Original Article

Hand digit ratio (2d:4d) and gastric cancer risk: a cross-sectional study among southeastern Brazilians

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Background: The ratio between the length of the second and fourth digit, known as digit ratio or 2D:4D, has been used as a biomarker for several diseases, clinical conditions and human's phenotypes, including cancer occurrence. We aimed to investigate whether there is a link between digit ratio and gastric cancer (GCA) risk among southeastern Brazilians.

Methods: This was a cross-sectional research, performed with 240 subjects (120 cases and 120 controls). Data source derived from the Oncology Department of Santa Casa Hospital, Montes Claros, Brazil. Digital measurements were performed with a digital Vernier caliper and the digit ratios in both hands were collected; plus, we calculated de difference between the ratios found in the right and the left hand (R-L). Baseline characteristics of both groups, such as smoking status, and alcohol consumption status, were compared between the two groups using Chi-square test. Shapiro-Wilk's test was used to check sample distribution. Subsequently, a Student's *t*-test for unpaired samples was performed to compare the means of 2D:4D ratios and R-L among groups were performed. All analyses included a 5% level of significance.

Results: Subjects at the case group had the highest digit ratio, especially on the right hand, when observing the overall average and for the female gender. Regarding the R-L, patients with GCA had higher differences than the control group, most DR-L consequently high levels of estrogen and low testosterone levels. Left digit ratio did not differed significantly between cases and controls; however, R2D:4D and R-L were (P=0.0013).

Conclusions: The results suggest that the main reason why a higher estrogen exposure in utero causes higher cancer risk among women still need to be established.

Keywords: Digit ratio; 2D:4D, gastric cancer (GCA); risk factors

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Introduction

The ratio between the length of the second e fourth fingers is known as digit ratio (or 2D:4D). According to Manning *et al*. (1), it has been almost 20 years since the hypothesis of fetal exposure to sexual hormones (both testosterone and estrogen) may affect 2D:4D, in a way that a low 2D:4D may indicates higher testosterone levels and lower estrogen levels in fetuses.

Digit ratio has been used as a biomarker for several diseases, clinical conditions and human's phenotypes (2). In that matter, 2D:4D has been included in *Oncology* studies

to investigate whether the digit ratio can influence cancer occurrence in adulthood. For instance, several types of studies managed to establish a positive correlation between cancer occurrence and 2D:4D numbers, such as prostate cancer (3), breast cancer (4), gastric cancer (GCA) (5), colorectal cancer (6) and oral cancer (7).

Worldwide, GCA is the fifth most common cancer worldwide, with 952,000 new cases of recorded globally in 2012. That counted as seven per cent of all new cases of cancer. Men are twice as likely as women to develop stomach cancer, and it is more common in older adults (8). In 2016, 12.920 new cases of GCA are expected among Brazilian men and 7,600 new cases among Brazilian women. The majority of cases (86%) correspond to sporadic adenocarcinoma (9). The main etiological factors for GCA are alcohol and tobacco consumption, *Helicobacter pylori* (*H. pylori*) infections and nutritional factors such as high salt intake (10). Other etiological factors are more difficult to control and include pernicious anemia, blood type A, history of non-syndromic colon cancer, Li-Fraumeni syndrome and atrophic gastritis (11).

We aimed to investigate whether 2D:4D is correlated to GCA among men and women retrospectively. Given the diagnosis of GCA, we hypothesized that low 2D:4D or R-L and, subsequently, a lower exposure to estrogen, were connected to the prevalence of GCA among southeastern Brazilians.

Methods

Study design

A cross-sectional study was performed with 120 patients with GCA (case group) and 120 healthy subjects (control group). Sample size was calculated according to a specific formula for sample calculation using averages of independent groups (12), which adopted a significance level of 5% and power of 80%. The mean values and standard deviations (SD) used in the sample formula were based on the results of a Brazilian study that compared average 2D:4D among individuals with and without the disease [0.96 (±0.04) and 0.94 (±0.04), respectively] (13). Thus, this study would require at least 63 individuals in each group.

Written informed consent was obtained, and the study was carried out with approval from the Human Research Ethics Committee of the University (311.756/2013).

Selection of cases and controls

Patients diagnosed with GCA by physical exam, endoscopy and histological examination were recruited from the Oncology Department of a southeastern Hospital in Brazil, and met the following inclusion criteria: having a diagnosis of GCA and undergoing treatment at the institution.

After identifying the cases, the control group was selected from medical records of patients who were assisted by primary care physicians in health public services and received normal results from preventive examinations performed in the last year. The controls were healthy subjects, age and sex-matched accordingly to the case group. Exclusion criteria for both groups included: history of fingers' fractures either in one or both hands and hormonal disorders.

Data collection and 2D:4D measurements

Two measurements were taken, both by the same researcher; the second measurement was blind to the first and was performed 30 minutes after the first one. Measurements were taken from the tip of the finger to the basal crease. The length of the second (index) and fourth (ring) fingers were measured using digital Vernier calipers with a resolution of 0.01 mm. When two creases were visible at the base of the digit, the crease proximal to the palm was chosen. The analyzed ratio was the mean of the two measurements performed. The right minus left 2D:4D was calculated as the difference between the right and left 2D:4D (R-L) (3).

Statistical methods

A descriptive and comparative statistical analysis was initially carried out with baseline characteristics from both groups, such as family history of GCA, smoking status and alcohol consumption status; this analysis was performed using Chi-square test. Shapiro Wilk's test was used to check sample distribution and revealed that both hands 2D:4D followed a normal distribution. So, subsequently, a Student's *t*-test for unpaired samples was performed to compare the means of 2D:4D ratios and R-L among groups. All analyses were conducted using IBM SPSS Statistics (SPSS, version 20.0; SPSS Inc., Chicago, Illinois, USA) with a significance level of 5%.

Results

Intraobserver reliability was high for raw digit measurements, with ICC's for left and right index and ring fingers all being greater than 0.98. Intraclass correlation coefficients for 2D:4D ratio and R-L were lower than those for raw

digit measurements (0.972 for right, 0.970 for left 2D:4D, and 0.002 for R-L), but still suggested that the observed variability in digit ratio was due to individual differences rather than measurement error.

For our research, we recruited 240 subjects (120 males, 60 patients and 60 age matched controls and 120 females, 60 patients and 60 age-matched controls). The age of the individuals in both groups ranged from 30 to 83 years with a mean age of 58.1 years (±12.4). Baseline characteristics are described in *Table 1*. Note that smoking status and alcohol consumption status did not differ significantly between groups. Hormone therapy was not reported. Adenocarcinomas (86.7%) were of type histologic in most GCA, followed by gastrointestinal stromal tumors (11%) and carcinoid tumors (2.3%). Choriocarcinomas and MALT lymphomas were not registered.

Table 1 Characteristics of patients with GCA group and control group

Variables	GCA group, mean (SD), n (%)	Control group, mean (SD), n (%)	P value*
Age	58.1 (12.4)	58.1 (12.4)	1.000
Gender			0.139
Male	60 (50.0)	60 (50.0)	
Female	60 (50.0)	60 (50.0)	
Smoking status			0.452
Never	93 (77.5)	98 (81.7)	
Former	23 (19.2)	20 (16.7)	
Current	4 (3.3)	2 (1.6)	
Alcohol consumption status			0.112
Never	96 (80.0)	90 (75.0)	
Former	12 (10.0)	23 (19.2)	
Current	12 (10.0)	7 (5.8)	
Total	120 (100.0)	120 (100.0)	

*, Chi-square test; SD, standard deviation; GCA, gastric cancer.

This study found that individuals with GCA showed the highest 2D:4D ratio grating in the control group, especially on the right hand, when observing the overall average and for the female gender. Regarding the RL, patients with GCA had higher differences than the control group, most RL consequently high levels of estrogen and low testosterone levels. L2D:4D did not differed significantly between cases and controls; however, R2D:4D and RL were (P=0.0013), as disclosed in *Table 2*. This outcome was observed particularly among females.

Discussion

In this study, females diagnosed with GCA presented significantly higher digit ratio than females without the disease, suggesting a lower testosterone exposure *in utero*. This finding corroborate with previous results found in a Brazilian study that compared means of 2D:4D ratios

Table 2 Comparison of right hand digit ratio (R2D:4D), left hand digit ratio (L2D:4D) and R-L between subjects with GCA (case group) and without GCA (control group)

Type of ratio	GCA group mean (SD)	95% CI	Control group mean (SD)	95% CI	P value*	Size effect
R2D4D	0.972 (0.039)	(0.964–0.979)	0.953 (0.036)	(0.947–0.960)	0.000	r=0.240
Male	0.966 (0.042)	(0.955–0.977)	0.955 (0.037)	(0.943–0.966)	0.178	r=0.136
Female	0.978 (0.035)	(0.967–0.986)	0.953 (0.033)	(0.945–0.962)	0.000	r=0.337
L2D4D	0.970 (0.039)	(0.963–0.977)	0.962 (0.035)	(0.956–0.968)	0.106	r=0.105
Male	0.966 (0.044)	(0.955–0.978)	0.962 (0.039)	(0.950–0.975)	0.628	r=0.049
Female	0.973 (0.032)	(0.965–0.981)	0.963 (0.032)	(0.955–0.971)	0.088	r=0.156
DR-L	0.002 (0.031)	(–0.004–0.007)	–0.009 (0.035)	(–0.015–0.003)	0.013	r=0.160
Male	–0.0007 (0.033)	(–0.009–0.008)	–0.0076 (0.034)	(–0.018–0.003)	0.312	r=0.102
Female	–0.005 (0.029)	(–0.003–0.012)	–0.009 (0.033)	(–0.018–0.001)	0.013	r=0.225

*, Student's *t*-test for unpaired samples; SD, standard deviation; CI, confidence interval; GCA, gastric cancer; R-L, right and the left hand.

of patients with GCA and healthy patients (5). Theirs results showed that cases had higher 2D:4D than controls (especially among men). Our results may differ among females since in our research we fourfold the female population included in the other paper.

High R2D:4D ratios indicating estrogen influence found in this study could be linked to tobacco consumption, which is another important etiological factor for GCA. Regardless, the smoker-ratio for this study among the GCA group was approximately a quarter of the subjects, which was similar to the control group.

A recent research conducted in China (14) tried to correlate GCA and 2D:4D among Chinese men. Their case group (n=94) had significantly lower digit ratio than controls (n=91). Both studies (ours and theirs) same similar methods, except for measurements techniques, since they used photographs to calculate all ratios. These results may differ from ours since they only included men, hence, is plausible to think that hormones could affect men and women in a different way when it comes to GCA risk.

In a Swedish cohort (15), it has also been demonstrated that estrogen exposure may protect men from having GCA. For that, we may imply that among women there is an unexplained pathway that causes women to have higher GCA ratios when they are exposed to higher concentrations of estrogen.

Conclusions

Therefore, we did not prove our hypothesis with our outcomes. Further research is required to check why women exposed to higher concentrations of estrogen have higher risks of developing GCA. Besides, this association (2D:4D and GCA risk) needs to be studied in different populations, so 2D:4D could be finally considered a putative marker for the screening of patients` susceptibility to developing GCA, since they are still scarce in the literature when it comes to GCA.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2016.12.18). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Human Research Ethics Committee of the University (311.756/2013) and written informed consent was obtained from all patients.

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