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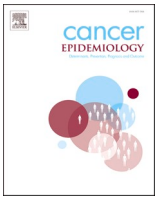

2D:4D digit ratio as a potential marker for prostate cancer risk

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ABSTRACT

Background: The second-to-fourth digit ratio (2D:4D) is thought to reflect prenatal exposure to sex steroids. We investigated the relationship between 2D:4D and odds of prostate cancer.
Method: Data were collected in PROtEuS, a population-based case-control study conducted in Montréal, Canada (2005–2012), including 1931 incident prostate cancer cases aged < 76 years and 1994 population controls. In-person interviews elicited information on potential risk factors. Digit lengths were measured by interviewers applying a standard protocol. Odds ratios (OR) and 95 % confidence intervals (CI) were estimated using unconditional logistic regression adjusting for potential confounders.
Results: The OR of prostate cancer for a standard deviation increase in 2D:4D was 0.91 (95 % CI: 0.85–0.98). For less and more aggressive cancers, ORs were 0.93 (95 % CI: 0.87–1.00) and 0.85 (95 % CI: 0.77–0.93), respectively. There was an interaction with ancestry (p=0.04), whereas the OR among men of African descent was 1.23 (95 % CI: 0.96–1.57, based on 128 cases).
Conclusion: Findings suggest an inverse association between 2D:4D and odds of overall prostate cancer, more pronounced for aggressive cancers. This supports the notion that high levels of testosterone *in utero,* estimated by a low 2D:4D ratio, are associated with a higher risk of prostate cancer. Contrastingly, a high digit ratio was associated with greater cancer odds among participants of African descent. Upon replication, 2D:4D could prove to be an easily measured marker of prostate cancer risk.

1. Introduction

Prostate cancer is the second most common cancer in men worldwide [1]. The mechanisms underlying this hormone-dependent cancer remain poorly understood. Studies of sex hormone levels in adulthood and prostate cancer risk are conflicting [2]. It has been proposed that *in utero* exposure to high levels of sex hormones could contribute to its development [3,4].

There is evidence that the second-to-fourth digit ratio, known as 2D:4D, is established *in utero*. It remains stable throughout life and differs by sex, with men tending to have lower ratios [5–7]. A low 2D:4D would reflect high prenatal testosterone exposure whereas an elevated ratio is a marker of high oestrogen levels. Some studies have shown 2D:4D variations in different ethnic groups, with a higher 2D:4D in Caucasians and a lower one in Blacks [8,9]. Based on these observations, 2D:4D has been proposed as a marker of prenatal exposure to sex hormones [5].

Finger development is under the control of genes whose expression is regulated by sex hormones [10,11]. Some of these genes are also involved in the development of cancer, suggesting an association of 2D:4D with carcinogenic events [11,12]. In support of this, several epidemiologic studies have observed associations between 2D:4D and colorectal [13] breast [14], and gastric [15] cancers. With respect to prostate cancer, studies have reported conflicting findings, suggesting either inverse, [16–21] positive [22] or no associations with 2D:4D [23,24]. However, most of these studies were based on small samples

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[16–19,21–23], only a few studies provided information on effect size [16,19–21,24] and the majority used 2D:4D as a categorical variable [19–21]. Furthermore, half did not investigate cancer aggressiveness. In a large population-based study, we aimed to estimate the association between 2D:4D and odds of prostate cancer, while overcoming these limitations.

2. Methods

2.1. Study population

Data were collected as part of PROtEuS (Prostate Cancer & Environment Study), a population-based case-control study carried out in Montreal, Canada assessing the role of environmental, occupational, lifestyle, and genetic factors in prostate cancer development. Study details have been presented elsewhere [25]. Briefly, eligible candidates were males, under 76 years old at diagnosis or recruitment, Canadian citizens registered on the provincial electoral list, and residents of the Montreal metropolitan area. Cases were newly diagnosed patients with histologically confirmed primary prostate cancer between September 2005 and December 2009, ascertained across pathology departments of seven French-speaking hospitals in the Montreal area. According to registry information, this covered over 80 % of all prostate cancer cases diagnosed in the Montreal region during the study period. Controls were randomly selected from French-speaking men on the electoral list, living in the same geographical area as the cases and were frequency-matched to cases by age (±5 years). Eligible controls had no history of prostate cancer. Response rates were 79 % for cases and 56 % for controls.

Ethics committees of all participating institutions approved the study protocol and all participants provided written informed consent.

2.2. Data collection

Face-to-face interviews collected information on a wide range of potential risk factors as well as a medical history including prostate cancer testing by prostate-specific antigen (PSA) and digital rectal examination (DRE). For 3 % of cases and 4 % of controls, a proxy, usually the spouse, provided information. The degree of tumor aggressiveness, defined by the Gleason score, was collected from prostate biopsy pathology reports at diagnosis. A score ≤ 6, or a score equal to 7 with a primary score of 3, was indicative of low-grade cancer and a score equal to 7 with a primary score of 4, or a score ≥ 8, was indicative of high-grade cancer (referred to here as Classification 1) [26]

Trained interviewers measured the length of the second (index) and the fourth (ring) fingers of the right hand to the nearest millimeter using a clear plastic ruler according to a standardized protocol. Measurements were undertaken on the ventral surface of the fingers from the tip to the basal crease. Interviewers were instructed to take two concordant measurements to insure consistency. The choice of the right hand was motivated by findings of a meta-analysis suggesting that the right hand ratio might be more sensitive to prenatal sex steroids than the left hand ratio [27]. For 24 subjects (0.6 %) with abnormalities in the right hand (severe arthritis, finger amputation, etc.), measurements were not possible, and these participants were excluded from the study population.

2.3. Statistical analysis

We estimated odds ratios (OR) and 95 % confidence intervals (CI) for the association between 2D:4D and odds of prostate cancer using unconditional logistic regression according to a standard deviation increase in 2D:4D, to facilitate comparisons with the literature. Based on current knowledge on the topic, a directed acyclic graph (DAG) was drawn to identify potential confounders. Co-variables retained for adjustment were age at index date, i.e., at diagnosis or interview (continuous), ancestry (Sub-Saharan African, European, Others) [8,9], height (continuous) and socioeconomic position (SEP) based on the father's occupation at birth, to account for potential socioeconomic stress experienced by the mother during pregnancy. Towards this, we dichotomized the European Socio-economic Classification (ESeC) into advantageous (categories 1–7) and disadvantageous (categories 8–10). Two models were implemented: model 1 adjusted for age only and model 2 adjusted for all four potential confounders. We repeated all analyses considering cancer aggressiveness using a multinomial logistic regression with the control group as the reference population. We used restricted cubic splines to check the linearity assumption of quantitative variables.

Approximately 10 % of subjects had missing data for at least one of the variables included in the models. Namely, we had 7.1 % of missing data for 2D:4D, almost half of the time, because the interview was conducted with a proxy; missing values for ethnicity and height corresponded to 0.7 % and 0.6 %, respectively. Assuming that data were missing at random, we performed multiple imputations by chained equations generating 20 datasets. We also conducted sensitivity analyses on complete cases to evaluate the robustness of findings.

We performed additional analyses: 1) we investigated whether the relationships under study varied according to the mother's smoking status during pregnancy. The underlying hypothesis was that maternal smoking during pregnancy would influence the level of circulating prenatal hormones, consequently the 2D:4D, since these are inversely related [28]; 2) we tested a possible interaction with age (<60 and ≥ 60 years), as certain genetic mutations or alterations may be common in younger individuals, influencing the development and progression of the disease [29,30]; 3) we tested a potential interaction with ancestry (Sub-Saharan African, European and others) as different ethnic groups may exhibit variations in genetic and hormonal profiles and there is evidence that Black pregnant women have elevated *in utero* androgen levels [3,30]; 4) we defined aggressive cancer using a stricter definition, i.e., a Gleason score ≥ 8 as recently recommended [31]; and 5) we restricted controls to those who had been tested for prostate cancer within the previous 2 years, to reduce the likelihood of latent cases in the control series.

All analyses were performed using R Statistical Software (version 4.3.0; R Core Team 2023).

3. Results

Characteristics of the 1919 cases and 1982 controls retained for analysis are presented in Table 1. The average age was 64 years for cases and 65 years for controls. Most (85 %) subjects were of European ancestry and cases were more likely than controls to be of Sub-Saharan African ancestry. Cases had more often a family history of prostate cancer. Nearly all cases and 78.1 % of controls had been tested by PSA and/or DRE for prostate cancer within the 2 years preceding the study. The mean 2D:4D was slightly lower for cases (0.965±0.038) than for controls (0.968±0.036). We also observed that the ratio was lower for controls of Sub-Saharan African ancestry than for those of European descent (0.963±0.038 vs 0.969±0.036).

The intra-class correlation in measurements between interviewers was equal to 0.02, indicating a low cluster effect. To confirm this, we used generalized estimating equation models using exchangeable matrices, considering the grouping of subjects within clusters represented by the interviewers. Results were similar to those presented in our main analyses (data not shown).

3.1. Association between 2D:4D and prostate cancer risk

Table 2 presents results for the association between 2D:4D and overall prostate cancer, and by cancer aggressiveness. ORs are shown for two models according to a standard deviation increase (0.037) in 2D:4D. We found an inverse association between 2D:4D and odds of overall prostate cancer and by tumor aggressiveness, with a more pronounced

Table 1
Selected characteristics of prostate cancer cases and controls, PROtEuS, Montréal, Canada, 2005–2012.

Characteristics	Cases (n=1916)	Controls (n=1982)
Age in years, mean (SD)	63.5 (6.80)	64.8 (6.88)
Height (cm), mean (SD)	173.5 (6.75)	173.5 (6.96)
2D:4D, mean (SD)	0.965 (0.038)	0.968 (0.036)
Ancestry, n (%)		
Sub-Saharan African	128 (6.7)	88 (4.5)
Asian	24 (1.3)	72 (3.7)
European	1677 (88.1)	1675 (85.1)
Others	75 (3.9)	133 (6.8)
Highest level of education, n (%)		
Elementary	441 (23.1)	428 (21.6)
High school	571 (29.9)	574 (29.0)
College	312 (16.3)	371 (18.7)
University	587 (30.7)	607 (30.7)
Mother smoking during pregnancy, n (%)		
Yes	204 (11.7)	215 (11.9)
First-degree relative with prostate cancer, n (%)		
Yes	443 (24.0)	195 (10.1)
Timing of last prostate cancer test (PSA and/or DRE), n (%)		
In the last 2 years	1896 (99.8)	1505 (78.1)
> 2 years	1 (0.1)	233 (12.1)
Never tested	3 (0.2)	188 (9.8)

Table 2
Odds ratios and 95 % confidence intervals for one standard deviation[a] increase in 2D:4D and odds of prostate cancer, overall and by tumor aggressiveness, PROtEuS, Montréal, Canada, 2005–2012.

	n controls	n cases	OR[b] (95 % CI)	OR[c] (95 % CI)
Overall prostate cancer	1982	1916	0.91 (0.85–0.97)	0.91 (0.85–0.98)
Gleason classification 1[d]				
Low-grade tumor	1982	1483	0.93 (0.87–1.00)	0.93 (0.87–1.00)
High-grade tumor	1982	433	0.84 (0.75–0.94)	0.85 (0.77–0.93)
Gleason classification 2[e]				
Low-grade tumor	1982	1693	0.92 (0.86–0.99)	0.93 (0.87–0.99)
High-grade tumor	1982	223	0.79 (0.69–0.92)	0.80 (0.71–0.92)

[a] Standard deviation of 0.037.
[b] Adjusted for age.
[c] Adjusted for age, ancestry, height, and socioeconomic position based on the father's occupation at the time of birth.
[d] Gleason classification 1: low-grade corresponds to a Gleason score of ≤6 or equal to 7 with a primary score of 3; high-grade corresponds to a Gleason score of equal to 7 with a primary score of 4 or ≥8.
[e] Gleason classification 2: low-grade corresponds to a Gleason score <8; high-grade corresponds to a Gleason score ≥8.

inverse association for the latter. Marginal differences were observed between the age-adjusted and the full model. After full adjustments, ORs were 0.91 (95 % CI 0.85–0.98), 0.93 (95 % CI 0.87–1.00) and 0.85 (95 % CI 0.77–0.93) for overall, low-grade, and high-grade cancers, respectively. Supplementary Table S1 presents associations for a continuous variable, per increment of centi units (0.01) in 2D:4D as well as for 2D:4D tertiles.

There was no evidence that maternal smoking during pregnancy or subject's age at diagnosis / interview (<60 years, ≥60 years) were effect modifiers of the associations studied (data not shown). Conversely, a statistically significant interaction with ancestry (modelled as Sub-Saharan African, European, Others) was observed (p=0.04). Interaction terms were in line with a positive association between 2D:4D among men of African descent (OR=1.23; 95 %CI 0.96–1.57, based on 128 cases and 88 controls). Contrastingly, an inverse association was found among men of European descent (OR=0.89; 95 %CI 0.83–0.96, based on 1677 cases and 1675 controls) and those from other ancestries (OR=0.95; 95 %CI 0.71–1.27, based on 75 cases and 133 controls).

Using the more restrictive Gleason score classification 2 (high-grade corresponding to a score ≥8), the inverse association for the full model was more pronounced for high-grade cancers, albeit based on fewer cases.

Findings based on complete data were consistent with those from imputed data. Excluding proxies before imputation yielded marginal differences in estimates (data not shown).

Analyses restricted to controls recently tested (previous 2 years) for prostate cancer led to stronger inverse associations. In the fully adjusted model, ORs were 0.89 (95 % CI 0.83–0.96), 0.91 (95 % CI 0.85–0.98) and 0.83 (95 % CI 0.76–0.91) for overall, low-grade, and high-grade cancers, respectively.

4. Discussion

We found an inverse association between 2D:4D and odds of overall prostate cancer. It was stronger for high-grade cancers and remained unaltered when considering potential confounders. There was evidence of an interaction with ancestry, consistent with a positive association among men of Sub-Saharan African ancestry.

Some studies have investigated a potential 2D:4D-prostate cancer relationship. Rahman et al.'s case-control study comparing three groups based on whether self-measurement of the index was shorter, equal or longer than that of the ring finger, found that men with high 2D:4D (longer index) had a lower odds of prostate cancer compared to those with a low ratio (OR 0.67, 95 % CI 0.57–0.80) [20]. They also observed a strong inverse association between 2D:4D and prostate cancer diagnosed before the age of 60 (OR 0.13, 95 % CI 0.09–0.21). Our study, including 521 cases in that age group, did not replicate this finding, nor did that of Muller et al.[24]. Furthermore, using data from the BBC online survey [32] and DALY's (disability-adjusted life years) data from Global Health Estimates 2015, Manning and Fink [33] reported a negative correlation across a large sample (>250,000) in a multi-country study, providing further support to our overall findings. Two smaller studies dichotomizing 2D:4D found that men with a ratio <0.95 had higher detection rate [19] and risk [21] of prostate cancer. Finally, two studies observed that men with prostate cancer had lower ratios than non-cases when exploring group differences and correlations [16–18]. In contrast with the aforementioned findings, two studies reported no association. The first compared mean differences across three groups (cases, high-risk group, and low-risk group) [23]. The second was a cohort study with 686 cases accrued at the end of follow-up [24]. No association emerged with prostate cancer overall or by tumor aggressiveness. Finally, a small cross-sectional study of 40 Nigerian subjects found a higher 2D:4D among cases than non-cases [22].

Several reasons can explain the discrepant findings across studies [34]. Various assessment methods were used to estimate 2D:4D, with different levels of accuracy, including qualitative assessment (longer vs. shorter finger), measurement with a tape [22], caliper [17–19,21], photographs and scanner [8,16,23], some of which were carried out by subjects themselves or trained professionals as in our study. Nearly all studies to date have been quite small; nine were based on less than 250 cases, of which five had less than 70 cases. The largest studies to date included 686 [24] and 1524 [20] cases, whereas we had 1916. Ethnic heterogeneity of study populations (Europe, America, Africa, Asia, and Australia) could also explain the discordant findings.

Our results align with a stronger inverse association with aggressive prostate cancer. Accordingly, Oh et al. assessed the relationship between 2D:4D and prostate cancer detection rate and biopsy findings (indices of tumor volume, number of cores involved, etc.) and observed that

subjects (n=18) with a Gleason score ≥9 belonged to the lower 2D:4D group [19]. The four other studies found no association with aggressiveness [8,18,21,24]. Studies varied in their classifications according to Gleason scores and nearly all were hampered by limited sample sizes.

Men of African ancestry have a well-documented higher risk of prostate cancer [30]. Common genetic polymorphisms have been observed in this population [30]. Also, *in utero* androgen levels have been found to be elevated in Black pregnant women [3]. Studies including ours, have suggested that Black men have lower ratios than Whites [9]. Waters et al. studied 2D:4D and prostate cancer severity and observed that Black men with prostate cancer were 3.7 times more likely to have a low ratio than Whites [8], suggesting a potential negative association between the 2D:4D and odds of prostate cancer among Blacks, although the absence of a control group in this study does not allow for a firm conclusion. A cross-sectional study of 40 Nigerian subjects observed that prostate cancer cases had a greater ratio than men with benign prostate hypertrophy [22]. Our study is the first to document a positive association between 2D:4D and prostate cancer risk among men of Sub-Saharan African ancestry. The limited number of men it is based on, and/or the presence of co-factors unaccounted for, might explain this.

A potential mechanism behind the 2D:4D-prostate cancer risk association may involve disruption in the expression of genes implicated in finger development, differentiation, and carcinogenesis [10–12]. These genes also control urogenital system differentiation, potentially affecting prenatal testicular androgen production [7]. It has been postulated that early exposure to sex hormones is a risk factor for many cancers later in life, including prostate cancer [3,4]. A study on prostate cancer and anogenital distance, an alternative marker of *in utero* sexual development, suggested that a phenotype reflecting normal *in utero* sexual development in men is associated with lower prostate cancer risk [35].

Our study has some limitations. First, the method (e.g., plastic ruler) used for finger length measurement potentially led to measurement error. Currently, there is no standardized method but measurement precision was found to be acceptable for plastic ruler, caliper, and computer software methods, and highest with computer software [36]. Our interviewers followed a standardized protocol, two measures were taken to assure consistency, and measurement was likely independent of disease status, leading to non-differential misclassification and an underestimation of the ORs. Finally, residual confounding cannot be ruled out due to suboptimal adjustment or absence of adjustment for unknown potential confounders.

It is worth acknowledging the several strengths of this study. It is the largest to date in terms of the number of exposed cases, on which statistical power resides, and we had information on cancer aggressiveness. Our study is also amongst the few to have assessed the effect size of the relationship between the 2D:4D and odds of prostate cancer. Whereas several studies have used the 2D:4D as a categorical variable, it was used continuously in our study after checking linearity assumptions, thereby improving statistical power, informativeness and precision of estimates. A DAG was used to identify potential confounders. We were able to explore associations among men of African ancestry. Finally, a major strength of this study lies in its exceptional study population in terms of prostate cancer detection, both among cases and controls. Indeed, 95 % of participants had been tested for prostate cancer within the five years preceding their participation into the study. Despite the absence of a screening program in Quebec, at the time of study, there was very high adherence to prostate cancer screening as part of routine yearly medical exams, covered by free and universal access to health care. As screening practices are associated with prostate cancer, and with sociodemographics and lifestyle behaviors [37], lack of consideration of detection practices will introduce bias in studies where screening coverage is uneven [38–40]. Moreover, our extensive data on screening enabled us to conduct sensitivity analyses to address the important issue relative to the presence of latent cases in our non-case series, which is largely overlooked in epidemiological studies of prostate cancer. We can therefore conclude with high confidence that the results from our study are unlikely to be biased due to screening practices among study subjects.

Our novel observation of a positive association among men of African descent, which contrasts to that among Caucasians, requires replication in future studies based on larger samples. The stronger association with aggressive prostate cancer is also noteworthy, especially in the context of our limited ability to predict well aggressive cancers using currently available tests such as PSA. Further validation of the 2D:4D as a marker of prenatal hormone exposure is highly desirable as this could provide insights into the hormonal mechanisms underlying the prostate cancer carcinogenesis process (Manning and Fink [41]).

5. Conclusion

Our results confirm quantitatively an inverse association between 2D:4D and odds of prostate cancer, suggesting that high testosterone levels *in utero* may increase prostate cancer risk, especially for aggressive cancers. Studying genetic factors common to 2D:4D and prostate cancer may help understand the underlying mechanisms.

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CRediT authorship contribution statement

Philippe Corsenac: Writing – review & editing. **Marie-Claude Rousseau:** Writing – review & editing. **Hugues Richard:** Writing – review & editing. **Leslie Kouam:** Formal analysis, Methodology, Writing – original draft. **Belinda Nicolau:** Writing – review & editing. **Marie-Elise Parent:** Conceptualization, Investigation, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2024.102635.

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