# $\operatorname{BIUI}$ Anogenital distance and the risk of prostate cancer

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Study Type – Prognosis (cohort) Level of Evidence 2b

#### **OBJECTIVES**

• To measure anogenital distance in patients with prostate cancer and control subjects without cancer.

• To evaluate the association of anogenital distance with prostate cancer in a case-control study in Spain.

# MATERIALS AND METHODS

• Anogenital distances from anus to upper penis (AGD<sub>AP</sub>) and from anus to scrotum (AGD<sub>AS</sub>) were measured in 60 patients with prostate cancer in two hospitals in Barcelona and in 52 urological controls.

• Each measurement was performed three times by the same trained examiner using a digital caliper

# RESULTS

• Patients had an  $\approx$ 5 mm shorter AGD<sub>AP</sub> than controls, whereas no difference was observed for AGD<sub>AS</sub>.

• A higher AGD<sub>AP</sub> was associated with a lower risk of prostate cancer, with an

# What's known on the subject? and What does the study add?

In animals, anogenital distance has been shown to be related to the action of fetal androgens, and exposure to chemicals such as dioxins that exhibit antiandrogenic activity results in shorter distances in male rats. In studies conducted in children, anogenital distance has been associated with endocrine disruptors such as phthalates. Studies conducted in young adults found that a shorter anoscrotal distance was a predictor of low sperm concentration, and a longer anoscrotal distance was associated with fatherhood, a higher sperm density and a higher total motile sperm count.

The present study is the first to report anogenital measurements in adults in relation to the risk of cancer, showing that a phenotype reflecting normal *in utero* sexual development in males is associated with a lower risk of prostate cancer. There are two published studies evaluating sperm quality and fatherhood suggesting a connecting mechanism related to the disruption of androgen-mediated pathways *in utero* that affects reproductive potential and the risk of prostate cancer.

adjusted odds ratio per 5 mm increase in AGD<sub>AP</sub> of 0.83 (95% confidence interval, 0.70–0.99, P = 0.03).

# CONCLUSIONS

• The present study is the first to report anogenital measurements in adults in relation to the risk of cancer.

• The present study showed that a phenotype reflecting normal *in utero* sexual development in men is associated with a lower risk of prostate cancer.

• There are two published studies (Mendiola *et al. Environ Health Perspect* 2011; **119**: 958–63; Eisenberg *et al. PLoS One* 2011; **6**: e18973) evaluating sperm quality and fatherhood suggesting a connecting mechanism related to the disruption of androgen-mediated pathways *in utero* that affects reproductive potential and the risk of prostate cancer.

# **KEYWORDS**

anogenital distance, case-control study, prostate cancer

#### **INTRODUCTION**

The importance of fetal exposure with respect to the development of prostate cancer was proposed in the early 1990s [1], although little evidence has been provided subsequently. Androgens are critical for the development of the male reproductive system during gestation and they stimulate the growth of the perineal region in male offspring [2]. Anogenital distance (i.e. the distance between the centre of the anus and the genitals) is a sexually dimorphic phenotype that tracks through life, with men having longer anogenital distances than women. In animals, anogenital distance has been shown to be related to the action of fetal androgens, and exposure to chemicals such as dioxins that exhibit antiandrogenic activity results in shorter distances in male rats [3]. In studies conducted in children, anogenital distance has been associated with endocrine disruptors such as phthalates [4]. Studies



FIG. 1. Landmarks for the measurement of anogenital distances (AGD, distance from anus to upper penis; ASD, distance from anus to scrotum) in men. Adapted with permission from Sathyanarayana et al. [12].



conducted in young adults reported that a shorter anoscrotal distance was a predictor of a low sperm concentration [5], and a longer anoscrotal distance was associated with fatherhood, a higher sperm density and a higher total motile sperm count [6]. In the present study, we evaluated the association of anogenital distance with the risk of prostate cancer.

# MATERIALS AND METHODS

Patients with prostate cancer were identified at the Hospital del Mar, Barcelona, and Hospital Germans Trias i Pujol, Badalona, Spain, within the context of a large multicentric case-control study (Estudio Multi Caso Control de Cáncer en España, MCC-SP; http://www.mccspain.org). Anogenital distance from anus to upper penis (AGD<sub>AP</sub>) and anoscrotal distance (AGD<sub>AS</sub>, anus to scrotum) (Fig. 1) were measured in 60 consecutive patients with histologically confirmed prostate cancer and in 52 controls who were randomly selected from the outpatients list of the Urology Departments, and were residents in the catchment areas of the hospitals. Controls comprised subjects who were diagnosed with LUTS (65%) or conditions other than prostate cancer (35%), with a PSA level <4 ng/mL and a normal DRE. LUTS included conditions such as urinary incontinence, hyperplasia or chronic prostatitis, all with a confirmed cancer-free status. All participants provided their written informed

#### TABLE 1 Characteristics of the study participants and anogenital distances

Characteristic	Patients with prostate cancer ( $n = 60$ )	Controls $(n = 51)$	P
Weight (kg), mean (SD)	77 (10)	78 (12)	0.56
Height (cm), mean (SD)	168 (6)	169 (7)	0.32
Body mass index (kg/m²), mean (SD)	27.4 (3.1)	27.3 (3.8)	0.91
AGD <sub>AP</sub> (mm), mean (SD)	119.4 (12.7)	124.9 (13.7)	0.03
Tertiles AGD <sub>AP</sub> , <i>n</i> (%)			
Shortest	31 (52)	17 (33)	0.14
Medium	16 (27)	17 (33)	
Longest	13 (22)	17 (33)	
AGD <sub>AS</sub> (mm), mean (SD)	34.8 (10.9)	35.6 (12.6)	0.71
Tertiles AGD <sub>AS</sub> , n (%)			
Shortest	21 (35)	17 (33)	0.73
Medium	23 (38)	17 (33)	
Longest	16 (27)	17 (33)	

 $AGD_{AB}$  anogenital distance from anus to upper penis;  $AGD_{AS}$ , anogenital distance from anus to scrotum.

consent for participation and the protocol of the study was accepted by the ethics committee of the centre.

Anogenital measurements were carried out using a gynecological examination couch in accordance with a modified protocol previously reported by Swan et al. [4]. Both patients and controls adopted a supine frog-legged position for the measurements. Each measurement was performed three times by the same trained examiner using a digital caliper (model 5900601; Comecta SA, Barcelona, Spain). The AGD<sub>AP</sub> and AGD<sub>AS</sub> reported were the mean of three measurements. If one of the measures differed by more than 5 mm, it was discarded and the mean was calculated with two measurements. Odds ratios (ORs) and 95% CIs were estimated from logistic regression adjusting for age, examiner, weight and height. The pattern of the exposure-response relationship was evaluated through a generalized additive model, using a smoothed spline (two degrees of freedom) for the continuous anogenital variable adjusting by age, examiner, weight and height. Adjustment for body mass index instead of weight and height gave almost identical results. Exposure-response was also examined by grouping subjects using tertiles as category boundaries defined by the distribution of controls.

#### RESULTS

A description of main characteristics of the study subjects is provided in Table 1. All participants were Caucasians. Both  $AGD_{AP}$  and  $AGD_{AS}$  were normally distributed, with a mean (sD)  $AGD_{AP}$  of 122.0 (13.4) mm and a mean (sD)  $AGD_{AS}$  of 35.2 (11.7) mm.  $AGD_{AP}$  and  $AGD_{AS}$  were moderately correlated (Pearson coefficient = 0.39, P < 0.001). Within-examiner variability was calculated and a difference of 1.43 mm for  $AGD_{AP}$  (1.34% of mean  $AGD_{AP}$ ) and 0.63 mm for  $AGD_{AS}$  (2.03% of mean  $AGD_{AS}$ ) was found.

Patients had an  $\approx 5$  mm shorter AGD<sub>AP</sub> than controls, whereas no differences were observed for AGD<sub>AS</sub>. A higher AGD<sub>AP</sub> was associated with a lower OR for prostate cancer (OR per 5 mm increase in  $\mathsf{AGD}_{\mathsf{APr}}$ 0.83; 95% Cl. 0.70-0.99; P = 0.03). Exposure-response evaluated through a generalized additive model (Fig. 2) showed a clear downward trend in the risk of prostate cancer with an increasing length of AGD<sub>AP</sub>. ORs by tertiles of AGD<sub>AP</sub> indicated a similar pattern of a reduction in risk with increasing AGD<sub>AP</sub>, although the strata-specific estimates were not statistically significant. The OR was 0.45 (95% Cl, 0.17-1.18) for the medium tertile of AGD<sub>AP</sub> compared to the shortest and 0.37 (95% Cl, 0.13-1.07) for the longest tertile of AGD<sub>AP</sub> compared to the shortest. This association was not observed for  $AGD_{AS}$ 

FIG. 2. Anogenital distance length (distance from anus to upper penis, AGD<sub>AP</sub>) and the risk of prostate cancer. Log odds (solid line) and 95% CI (dotted lines) using a generalized additive model with a smoothed spline for AGD<sub>AP</sub> adjusting for age, examiner, weight and height.



(OR per 5 mm change, 0.96; 95% Cl, 0.82–1.13), although a decreased odds ratio was found for the longest tertile  $AGD_{AS}$  compared to the shortest (OR, 0.74; 95% Cl, 0.28–1.94).

# DISCUSSION

In the present study, we found that longer anogenital distance, comprising a phenotype associated with normal in utero sexual development in men, was associated with a lower risk of prostate cancer. Similar to the findings reported in the present study, evidence from two studies in adults evaluating sperm guality [5,6] and fatherhood [6] also indicates that a male pattern for anogenital distance is associated with higher sperm counts and fatherhood. These studies suggest a connecting mechanism related to the disruption of androgen-mediated pathways in utero that affects reproductive potential and the risk of prostate cancer. The presence of androgens is crucial in the normal developmental process and the onset of activity of the prostate [7], and the presence of oestrogens in excess during this development may contribute to the incidence of prostatic carcinoma [8]. By contrast to these findings, a recent study evaluating self-reported length of the second (index) finger (2D) and the fourth (ring) finger (4D) of the right hand, comprising another marker of in utero sexual development, found that a high 2D : 4D ratio, which is the typical female pattern, was associated with a lower risk of prostate cancer [9]. However, another study did not confirm this association [10].

In animals, anogenital distance was shown to be a stable phenotype that persists through life [11]. Whether this is true also in humans remains unknown, as do the potential factors that could modify anogenital distance after birth. There are two studies in young adults suggesting that anogenital distance measured in adulthood is related to reproductive effects [5,6]. Differences between the findings for AGD<sub>AP</sub> and AGD<sub>AS</sub> have also been reported [5] and may reflect a measurement error (although this was probably low in the present study) or possibly different effects associated with these anthropometric differences.

A limitation of the present study is the number of subjects, although the small sample size was similar to that reported in other studies on anogenital distance in adults [5,6]. We selected hospital outpatient controls without a diagnosis of cancer rather than population controls because of difficulties in measuring anogenital distances in random population samples. The present study identified AGD<sub>AS</sub> distances that are shorter than those reported by Mendiola et al. [5] but similar to those reported by Eisenberg et al. [6]. AGD<sub>AP</sub> distances are only reported in the previous study by Mendiola et al. [5] and were similar to those observed in the present study.

The present study is the first to report anogenital measurements in adults in relation to the risk of cancer, showing that a phenotype reflecting normal *in utero* sexual development in men is associated with a lower risk of prostate cancer.

# ACKNOWLEDGEMENTS

The work reported in the present study was supported by the Instituto de Salud Carlos III-FEDER (PI08/1770). We thank Barceloneta Primary Health Center (Barcelona) for providing us with medical offices for conducting the measurements; Elena Martinez Prats and M<sup>a</sup> Jesus Esteve Garcia from CAP Barceloneta; Montserrat Llopart from the Urology Department of Hospital del Mar; and Cecilia Persavento from Centre for Research in Environmental Epidemiology (CREAL) for their collaboration in the field work. We also thank Lila Papadopoulou from CREAL for commenting on an earlier draft of the manuscript.

# **CONFLICT OF INTEREST**

None declared.

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Abbreviations: AGD<sub>AP</sub>, anogenital distance from anus to upper penis; AGD<sub>AS</sub>, anogenital distance from anus to scrotum; OR, odds ratio.