Decreased digit ratio (2D:4D) and gastric cancer in Chinese men☆

Youjing Sheng [a], Wenli Qian [a], Lu Wang [b], Zhenghao Huo [a], Hong Lu [a,*], Haochen Yu [a], Zhi Geng [a], Ping Cheng [c]

[a] Ningxia Medical University, Key Laboratory of Fertility Preservation and Maintenance of Ministry of Education/Key Laboratory of Reproduction and Genetics/Department of Medical Genetics and Cell Biology, Yinchuan 750004, PR China
[b] Clinical Medicine Science, Peking University Health Science Center, Beijing 100191, PR China
[c] Surgical Oncology of General Hospital of Ningxia Medical University, Yinchuan 750004, PR China.

ARTICLE INFO

ABSTRACT

Background: The development of finger length is influenced by the level of hormones during pregnancy in the womb. The relative length of 2nd to 4th digit (2D:4D) is considered as a putative marker for prenatal hormone exposure and may represent an individual susceptibility to certain diseases, particularly those hormone-related cancers (e.g., gastric cancer).
Aims: The aim of this study is to investigate whether there is a possible relationship between 2D:4D ratio and gastric cancer (GCA) in Chinese men.
Methods: 94 male patients with GCA and 91 controls were chosen to participate in this study. Photographs of both hands were collected and then the lengths of second and fourth digits of both hands were measured. Left hand, right hand, mean hand, and right minus left hand (ΔR-L) 2D:4D ratios were analyzed and compared.
Results: In GCA group, 2D:4D ratios were significantly lower (right hand: $p < 0.01$; left hand, mean hand: $p < 0.001$) than controls. No association was observed between 2D:4D ratio and tumor staging (neither in tumor size (T) nor in lymph node involvement (N) or distant metastases (M)). There was also no correlation between 2D:4D ratio and age of onset.
Conclusions: Decreased 2D:4D ratio may be an indicator for forecasting the susceptibility to develop GCA.

© 2016 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Digit ratio refers to the ratio of human finger length. It is determined during embryonic development and then changes little after sexual maturation [1]. The ratio which is known as the 2nd to 4th digit ratio (2D:4D) is a sexually dimorphic trait. Previous studies have reported that 2nd digit is usually shorter than 4th digit in males than in females, which results in a relatively lower 2D:4D ratio [2].

Several studies have shown that the development of finger length is influenced by the level of hormones during pregnancy in the womb [1]. Malas et al. [3] suggested that the 2D:4D ratio was probably fixed when fetus started to produce testosterone in week 8 and testosterone peaks in weeks 11 or 12 to 14. It has been demonstrated that 2D:4D ratio is negatively related to prenatal testosterone (PT) and positively related to prenatal estrogen (PE). Furthermore, there is evidence that 2D:4D measures are unrelated to the concentrations of adult circulating sex steroids [4]. So, recent years, 2D:4D ratio is considered as a useful

biomarker for prenatal hormone exposure or sensitivity to testosterone and estrogen. Up to now, there are a number of researches investigating the correlation between 2D:4D ratio and sex steroids related diseases, such as some cancers, coronary artery disease (CAD) and infertility. Jung et al. [5] found that 2D:4D ratio was related to the level of prostate specific antigen (PSA) and the patients with lower 2D:4D ratio had higher risk of prostate cancer. Muller et al. [6] reported a direct association between left hand, ΔR-L 2D:4D ratios and the breast cancer. They suggested that lower exposure or sensitivity to PT might be associated with lower risk of breast cancer. Wu et al. [7] observed that the male patients with CAD had significantly higher 2D:4D ratios than controls in both hands. Similar with earlier studies, Lu et al. [8] also found that the patients with infertility had higher 2D:4D ratios than controls. All above evidence implied that the 2D:4D ratio may be correlated with the risk of many hormone-related diseases.

Gastric cancer (GCA) is one of the most common cancers in China, and it is the leading causes of cancer-related mortality in malignant tumor [9]. Several epidemiologic studies have suggested that prenatal sex hormones (PE and PT) may play an important role in gastric carcinogenesis [10–12]. The earlier finding in a Brazilian sample (mainly men but some women) by Nicolas et al. [13] gave mixed results, such that (a) the patients with GCA had lower ΔR–L 2D:4D ratio compared to controls suggesting they had been exposed to higher PT than PE, and (b) the patients had higher left 2D:4D ratio suggesting that they had

been exposed to low PT, particularly so for males. Their findings predict that 2D:4D may be a biological marker for the screening of patients' susceptibility to GCA.

Based on the findings mentioned above, here we speculate that there may also be a link between 2D:4D ratio and GCA from Chinese populations. As GCA is more frequent in males than in females, so, in this study, only men were chosen for investigating the relationship between 2D:4D ratio and GCA.

2. Subjects and methods

2.1. Participants

All individuals were Han nationality including 185 adult males (age: 25–77 years). The present study was performed at Yinchuan city which located in the Ningxia Region, China.

Patients: 94 male patients with GCA (age: 25–77 years, mean age $\pm$ S.D. = 55.22 $\pm$ 9.59 years) were recruited from the general tumor hospital affiliated to Ningxia Medical University. All of them were diagnosed by clinical and histological analysis.

Controls: 91 resident natives (age: 35–76 years, mean age $\pm$ S.D. = 52.78 $\pm$ 10.48 years) were invited to participate in this research, and all were presented healthy physical and mental states.

2.2. Ethical statements

This study was approved by the Ningxia Medical University Committee for the Protection of Human Subjects. The participants had informed written consent before the experiment.

2.3. Digit measurement

According to the methodology proposed by Nicolás and Jorge [14], each Individual's images of both hands were obtained by a digital camera (Canon M3, Japan). Photographs were collected under the same camera configuration to avoid discrepancies between images. When taking photos, the participants were required to keep their wrists, hand palms and fingers extended and placed on a horizontal table; and the experimenter was required to keep the camera perpendicular to the palms side under the same height. The subjects with finger injured or uncompleted were excluded. All images were input into the computer and checked to insure the creases of the fingers were visible clearly. The lengths of the second and fourth digits of both hands were measured by the image analysis software (Image-Pro plus 6.0) and accurate to 0.01 mm. As described in the previous study [14], the digit length was measured from the most proximal crease up to the tip of the finger. To minimize measurement errors, each digit was measured twice and the average value was calculated as the last result. 2D:4D ratio was computed by dividing the length of the second finger by that of the fourth finger. The mean 2D:4D shown the average value of left 2D:4D and right 2D:4D, ΔR-L 2D:4D was obtained by the right 2D:4D minus left 2D:4D.

2.4. Statistical analysis

We use the following methods for statistical analysis: Remeasurement reliability was high for the first and second 2D:4D ratios (intraclass correlation coefficients (ICC), patients: left 2D:4D: $r = 0.955$, F(93) = 21.996, $p < 0.001$; right 2D:4D: $r = 0.962$, F(93) = 26.254, $p < 0.001$; controls: left 2D:4D: $r = 0.993$, F(90) = 148.873, $p < 0.001$; right 2D:4D: $r = 0.986$, F(90) = 71.314, $p < 0.001$). Differences of 2D:4D ratio and ages between the patients with GCA and controls were analyzed by independent sample t-test. The Pearson correlation coefficient test was used to investigate the

correlations between 2D:4D ratio and age, the TNM staging (tumor size [T], lymph node metastasis [N], distant metastasis [M]). Data were all conducted by using SPSS software (Version 19.0), with a significance level of $p < 0.05$.

3. Result

All controls and most patients (66%) didn't have familial history of malignancy. The rates of alcohol consumption were similar between controls (33%) and patients (32%). Tobacco consumption was significantly higher in the GCA group (62%) than in controls (47%) ($\chi^2 = 3.894$, $p = 0.048$). Most patients were diagnosed as low-differentiated adenocarcinoma, while few were gastric mucinous adenocarcinoma. Signet-ring cell carcinoma of gastric was also included. Related hormone therapy was not reported.

The ranges of 2D:4D ratio between patients (left 2D:4D: 0.870–1.044; right 2D:4D: 0.855–1.038; mean 2D:4D: 0.874–1.027; ΔR-L 2D:4D: −0.079–0.163) and controls (left 2D:4D: 0.899–1.028; right 2D:4D: 0.905–1.001; mean 2D:4D: 0.905–1.000; ΔR-L 2D:4D: −0.062–0.103) were similar.

There was no significant difference between left and right 2D:4D ratios in both patients and controls ($p > 0.05$).

3.1. Mean values of 2D:4D ratio and age

The mean values of age and 2D:4D ratio of both hands between controls and patients were shown in Table 1.

We found that the age was similar between GCA patients and controls. Mean values of 2D:4D ratio were significantly lower in patients compared to that of controls (right hand: Cohen's effect size $d = 0.45$, $p < 0.01$; left hand: $d = 0.56$, $p < 0.001$; mean hand: $d = 0.61$, $p < 0.001$).

3.2. The relationship between 2D:4D ratio and TNM staging, age of onset

Correlations between 2D:4D ratio and TNM staging, age of onset in GCA group were shown in Table 2.

2D:4D ratio did not show any correlation with tumor staging (neither in tumor size (T) nor in lymph node involvement (N) or distant metastases (M)) ($p > 0.05$). There was also no relationship between the age of onset and 2D:4D ratio ($p > 0.05$) (Table 2).

3.3. Relationships between lower/higher 2D:4D ratio and TNM staging, age of onset

In order to extend to explore whether there is a link between 2D:4D ratio and GCA, we divided 2D:4D ratio of GCA patients into two groups (lower 2D:4D and higher 2D:4D) by median (Table 3). And then tested the relationships between lower/higher 2D:4D ratio and TNM staging, age of onset respectively again (Table 4).

There were significant differences between lower 2D:4D ratio and higher 2D:4D ratio in both hands ($p < 0.001$). Whatever lower and higher 2D:4D ratio, there was still no correlation observed between 2D:4D ratio and TNM staging and age of onset (all $p > 0.05$).

Table 1
Mean values of 2D:4D ratio and age in GCA and controls (mean, SD).

	GCA (N = 94)	Controls (N = 91)	t	p
Age	55.22 (9.59)	52.78 (10.48)	−1.656	0.100
Right 2D:4D	0.948 (0.038)	0.962 (0.022)	3.157	0.002[*]
Left 2D:4D	0.946 (0.036)	0.963 (0.024)	3.792	0.000[**]
Mean 2D:4D	0.947 (0.031)	0.963 (0.020)	4.070	0.000[**]
ΔR–L 2D:4D	0.002 (0.040)	−0.000 (0.022)	−0.0541	0.589

[*] $p < 0.01$ (difference of 2D:4D between GCA and controls).
[**] $p < 0.001$ (difference of 2D:4D between GCA and controls).