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Editorial

Second to fourth digit ratio: A predictor of disease in later life?

The ratio of the lengths of the index (2D) and ring (4D) fingers, expressed as the ratio 2D:4D has been proposed as a marker of prenatal androgen action [1]. Recently there has been a great deal of interest in 2D:4D and risk of disease in adulthood. Here I briefly discuss the rationale behind the use of 2D:4D in studies of hormone-related diseases in later life – with particular regard to cancers of the breast and prostate – as well as the difficulty of interpreting the results of such studies. Though the focus of this article is on breast and prostate cancer, the rationale and difficulties presented apply equally to other diseases.

1. Why study 2D:4D?

Both breast and prostate cancer are considered to develop as a result of hormonal carcinogenesis, whereby hormones enhance cell proliferation and cell division, and the accumulation of genetic errors that arise during cell division eventually result in a malignant phenotype [2]. While the evidence for the role of both endogenous and exogenous hormones in the aetiology of breast cancer in humans is both substantial and compelling [3], there are no established hormonal risk factors for prostate cancer in humans.

Much of the evidence linking hormones to breast cancer risk comes from studies of observable hormone-related events throughout the lifecourse such as age at menarche, pregnancy factors, and age at menopause, as well as use of exogenous hormones. Men do not experience such observable events, nor is there widespread use of exogenous hormone preparations by men. As a result, most studies of hormone exposure and prostate cancer have employed a single measure of circulating hormones in adulthood to assess exposure [4]. This approach is limited as hormone levels vary with age: men are exposed to hormones throughout their lifespan, and a single measurement of circulating hormones in adulthood may not assess critical exposure. This limitation applies equally to studies of circulating hormones and other diseases, especially studies of pre-menopausal women for whom circulating concentrations of hormones vary dramatically throughout the menstrual cycle.

Consequently, there has been much interest in identifying surrogate measures of hormone exposure throughout the lifespan in an attempt to better elucidate the hormonal aetiology of disease. 2D:4D is one such marker, which has been specifically proposed as a proxy for potentially critical prenatal exposure to androgens.

Several converging lines of evidence suggest that prenatal sex hormone exposure is associated with 2D:4D, and much of this evidence has been previously reviewed [5]. To cite just two examples: the development and differentiation of both the genitals and digits is controlled by the HoxA and HoxD genes [6], and it has been reported that right hand 2D:4D measured at 2 years of age is negatively correlated with the ratio of testosterone to oestradiol measured by amniocentesis in the second trimester [7].

Perhaps the best evidence that speaks to the developmental basis of 2D:4D has come from a study employing a mouse model [8]. In this study, treatment of pregnant females with an antiandrogen that specifically binds to and inactivates the androgen receptor led to male offspring developing higher 2D:4D than controls. Similarly, when pregnant females were treated with dihydrotestosterone their female offspring developed lower 2D:4D than controls. Administration of an antiandrogen, dihydrotestosterone, or oestradiol postnatally did not substantially affect 2D:4D, indicating that 2D:4D depends critically on prenatal, but not early postnatal hormone activity.

On the basis of the collected evidence, 2D:4D has been used as a marker of prenatal exposure to androgens, with lower 2D:4D indicating greater exposure, in numerous studies of disease in adulthood. For instance, there is some evidence that 2D:4D is associated with breast cancer risk and age at onset of breast cancer [9,10]. Similarly, there is some evidence that prostate cancer risk is inversely associated with 2D:4D [11–13], though no such association was observed in a prospective cohort study [14].

2. Interpreting studies of 2D:4D

The principal difficulty for interpretation of studies of 2D:4D and disease is that the primary association of interest is inestimable. That is, we can estimate the association between 2D:4D and disease (an association that is of no substantive or causal interest *per se*), but cannot estimate the association between prenatal androgen exposure and disease. This is not unique to 2D:4D, as clearly this complication of interpretation applies to all studies employing a proxy measure of the target exposure. However the difficulty for studies of 2D:4D is particularly acute because, despite the compelling evidence to suggest that 2D:4D is associated with prenatal androgen exposure, this association is still not well characterised. Additionally, any association between 2D:4D and prenatal androgen exposure will necessarily be very weak, given the substantial overlap in the distributions of 2D:4D for males and females (see [15], for example). Thus, an association between 2D:4D and a disease can only be interpreted as an *indication* that prenatal androgen exposure might be associated with the disease, and only to the extent that 2D:4D reflects differences in prenatal androgen exposure.

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3. Conclusions

2D:4D is a simple, easy to measure marker of prenatal androgen exposure that has been applied in numerous studies of adult diseases and disorders, including cancers of the breast and prostate. At present, detailed interpretation of the results of these studies is difficult due to the fact that they can only provide an indication that prenatal androgen exposure might be associated with risk, and the magnitude of any association cannot be quantified. Thus, there is a need to better characterise 2D:4D and what it represents in terms of prenatal hormone exposure in humans. While the work of Zheng and Cohn using a mouse model has begun to elucidate the developmental basis of 2D:4D [8], a better understanding of the hormonal determinants of 2D:4D in humans would provide a stronger basis for the interpretation of these studies. Despite this current limitation, 2D:4D remains a valuable window into the prenatal hormonal environment.

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