

# Comment on: 'Second to fourth digit ratio (2D:4D), breast cancer risk factors, and breast cancer risk: a prospective cohort study'

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Sir,

We read with interest the findings presented by Muller *et al* (2012) evaluating associations between second to fourth digit ratio (2D:4D) and breast cancer risk in a cohort in Melbourne. They reported a modest positive association between left 2D:4D and breast cancer risk. They also observed an inverse association for  $\Delta_{r-1}$ , which is the difference between right and left 2D:4D, particularly for poorly or undifferentiated tumours.

We were concerned that the authors focused on the  $\Delta_{r-1}$  marker in their interpretations, as this marker has a lower reliability than 2D:4D. At the same time, the 2D:4D ratio has lower reliability than finger lengths. This is understandable, as the ratio is a computed variable of two-digit lengths, and thus their associated uncertainty is propagated following a specific function of both variables. Therefore,  $\Delta_{r-1}$  contains the error associated to both right and left 2D:4D ratios. The authors showed results on their measurement reliability in respect to digit lengths and 2D:4D ratios, but not for  $\Delta_{r-1}$ , although they based their conclusions on this marker.

We previously conducted a validation study of these traits in the framework of an ongoing case-control study with more than 10 000 recruited participants. We assessed the reliability of these measures using a physical direct method with calipers, and compared it with those determined using a computer-assisted analysis on scanned images in 50 subjects. We found similar results than Muller *et al* in regard to digit lengths and ratios reliability. However, intraclass correlation coefficients (ICCs) for  $\Delta_{r-1}$  were lower than 0.50, and variability owing to individual differences was around 30%. These results were observed for both direct and scan method, being even lower for women. These observations mean that only 30% of the  $\Delta_{r-1}$  variation was produced by real differences between subjects. Allaway *et al* (2009) showed that ratios

using the scan method with computer-assisted analysis presented slightly higher ICCs than those using photocopies. Thereby, it is expectable that the results we observed for  $\Delta_{r-1}$  could be obtained using photocopies, which is the method that was used in the Melbourne cohort. Same results have been described previously by Voracek *et al* (2007), who found 'ICCs unacceptably low (mostly less than 0.5)' for  $\Delta_{r-1}$ , and remarked that 'the direction and magnitude of the sex effect changed erratically across investigators'.

Hopefully, misclassification will be non-differential between cases and controls, what would reinforce Muller's findings as this situation usually produce bias towards the null. However, if the exposure variable has more than two levels, like it is the case, bias away from the null may be present (Rothman *et al*, 2008).

In conclusion, based on the previous observations, we believe that detailed information on the reliability of these measurements is needed in studies reporting associations with cancer risk, in particular specifying the variance components for all the markers involved.

## REFERENCES

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Published online 27 November 2012

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