*, *b*, and *d* are overexpressed in head and neck cancers (Destro et al., 2010; Hassan et al., 2006). OSCC carcinogenesis could also reside on other genetic factors, such as the action of the androgen receptor gene, as proposed by Santos et al. (2004) or variants in the LIN28b gene—which regulates development by interacting with let-7 precursors—which has also been correlated to digit ratio. This gene has been demonstrated to promote neoplastic transformation and to be associated with more aggressive malignancies in humans (Viswanathan et al., 2009).

Despite recent research having associated OSCC to several etiological factors, its main risk factors continue to be alcohol and especially tobacco consuming. Based on the established carcinogenic effects of tobacco (Scully and Bagan, 2009), only smokers were selected for this study. Alcohol consumption and familial history of neoplasia, other classic etiological factors, were similar between 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 malignization of their lesions while others remain with indolent premalignant lesions or even unaffected, despite having the same deleterious habits.

Although some authors suggest that indirect measurements could weaken the results of digit ratio studies (Manning and Fink, 2010), every measurement methodology has intrinsic errors and thus, distortions on the relative lengths may occur. A standardized method of image capturing was suggested and, if distortions occurred, they should be similar for all images. However, the necessity of both methodological and epidemiological studies to further investigate the strength of the findings is endorsed.

Males diagnosed with OSCC in our study presented more feminized digit ratio, especially when compared to males that did not present oral lesions. This finding could add to the complex etiology of OSCC carcinogenesis. This is the first study to evaluate the correlation between oral cancer and digit ratio. We believe that this study could add to the discussion about the etiology of oral squamous cell carcinoma by providing a possible putative marker for the screening of patients in risk to develop these malignancies. It also points to the necessity to further investigate the relations between OSCC and genetic and hormonal factors that could be represented by digit ratios.

LITERATURE CITED

Brabin L, Roberts SA, Farzaneh F, Fairbrother E, Kitchener HC. 2008. The second to fourth digit ratio (2d:4d) in women with and without human papillomavirus and cervical dysplasia. Am J Hum Biol 20:337–341.

Berenbaum SA, Bryk KK, Nowak N, Quigley CA, Moffat S. 2009. Fingers as a marker of prenatal androgen exposure. Endocrinology 150:5119–5124.

Coates JM, Gurnell M, Rustichini A. 2009. Second-to-fourth digit ratio predicts success among high-frequency financial traders. Proc Natl Acad Sci USA 106:623–628.

Destro MF, Bitu CC, Zecchin KG, Graner E, Lopes MA, Kowalski LP, Coletta RD. 2010. Overexpression of HOXB7 homeobox gene in oral cancer induces cellular proliferation and is associated with poor prognosis. Int J Oncol 36:141–149.

Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen

M, Goede SL, Ries LA. 2010. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 116:544–573.

Hassan NM, Hamada J, Murai T, Seino A, Takahashi Y, Tada M. 2006. Aberrant expression of HOX genes in oral dysplasia and squamous cell carcinoma tissues. Oncol Res 16:217–224.

Jung H, Kim KH, Yoon SJ, Kim TB. 2010. Second to fourth digit ratio: a predictor of prostate-specific antigen level and the presence of prostate cancer. BJU Int, no. doi: 10.1111/j.1464-410X.2010.09490.x

Manning JT. 2002. Digit ratio: a pointer to fertility, behavior, and health. New Brunswick, NJ: Rutgers University Press. 192 p.

Manning JT, Bundred PE, Flanagan BF. 2002. The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene? Med Hypotheses 59:334–336.

Manning JT, Bundred PE, Newton DJ, Flanagan BF. 2003a. The second to fourth digit ratio and variation in the androgen receptor gene. Evol Hum Behav 24:399–405.

Manning JT, Callow M, Bundred PE. 2003b. Finger and toe ratios in humans and mice: implications for the aetiology of diseases influenced by HOX genes. Med Hypotheses 60:340–343.

Manning JT, Fink B. 2010. Digit ratio, nicotine and alcohol intake and national rates of smoking and alcohol consumption. Pers Individ Dif 50:344–348

Manning JT, Scutt D, Wilson J, Lewis-Jones DI. 1998. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum Reprod 13:3000–3004.

Matchock RL. 2008. Low digit ratio (2D:4D) is associated with delayed menarche. Am J Hum Biol 20:487–489.

Medland SE, Zayats T, Glaser B, Nyholt DR, Gordon SD, Wright MJ, et al. 2010. A variant in LIN28B is associated with 2D:4D finger-length ratio, a putative retrospective biomarker of prenatal testosterone exposure. Am J Hum Genet 86:519–525.

Santos ML, Sibov TT, Nishimoto IN, Kowalski LP, Miracca EC, Nagai MA. 2004. The CAG repeat polymorphism in the androgen receptor gene (AR) and its relationship to head and neck cancer. Oral Oncol 40:177–182.

Scully C, Bagan JV. 2009. Oral squamous cell carcinoma: overview of current understanding of aetiopathogenesis and clinical implications. Oral Dis 15:388–399.

Viswanathan SR, Powers JT, Einhorn W, Hoshida Y, Ng TL, Toffanin S, et al. 2009. Lin28 promotes transformation and is associated with advanced human malignancies. Nat Genet 41:843–848.

Wang Z, Feng X, Liu X, Jiang L, Zeng X, Ji N, et al. 2009. Involvement of potential pathways in malignant transformation from oral leukoplakia to oral squamous cell carcinoma revealed by proteomic analysis. BMC Genomics 10:383.

24

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

ORIGINAL ARTICLE

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

Hopp Renato Nicolás; Jorge Jacks

Department of Oral Diagnosis, Piracicaba Dental School, Piracicaba, São Paulo, Brazil

Correspondance: Renato Nicolás Hopp. Address: Avenida Limeira, 901, Piracicaba, São Paulo, Brazil, 13414-903. Address: Avenida Limeira, 901, Piracicaba, São Paulo, Brazil, 13414-903. Telephone: 55-192-1065-267. Fax: 55-192-1065-320. E-mail: renhopp@gmail.com

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 (α=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 (α= 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.

Conflicting of interest

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

Acknowledgements

References

[1]   Manning JT, Scutt D, Wilson J, Lewis-Jones DI. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum Reprod 1998;13:3000-04. PMid:9853845 http://dx.doi.org/10.1093/humrep/13.11.3000

[2]   Manning JT, Bundred PE, Flanagan BF. The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene? Med Hypotheses 2002;59:334-36. http://dx.doi.org/10.1016/S0306-9877(02)00181-0

[3]   Manning JT, Callow M, Bundred PE. Finger and toe ratios in humans and mice: implications for the aetiology of diseases influenced by HOX genes. Med Hypotheses 2003;60:340-43. http://dx.doi.org/10.1016/S0306-9877(02)00400-0

[4]   Manning JT. Digit Ratio: A Pointer to Fertility, Behavior, and Health. Rutgers University Press. pp192, 2002

[5]   Hopp RN, Jorge J. Right hand digit ratio (2D:4D) is associated with oral cancer. Am J Hum Biol 2011;23:423-25. PMid:21445935 http://dx.doi.org/10.1002/ajhb.21144

[6]   Jung H, Kim KH, Yoon SJ, Kim TB. Second to fourth digit ratio: a predictor of prostate-specific antigen level and the presence of prostate cancer. BJU Int. 2011;107:591-96. PMid:20633006 http://dx.doi.org/10.1111/j.1464-410X.2010.09490.x

[7]   Rahman AA, Lophatananon A, Brown SS, Harriss D, Anderson J, Parker T et al. Hand pattern indicates prostate cancer risk. Br J Cancer. 2011;104:175-77. PMid:21119657 http://dx.doi.org/10.1038/sj.bjc.6605986

[8]   Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN et al. Annual Report to the Nation on the Status of Cancer, 1975-2006, Featuring Colorectal Cancer Trends and Impact of Interventions (Risk Factors, Screening, and Treatment) to Reduce Future Rates. Cancer. 2010;116:544-73. PMid:19998273 http://dx.doi.org/10.1002/cncr.24760

[9]   Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. Front Biosci. 2006;11:1388-413. PMid:16368524 http://dx.doi.org/10.2741/1891

[10] Coates JM, Gurnell M, Rustichini A. Second-to-fourth digit ratio predicts success among high-frequency financial traders. Proc Natl Acad Sci U S A 2009;106:623-28. PMid:19139402 http://dx.doi.org/10.1073/pnas.0810907106

[11] Brabin L, Roberts S A, Farzaneh F, Fairbrother E, Kitchener HC. The second to fourth digit ratio (2d:4d) in women with and without human papillomavirus and cervical dysplasia. Am J Hum Biol 2008;20:337-41. PMid:18203126 http://dx.doi.org/10.1002/ajhb.20731

[12] Matchock RL. Low digit ratio (2D:4D) is associated with delayed menarche. Am J Hum Biol 2008;20:487-89. PMid:18348172 http://dx.doi.org/10.1002/ajhb.20763

[13] Ozdogmus O, Cakmak YO, Coskun M, Verimli U, Cavdar S, Uzun I. The high 2D:4D finger length ratio effects on atherosclerotic plaque development. Atherosclerosis. 2010;209:195-96. PMid:19729164 http://dx.doi.org/10.1016/j.atherosclerosis.2009.08.023

[14] Manning JT, Bundred PE, Newton DJ, Flanagan BF. The second to fourth digit ratio and variation in the androgen receptor gene. Evol Hum Behav 2010;277:3353-61.

[15] Damber JE, Aus G. Prostate cancer. Lancet. 2008;371:1710-21. http://dx.doi.org/10.1016/S0140-6736(08)60729-1

[16] Manning, JT, Fink B. Digit ratio, nicotine and alcohol intake and national rates of smoking and alcohol consumption. Pers Individ Dif 2010;50:344-48. http://dx.doi.org/10.1016/j.paid.2010.10.016