

Digit Ratio (2D:4D) and cancer : What is known so far?

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Review Article

Abstract

The ratio between the second and fourth digits is a proxy marker for prenatal exposure and sensitivity to sexual hormones, which can be genetically influenced. The influence of prenatal hormone exposure can reflect on adult life traits such as psychological traits, athletic performance and diseases such as cardiovascular. An important and newly explored field on digit ratio research is its correlation to different types of cancer, as a marker for prevalence and severity. In this review, the different types of cancer already correlated to digit ratios are discussed.

Keywords: Prenatal testosterone; Digit ratio; Cancer

Introduction

The ratio between the second and fourth digits, also known as digit ratio or 2D:4D is a proxy marker for the prenatal influence of sexual hormones - mainly testosterone and estrogen. It is negatively correlated to prenatal testosterone (PT), i.e., the lower the ratio between the index and ring finger, the higher the exposure and sensitivity to PT. Conversely it is positively correlated to prenatal estrogen (PE). There is evidence that prenatal exposure and sensitivity to testosterone are inversely correlated to 2D:4D, especially in the right hand, as well as to the difference between the right and left 2D:4D (Δ_{r-l}).^{1,2}

The exposure and sensitivity to PT and PE is regulated genetically. Nineteen genes have been identified to influence in digit ratio establishment in mice³ and the HOX, androgen receptor (AR) and LIN28B have been speculated to reflect on digit ratio in humans.^{4,5} Each gene is either correlated to PT or PE, being up or down regulated by the exposure to these hormones, but no gene is influenced in the same direction by PT and PE. This feature makes digit ratio a candidate marker for the action of these genes, and, subsequently for its use as a

predictor of disease susceptibility.

In recent years, three main work fronts have studied 2D:4D - psychological traits, body performance and adult-life disease susceptibility. As evidence was set out that 2D:4D may be predictive of susceptibility to cancers and that this may be particularly true in cancers that show sex differences in their occurrence, progression, and/or prognosis⁶, studies started to focus on the relationship between PT/PE and the susceptibility to prostate, breast and gastric cancers, among others. This review will focus on the studies investigating the correlations between 2D:4D and different types of cancer based on studies retrieved from PubMed, Scopus and Google Scholar using the keywords 'digit ratio', '2D:4D' and 'cancer'.

Prostate cancer

Prostate cancer is the cancer most connected to 2D:4D, which is being studied by several groups across the globe. However, not all studies can be compared due to differences in methodology and the choice of evaluation of one or both hands. Groups of different countries have evaluated the influence of right-hand 2D:4D, left-hand 2D:4D, as well as Δ_{r-l} over the prevalence and severity of prostate cancer, as well as prostatic-specific antigen and Gleason scores.

The first study to evaluate the correlations between 2D:4D and prostate cancer was performed in Korea.⁷ This study did not find a relationship between prostate volume and 2D:4D, but encountered significant negative correlation between

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2D:4D and PSA, in a sample of 366 men. The researchers evaluated only the right hand and, after dividing the patients into low (<0.95) and high (>0.95) digit ratio, found significant higher risks for prostate biopsy and prostate cancer (OR= 1.75 and 3.22, respectively). Another Korean study found an association between digit ratio, prostate cancer volume and Gleason score, after investigating 770 men with lower urinary tract symptoms.⁸ Again, the patients were divided into low or high digit ratio. The “low” group presented higher cancer detection rates ($p < 0.005$) and more voluminous tumors ($p = 0.005$) as well as higher Gleason scores ($p = 0.01$).

A larger sample was analyzed in a cohort study in the United Kingdom, based on data from 4568 patients.⁹ This study found negative correlations between 2D:4D and prostate cancer and suggested protective effects of prenatal testosterone (OR = 0.67), especially in younger patients. This study, however, analyzed hand patterns of the right hand with self-reports of patients of high or low ratio between the index and ring fingers. It must be noted that sometimes the looks of the ratio between the index and ring fingers can be deceitful. Nonetheless, given the large sample size, possible discrepancies on the analysis tend to be diminished.

A smaller but much admixed population was analyzed in Brazil for prostate cancer prevalence, and compared to a sample of benign prostatic hyperplasia (BPH).¹⁰ Once again, only right-hands were evaluated and males with prostate cancer presented lower digit ratios than the ones with no prostatic lesions. The authors suggested 2D:4D as a possible screening marker for prostate cancer incidence. A rather larger sample studied different ethnic background patients, comparing Caucasians to African-Americans in the USA.¹¹ This study found lower right-hand digit ratios for African-Americans with prostate cancer in comparison to Caucasians ($p < 0.001$), but no significant differences for Gleason scores or age at diagnosis, among other features.

A Spanish group tried to evaluate digit ratio as a predictor for prostate cancer in a sample of 204 men¹² using left-hand measurements correlated to PSA, sexual-hormone binding protein and Gleason scores. This study found a positive correlation between high digit ratios and prostate cancer incidence (OR = 4.4), especially in older patients. Conversely, The only study to evaluate both hands digit ratio and its correlations to prostate cancer - performed in Australia with a large sample of 6258 men (686 cases)¹³ - found no correlation between right or left 2D:4D after age 60, but found an inverse association for younger prostate cancer patients, inferring that 2D:4D could be a marker for cancer screening of early onset prostate cancer.

Regarding prostate cancer, the many studies published in the past years still do not point in the same direction. The dif-

ferent results may reside in the different methodologies (choice of hand of evaluation, technique use, data analysis) or in the different ethnic backgrounds of the samples (largely admixed or not, comparisons between Caucasians and African-Americans). As prostate cancer is a multifactorial disease, influenced by race and dietary habits, among others, the role of PT can be important, and larger multi-center studies may be necessary to clarify the possible role of digit ratios on the screening of this disease.

Testicular cancer

A single study has investigated the correlations between 2D:4D and testicular cancer¹⁴, evaluating 71 cases and 122 controls. This study found no correlations between testicular cancer and right-hand digit ratios. Other traits such as weight at birth and testicular volume were negatively correlated to 2D:4D by the same study, pointing to other factors that can influence testicular cancer.

Female cancers

Little has been published so far with regard to the correlations between female cancer and digit ratio. One study has investigated the correlation between 2D:4D, human papillomavirus (HPV) and cervical dysplasia in a British sample¹⁵ evaluating both right and left hands and found significantly higher digit ratios for HPV-positive women compared to HPV-negative. There was also a similar trend for persistent HPV infection. Moreover, women with cervical dysplasia had significantly higher digit ratios than HPV-negative women, regardless of ethnic background. The study concluded that PT has a negative correlation with persistent HPV infections and risk of cervical intraepithelial neoplasia

Recently, the first study on digit ratio and breast cancer has been published by an Australian group.² This study analyzed 573 breast cancer patients in a universe of 9044 women, investigating right, left and Δ_{r-l} 2D:4D and found a positive correlation between left hand 2D:4D and breast cancer risk, but negative correlations for Δ_{r-l} . Right-hand digit ratios along with Δ_{r-l} were negatively correlated with age at diagnosis, possibly being correlated to early onset breast cancer, especially Δ_{r-l} .

Oral cancer

One study has investigated the role of PT on the prevalence of oral squamous cell carcinoma, the most common mouth cancer.¹⁶ The investigators compared the right hand digit ratios of oral cancer patients, oral premalignant lesions patients and healthy subjects, matched by age and tobacco consumption. Oral cancer patients presented higher right-hand 2D:4D than subjects with oral premalignant lesions and healthy individuals ($p < 0.05$), pointing to an influence of the lack of prenatal androgen exposure on the onset of mouth cancer. Further studies regarding other types of oral cancer (salivary gland tumors, lip cancer) would be

welcome in the literature, as well as a comparison of tobacco-using habits (chewing, smoking and inverted smoking).

Gastric cancer

A recent study has correlated gastric cancer to 2D:4D¹⁷, in a pattern similar to the breast cancer study by Muller *et. al*². Overall, 116 individuals, age and sex matched were compared (57 cases and 59 controls). Left-hand 2D:4D (positively) and Δ_{r-1} (negatively) were associated to gastric cancer, particularly for males ($p = 0.001$ and $p = 0.0003$ respectively). The authors also investigated the correlations between 2D:4D and cancer staging, but found no significant correlation.

Discussion and Conclusion

Prenatal testosterone and prenatal estrogen influence the formation and establishment of digit ratios³ and can also influence the onset of psychological, behavioral or medical traits.^{6, 19} Digit ratio was proposed as a possible marker for disease predisposition in 2000¹⁹ and as a possible marker for the action of genes shortly thereafter.^{4, 18}

Today, it is known that 2D:4D can be a proxy marker for the action of about 22 genes,^{3, 4, 5, 18} many of which are connected to different types of cancer. Moreover, each gene is influenced either positively or negatively by PT or PE, and never in the same direction, both in women or men

The relationship between 2D:4D and cancer was first hypothesized for breast cancer,^{18, 20} but the first study to confirm a correlation was published in 2012.² Before that, correlations between 2D:4D and cancer had been established for prostate and mouth tumors, as well as for cervical cancer risk.

As the influence of PT/PE - reflected on the ratio between the 2nd and 4th digits seems to be especially true for sex-influenced cancers, there is still a broad field for investigations of the correlations between digit ratio and cancers. Even for the cancers already correlated to digit ratio, the exact directions in which PT/PE influence carcinogenesis is yet to be established. Further studies are welcome in the literature regarding digit ratio and cancer.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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