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Prostate volume and adverse prostate cancer features: Fact not artifact

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ABSTRACT

Purpose: A recent prostate cancer finasteride chemoprevention trial showed a higher rate of sextant biopsy-detected high grade prostate cancer (HGPCa) in finasteride exposed men, whose prostates were significantly smaller than those of controls. We investigated the association between prostate size and prostate cancer grade and stage in a large ($n = 3412$) single center radical prostatectomy cohort, which was unexposed to any form of hormonal manipulation.

Methods: Logistic regression models were used.

Results: Small prostates were associated with higher rate of HGPCa at biopsy and at radical prostatectomy (both $p < 0.001$), with higher rate of extracapsular extension ($p < 0.001$), seminal vesicle invasion ($p < 0.001$) and with tumor volume >3.4cc, after accounting for age, PSA, clinical stage and year of surgery.

Conclusions: Our findings demonstrate that prostate cancers located in small glands are fundamentally more aggressive than those located within larger glands. In consequence, prostate cancer detection and treatment strategies should account for prostate volume.

1. Introduction

Within the Prostate Cancer Prevention Trial (PCPT), the effect of finasteride resulted in 24% prostate size reduction and in 50% decrease in circulating serum prostate specific antigen (PSA).[1] Finasteride also reduced prostate cancer (PCa) prevalence by 25%. Concurrently, a higher rate of Gleason sum 7-10 PCa (37.0%) was seen in finasteride-exposed men, relative to the placebo group (22.2%, $p < 0.001$). This increase in high grade PCa (HGPCa) stirred many controversies.[2] Central in this debate is whether the increase in HGPCa found in finasteride exposed and size-reduced prostate glands is related

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to finasteride exposure or represents an artifactual association, unrelated to finasteride exposure.

The PCPT debate is new and ongoing. Conversely, the debate addressing the effect of gland size and prostate cancer rate and grade is not, but no consensus has been reached regarding the association between prostate volume and PCa characteristics. Studies addressing biopsy as well as pathologic specimens suggested that PCa diagnosed in small glands is associated with more unfavorable pathological characteristics.[3–5] However, a recent study failed to corroborate the relationship between gland size and pathological tumor grade.[6]

We hypothesized that small gland size may indeed predispose to unfavorable PCa, as was observed in the PCPT trial. We tested our hypothesis in a large series of 3400 biopsy and corresponding whole mounted radical prostatectomy (RP) specimens from individuals unexposed to hormonal manipulation.

2. Materials and Methods

2.1. Patient population

We relied on a single institution cohort of 4277 consecutive patients diagnosed with localized PCa based on ultrasound-guided needle biopsy and treated with RP, between January 1992 and June 2005 at the University of Hamburg. At RP, all men were unexposed to any type of hormonal therapy. Records of 865 men were excluded due to incomplete clinical or pathological data (age 33, prostate volume 412, biopsy Gleason sum 179, PSA 112, clinical stage 56, pathologic Gleason sum 73), which resulted in 3412 evaluable patients for analyses of PCa grade. Missing information about extra capsular extension and/or seminal vesicle invasion in 13 additional records resulted in 3399 evaluable men in extra capsular extension and seminal vesicle invasion analyses. Finally, 1173 consecutive records with available, computer-assisted planimetric tumor volume measurements were used in models addressing the association between prostate volume and tumor volume at RP.[7]

2.2. Clinical and pathologic evaluation

Prostate volume was measured prior to prostate biopsy, at the time of transrectal ultrasound (TRUS). All TRUS-derived prostate volume measures ($\pi/6 \times \text{length} \times \text{width} \times \text{height}$) were performed at our center. At prostate biopsy between 6 and 14 cores were taken. The Abbott AxSYM PSA assay (Abbott Park, Il, USA) was used, and pre-treatment PSA was measured prior to digital rectal examination and TRUS. The same pathologist (A.E.) assessed all biopsy and RP specimens. All RP specimens were inked over their entire surface and processed according to the Stanford protocol.[8] HGPCa at biopsy and at RP was defined as Gleason sum of 7 or higher. Since lymphadenectomies were not routinely performed in all patients, presence of lymph node invasion was not considered in the analyses.

2.3. Statistical analyses

Descriptive analyses addressed the relation between the variable of interest, namely prostate volume and (1) patient age at RP, (2) year of surgery and (3) pre-operative serum PSA. Separate univariable (UVA) and subsequently multivariable (MVA) logistic regression models tested the association between prostate volume and five distinct outcomes: (1) presence of HGPCa at biopsy, (2) presence of HGPCa at RP, (3) presence of extra capsular extension at RP, (4) presence of seminal vesicle invasion at RP and (5) presence of tumor volume above median (3.4cc) at RP. Covariates consisted of age, PSA, clinical stage and of the year of surgery. To allow for non-linear effects, prostate volume was modeled as a cubic spline. Moreover, to adjust for the extent of gland sampling, analyses addressing the association between prostate volume and the presence of HGPCa at biopsy were also adjusted for the number of biopsy cores. All statistics were performed with S-Plus Professional version 1. All tests were two sided tests with the significance level set at 0.05.

3. Results

Table 1 shows the descriptive statistics of the cohort. Data are displayed for each subcohort used in the analyses. Median patient age was 63 years. The majority had non-palpable disease (63–67%) and clinical stage T3 was recorded in 1%. PSA ranged from 0.12 to 50, with a median of 9ng/ml. Biopsy Gleason sum 6 or less was recorded in 65–69% of patients. TRUS-defined prostate volume ranged from 11 to 243cc, with medians from 43 to 44cc. The number of cores taken during prostate biopsy ranged from 6 to 14, with a median of 6. HGPCa was found in 1063 (31.2%) biopsies and in 1790 (52.5%) RPs. Extra capsular extension and seminal vesicle extension were recorded in respectively 697/3412 (20.4%) and 350/3412 (10.3%) cases. In the subset of 1173 men with available tumor volume, recorded tumor volume values ranged from 0.1–39.6cc (mean 5.1, median 3.4).

Fig. 1 shows the effects of age, PSA, and year of surgery on prostate volume (Fig. 1a–c). Increasing age, increasing PSA and more recent year of surgery were associated with larger prostate volumes. Table 2 shows the UVA and MVA analyses. Each model addressed one of the five endpoints: HGPCa at biopsy, HGPCa at RP, extra capsular extension, seminal vesicle extension or tumor volume in excess of the median (3.4cc). In UVA prostate volume represented a highly significant predictor of HGPCa at biopsy ($p < 0.001$), at RP ($p < 0.001$), of extra capsular extension at RP ($p < 0.001$), of seminal vesicle invasion at RP ($p < 0.001$) and of tumor volume at RP in excess of the median value of 3.4 cc ($p < 0.001$).

Fig. 2 shows the univariable relation between prostate volume, coded as a cubic spline, and the log odds of five distinct outcome variables: HGPCa at biopsy (Fig. 2A), HGPCa at RP (Fig. 2C), extra capsular extension at RP (Fig. 2E), seminal vesicle invasion at RP (Fig. 2G) and tumor volume at RP above the median value of 3.4cc (Fig. 2H). Increasing prostate volume at biopsy was inversely related to the log odds of HGPCa at biopsy. For all other endpoints, increasing prostate volume was initially associated with an increase in the log odds of either HGPCa at RP, of extra capsular extension at RP, of seminal vesicle invasion at RP and of tumor volume > median at RP. The increase was observed up to a prostate volume of approximately 45cc. Beyond the 45cc cut-off an inverse relationship between prostate volume and the log odds of all four endpoints was recorded.

Table 1 – Characteristics and descriptive statistics of the patients enrolled in models predicting high grade prostate cancer (HGPCa), extracapsular extension (ECE), seminal vesicle invasion (SVI), and tumor volume >3.4cc

Variables	Biopsy and RP HGPCa cohort	ECE and SVI cohort	Tumor volume cohort
Number of patients (n)	3412	3399	1173
Age			
Mean (median)	62 (63)	62 (63)	62 (63)
Range	39–78	39–78	39–75
Clinical Stage			
T1c	2272 (66.6%)	2267 (66.7%)	743 (63.3%)
T2	1105 (32.4%)	1098 (32.3%)	413 (35.3%)
T3	35 (1.0%)	34 (1.0%)	17 (1.4%)
PSA			
Mean (median)	8.7 (6.7)	8.7 (8.7)	9.0 (7.0)
Range	0.12–50	0.12–50	0.4–49.8
0–4.0	576 (16.9%)	575 (16.9%)	152 (13.0%)
4.01–10.0	1912 (56.0%)	1906 (56.1%)	678 (57.8%)
10.01–20.0	706 (20.7%)	704 (20.7%)	270 (23.0%)
Greater than 20	218 (6.4%)	214 (6.3%)	73 (6.2%)
Biopsy cores			
Mean (median)	7.5 (6)	–	–
Range	6–14		
6	1854 (54.3%)		
8	542 (15.9%)		
10	976 (28.6%)		
14	40 (1.2%)		
Biopsy Gleason sum			
6 or less	2349(68.8%)	2345 (69.0%)	768 (65.5%)
7	957 (28.0%)	950 (27.9%)	368 (31.3%)
8–10	106 (3.1%)	104 (3.1%)	37 (3.2%)
High grade PCa at biopsy	1063 (31.1%)	1054 (31.0%)	405 (34.5%)
Prostate volume (cc)			
Mean (median)	48.2 (44)	48.2 (44)	46.7 (43)
Range	11–243	11–243	13–149
ECE	697 (20.4%)	697 (20.5%)	401 (34.2%)
Missing	13 (0.4%)	–	–
SVI	350 (10.3%)	350 (10.3%)	127 (10.8%)
Missing	13 (0.4%)	–	2 (0.2%)
LNI	109 (3.2%)	101 (3.0%)	34 (2.9%)
Pathologic Gleason sum			
6 or less	1622 (47.5%)	1619 (47.6%)	532 (45.3%)
7	1721 (50.4%)	1713 (50.4%)	625 (53.3%)
8–10	69 (2.1%)	67 (3.0%)	16 (1.4%)
High grade PCa at RP	1790 (52.5%)	1780 (52.3%)	641 (54.6%)
Tumor volume (cc)			
Mean (median) Range	NA	NA	5.0 (3.4) 0.1–39.6
Tumor volume (cc) > median (3.4 cc)	NA	NA	598 (50%)

As shown in Table 2, except for patient age at RP, all variables demonstrated a statistically significant univariable association with each of the outcomes. Higher PSA values and more advanced clinical stages were associated with higher odds of HGPCa either at biopsy or RP, with higher odds of extra capsular extension, with higher odds of seminal vesicle invasion and with higher odds of tumor volume >3.4cc. Finally, the odds of high grade prostate cancer at biopsy or RP, as well as the odds of extra capsular extension, seminal vesicle invasion and tumor volume >3.4cc were lower in the more recent years of the study.

In multivariate analyses (Table 2), the same relationship between prostate volume and each of the five outcomes persisted. Prostate volume represented an independent predictor of HGPCa at biopsy and at RP (both $p < 0.001$), of extra capsular extension at RP ($p < 0.001$), of seminal vesicle invasion at RP ($p < 0.001$) and of tumor volume at RP >3.4cc ($p < 0.001$). As shown in Fig. 2, when all covariates (age, PSA, clinical

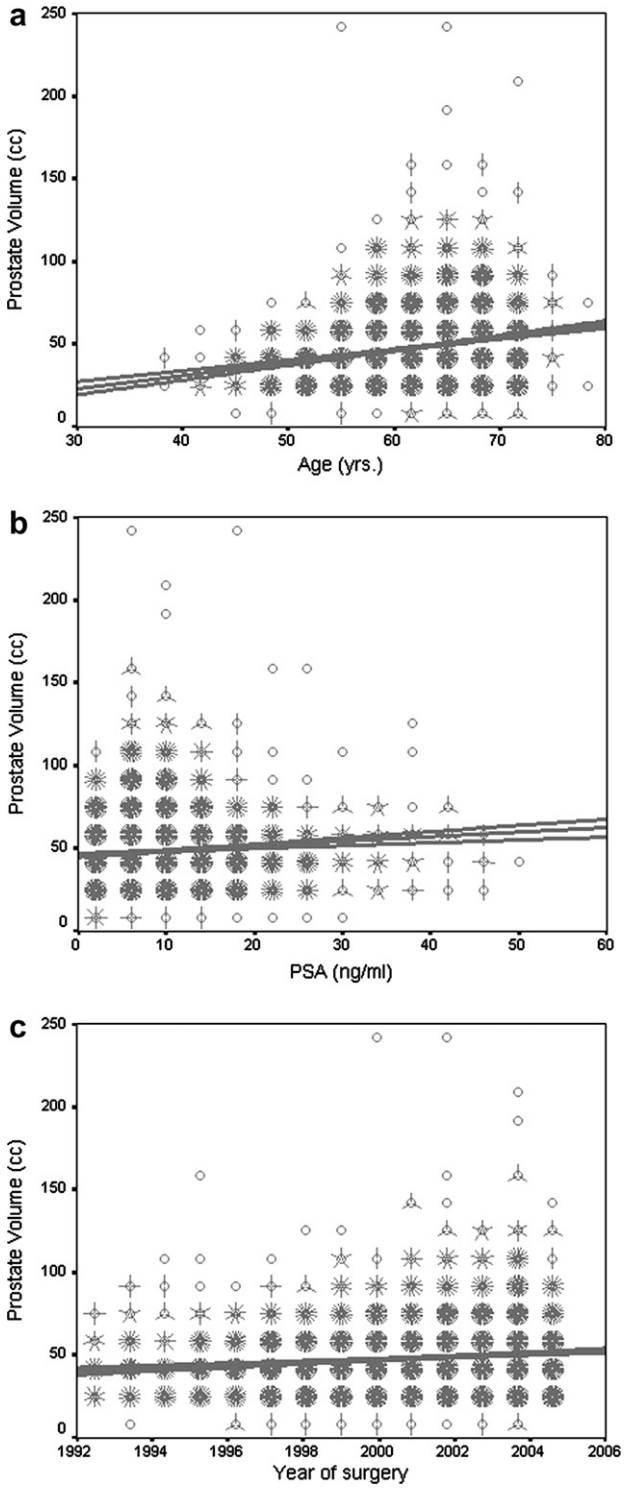

Fig. 1 – Scatterplots of the relationship between age (Panel a), PSA (Panel b), year of surgery (Panel c) and prostate volume. Sunflowers represent the observations and each petal represents one case.

stage, year of surgery and the number of cores in analyses of prostate volume and HGPCa at biopsy) were held constant, the relation between prostate volume and the five outcomes (Fig. 2b, d, f, h, j) remained virtually unchanged relative to its appearance in UVA plots (Fig. 2a, c, e, g, i). The same inverse relationship between increasing prostate volume and the log odds of HGPCa at biopsy was seen. Similarly, virtually the same biphasic relationships were seen between increasing prostate volume and the log odds of HGPCa at RP, extra capsular extension at RP, seminal vesicle invasion at RP and of tumor volume at RP > 3.4cc.

4. Discussion

The central controversy related to the PCPT findings focuses on the relationship between prostate volume and the rate of HGPCa at biopsy.[1] Two conflicting hypotheses have been advanced. One states that finasteride exposure may predispose to HGPCa.[2] The other postulates that finasteride-related size reduction resulted in more effective detection of HGPCa.[1] Several interpretations of these hypotheses were proposed.[5,6,9–19]

Some advocated that the increased rate of HGPCa was attributed to finasteride-related 24% prostate volume reduction. Volume reduction in turn facilitated the detection of HGPCa, due to more extensive and effective gland sampling.[9,10,12,14] Indeed, Karakiewicz et al. demonstrated that when the extent of gland sampling is held constant, a higher detection rate may be achieved in small glands (39% in glands <20cc) than in large glands (14% in glands >100cc).[3] Interestingly, the same investigators also demonstrated that gland size not only affects the detection rate, but is also associated with the distribution of Gleason sum. Lower Gleason sums (Gleason 5) were more frequently reported in larger glands relative to smaller glands, where higher Gleason sums prevailed (Gleason 6). These observations might be attributable to a biopsy gland size artifact, whereby small glands are sampled more effectively, with respect to PCa prevalence and to its grade. Moreover, large prostates may be more likely to be biopsied because of an elevated PSA resulting from benign glandular component and not PCa.[20]

An artifactual relationship between gland size and PCa prevalence and grade is possible, when biopsy specimens are examined. However, an artifactual relationship driven by the extent of gland sampling should have no bearing on the relationship between prostate volume and the rate of HGPCa at RP. This is especially true if statistical adjustment is made for age, PSA and clinical stage, which may predispose to more aggressive detection efforts. This relation was recently tested by Kulkarni et al,[6] who examined the effect of gland size on the prevalence of HGPCa at biopsy and at RP, in 369 men unexposed to hormonal therapy. At biopsy, large gland size was inversely related to HGPCa (odds ratio of 0.75, $p = 0.008$). Conversely, gland size was unrelated to the odds of HGPCa at RP (0.9, $p = 0.2$).

Freedland et al.[5] addressed the association between gland size and RP characteristics. Interestingly, in this much larger cohort ($n = 1602$), increasing gland size exerted a protective effect on the rate of HGPCa at RP. Moreover, large glands were also associated with lower prevalence of extra capsular extension and seminal vesicle extension.[5] Interestingly, the relationship between gland size and extra capsular extension and seminal vesicle invasion was biphasic. Up to 40cc, increasing prostate volume was associated with increasing rate of extra capsular extension. Past that cut-off, an inverse relationship between gland size and the extra capsular exten-

Table 2 – Association between prostate volume and high grade prostate cancer, extracapsular extension, seminal vesicle invasion and tumor volumes in excess of the median (=3.4cc) assessed within univariable and multivariable models

Predictors	HGPCa at Bx		HGPCa at RP		ECE at RP		SVI at RP		TV > 3.4 at RP	
	OR; p-value	OR; p-value	OR; p-value	OR; p-value	OR; p-value	OR; p-value	OR; p-value	OR; p-value	OR; p-value	OR; p-value
	UVA	MVA	UVA	MVA	UVA	MVA	UVA	MVA	UVA	MVA
Prostate volume*	-; <0.001	-; <0.001	-; <0.001	-; <0.001	-;<0.001	-; <0.001	-; 0.003	-; 0.004	-; <0.001	-; <0.001
Age	1.0; 0.6	1.0; 0.04	1.0; 0.1	1.0; 0.002	1.0; 0.4	1.0; 0.05	1.0; 0.09	1.0; 0.03	1.0; 0.1	1.0; 0.04
PSA	1.1; < 0.001	1.1; < 0.001	1.1; < 0.001	1.1; < 0.001	1.0; < 0.001	1.0; < 0.001	1.1; < 0.001	1.1; < 0.001	1.2; < 0.001	1.2; < 0.001
Clinical stage	-; < 0.001	-; < 0.001	-; < 0.001	-; < 0.001	-; < 0.001	-; < 0.001	-; < 0.001	-; < 0.001	-; < 0.001	-; < 0.001
T2 vs. T1c	3.1; < 0.001	2.7; < 0.001	3.1; < 0.001	2.7; < 0.001	2.7; < 0.001	2.4; < 0.001	3.3; < 0.001	2.6; < 0.001	2.3; < 0.001	1.8; < 0.001
T3 vs. T1c	11.6; < 0.001	7.9; < 0.001	10.1; < 0.001	6.9; 0.001	3.6; < 0.001	2.7; 0.008	6.2; < 0.001	2.8; 0.02	6.4; 0.004	3.1; 0.1
Biopsy cores	-;0.01	-;0.3	–	–	–	–	–	–	–	–
8 vs. 6	0.9; 0.5	0.9; 0.2								
10 vs. 6	0.8; 0.01	0.9; 0.5								
14 vs. 6	0.9; 0.8	1.7; 0.2								
Year of surgery	-; < 0.001	-; 0.2	-; < 0.001	-; 0.2	-; < 0.001	-; 0.4	-; < 0.001	-; 0.5	-; < 0.001	-; < 0.001
Q2 vs. Q1	0.8; 0.01	1.1; 0.6	0.6; < 0.001	0.9; 0.5	0.6; < 0.001	0.8; 0.2	0.6; < 0.001	0.9; 0.5	0.6; 0.003	0.6; 0.02
Q3 vs. Q1	0.7; < 0.001	1.2; 0.2	0.6; < 0.001	1.1; 0.2	0.5; < 0.001	0.8; 0.09	0.4; < 0.001	0.8; 0.2	0.5; < 0.001	0.7; 0.05
Q4 vs. Q1	0.5; < 0.001	0.9; 0.5	0.5; < 0.001	1.0; 0.8	0.5; < 0.001	0.8; 0.2	0.4; < 0.001	0.8; 0.2	0.3; < 0.001	0.4; < 0.001

UVA: univariable models.
MVA: multivariable models.
OR: odds ratio.
HGPCa: High grade prostate cancer defined as Gleason sum $\geqslant 7$.
Bx: biopsy.
RP: radical prostatectomy.
ECE: extracapsular extension.
SVI: seminal vesicle invasion.
TV > 3.4cc: tumor volume in excess of the median.
Q: quartiles.
* The variable was modeled as a cubic spline to allow non-linear effects.

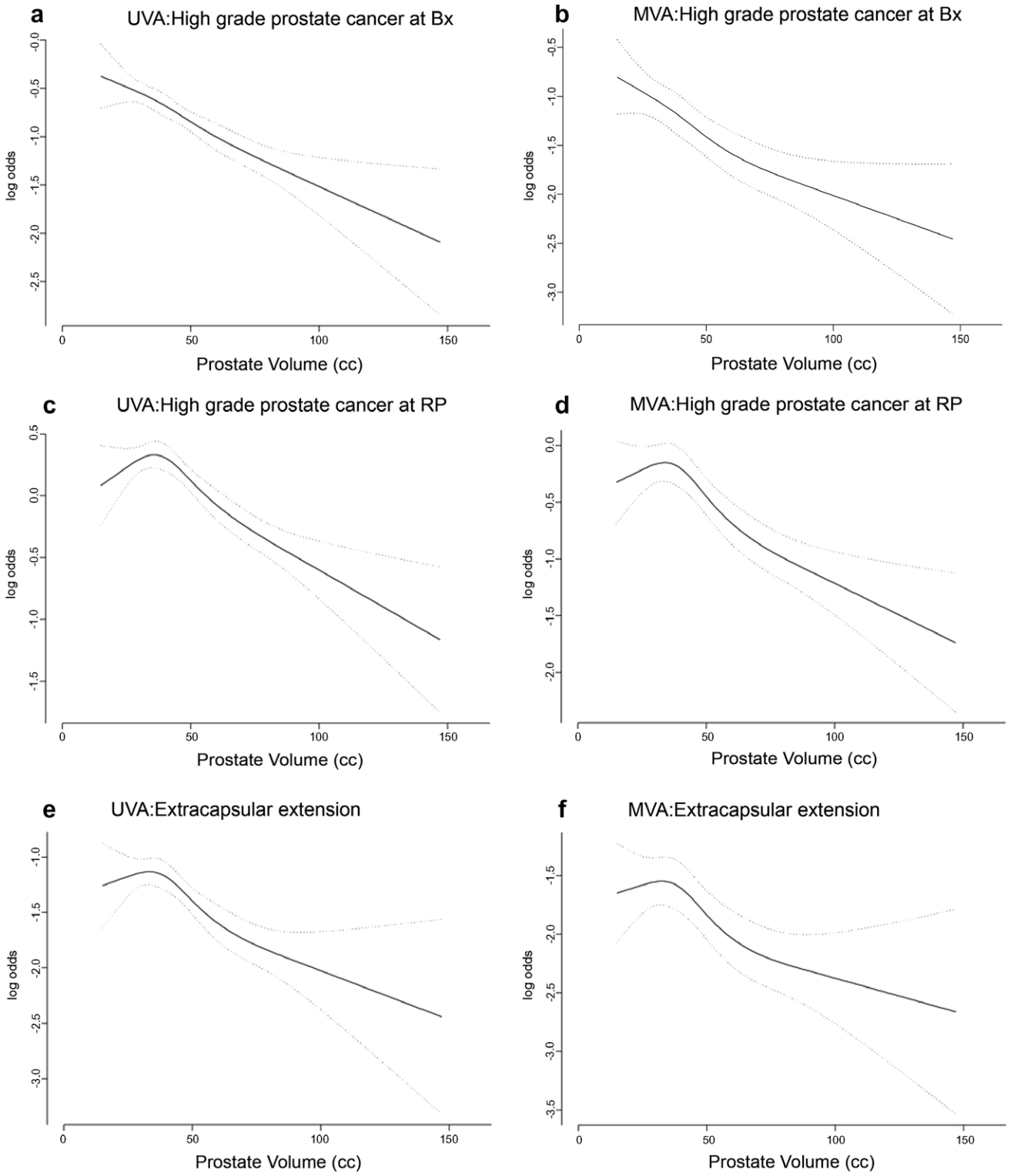

Fig. 2 – Univariable relation between prostate volume, coded as a cubic spline, and the log odds of five distinct outcome variables: high grade prostate cancer at biopsy (Panel 2a), high grade prostate cancer at radical prostatectomy (Panel 2c), extracapsular extension at radical prostatectomy (Panel 2e), seminal vesicle invasion at radical prostatectomy (Panel 2g) and tumor volume at radical prostatectomy greater the median value of 3.4cc (Panel 2h). The multivariable effect of tumor volume is represented in panels b, d, f and j. The dotted lines represent the 95% confidence intervals.

sion rate was noted. The same pattern was reported for seminal vesicle invasion, with a break point at 60cc. A monophasic inverse and protective effect was reported between gland size and RP HGPCa.[5]

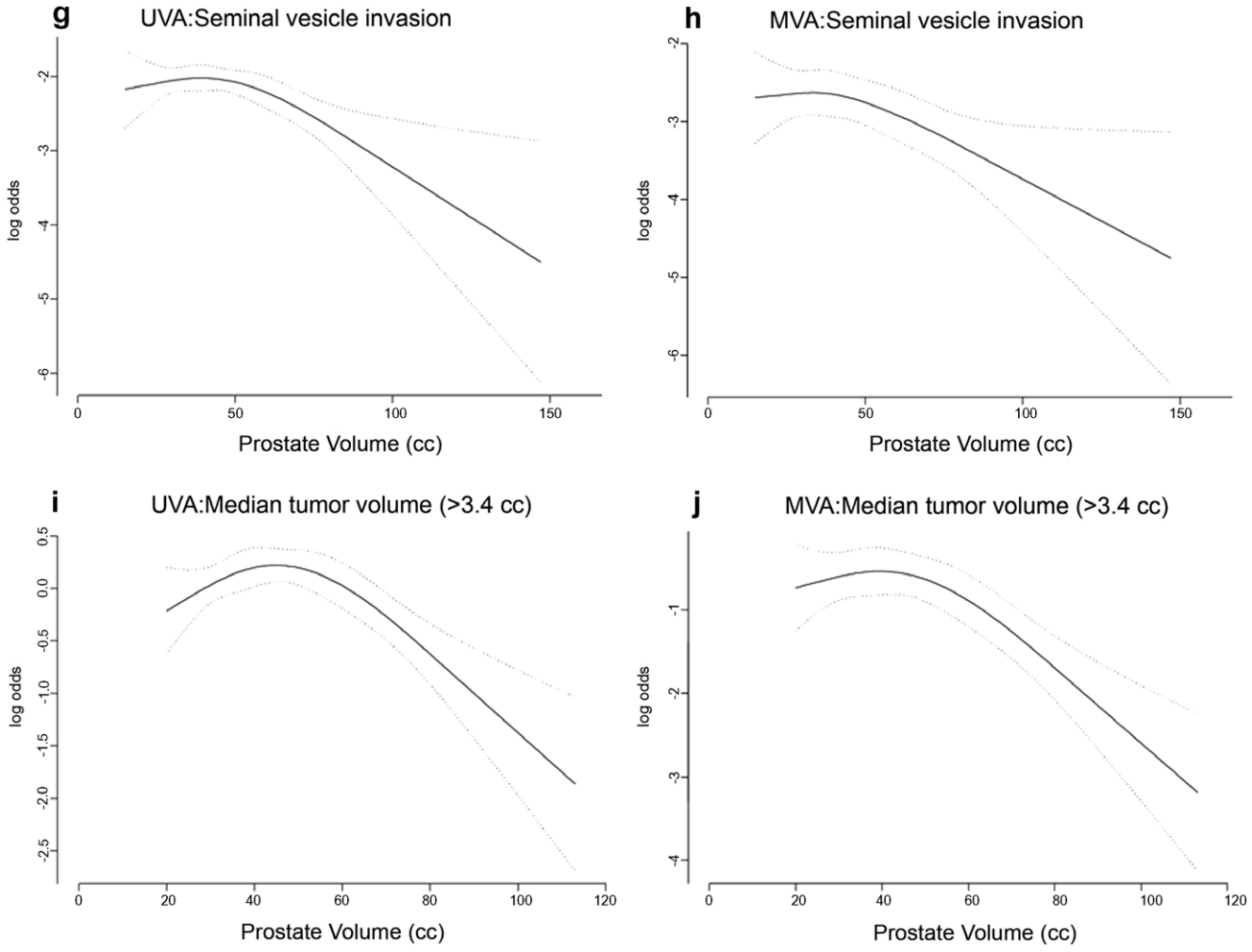

Fig. 2 *(continued)*

Taken together these studies indicate that PCa detection is higher in small glands. However, is PCa detection in small glands solely related to the extent of gland sampling? Moreover, is the protective effect between gland size and PCa grade seen in biopsy specimens also applicable to RP specimens?

We addressed these questions. Our analyses rely on the largest cohort ever examined for these endpoints. The data allowed us to test the relation between gland size and PCa stage and grade at both biopsy and RP, and this in the same patients. Our findings indicated that prostate sizes of contemporary RP patients are larger than those of their historic counterparts (Fig. 1a), which may indeed be related to more aggressive PCa detection in more recent years, if PSA originating from the benign component of these glands is accepted as a trigger for biopsy.[20] Interestingly, univariable cubic splines of the relation between prostate volume and the five pathological outcomes indicated that increasing gland size was associated with lower rate of HGPCa at biopsy (Fig. 2A), lower rate of HGPCa at RP, lower rate of extra capsular extension, seminal vesicle invasion and tumor volume at RP >3.4cc. It is noteworthy, that the biphasic relationship noted by Freedland was also seen in four of our analyses (Fig. 2C, E, G, I). Specifically, below the cut-off value of 45cc, increasing prostate volume was related to higher rate of HGPCa at RP (Fig. 2C), higher rate of extra capsular extension (Fig. 2E), higher rate of seminal vesicle invasion (Fig. 2G) and to higher rate of tumor volume at RP >3.4cc (Fig. 2I). Above the cut-off value of 45cc, increasing prostate volume was inversely related to all four endpoints.

In multivariable analyses, prostate volume represented an independent predictor of all five outcomes (all p values <0.001). The multivariate cubic spline depicting the relationship between prostate volume and the five outcomes virtually replicated the univariable graphs. It is important to emphasize that these analyses were adjusted for patient age, clinical stage, serum PSA, year of the biopsy as well as the number of biopsy cores that were obtained. Therefore, our analyses adjusted for patient biases, such as age, suspicious rectal examination findings and serum PSA. This statistical adjustment reduced or eliminated the bias related to more aggressive indications for biopsy in patients with PSA elevations related to benign prostatic hypertrophy. Moreover, we eliminated the bias related to patient's age, whereby the threshold for performing a biopsy may differ according to the individual's age. Rectal examination findings may also confound the relationship between prostate volume and PCa characteristics, as men with enlarged prostates may have more irregularities on rectal examination, which may prompt more biopsies. The

adjustment for year should reduce or eliminate the temporal effect related to potential changes in the approach to prostate biopsy. Finally, in the analyses addressing the relationship between prostate volume and HGPCa at biopsy, we also adjusted for the number of biopsy cores. The intent of this adjustment was to eliminate the artifactual effect of differential gland sampling, which may be introduced when prostate glands are biopsied in greater or lesser detail, relative to their size. Taken together, our overall results suggest that increasing gland size is associated with more favorable pathological grade and stage. These include a lower rate of HGPCa at biopsy and at RP, a lower rate of extra capsular extension, a lower rate of seminal vesicle invasion and lower rate of tumor volume >3.4cc at RP. The protective effect is most obvious for very large glands, i.e. prostates sized above the median of the distribution (44 cc. and above) or even in the top third of the distribution (52 cc. and above).

Our findings are consistent with Freedland's report.[5] Moreover, Freedland et al. also observed a biphasic relationship between gland size and the rates of extra capsular extension and seminal vesicle invasion. Differences related to coding of prostate volume may account for minor differences between recorded volume break points. Gland size assessment in the surgical specimen, as done by Freedland et al. vs. at TRUS, as done in our analyses, might also contribute to this difference. Differences in pathological characteristics also distinguish our and Freedland's cohorts. In our series, RP Gleason sum 7 was recorded in 50.4% of cases and 8–10 in 3% vs. respectively in 34% and 10% in Freedland's series. Interestingly, at biopsy 30% of our cohort had HGPCa on biopsy vs. 28% in Freedland's series. Despite these inter-cohort differences, both studies are in agreement that gland size affects PCa stage and grade at RP. The cumulative data from 5000 observations included in both studies indicate that the association between gland size and HGPCa is a fact and not solely a biopsy artifact.

Interpretation of the PCPT data of in the light of our and Freedland's findings indicate that in the PCPT study men with small prostates were at an à *priori* higher risk of harboring HGPCa. Moreover, finasteride exposed individuals experienced a gland size reduction, which facilitated the detection of their HGPCa, as outlined by Thompson et al. and by Serfling et al., where finasteride improved the performance characteristics of digital rectal examination,[21] PSA,[22] and prostate biopsy.[23] This in turn resulted in an increase in HGPCa at biopsy in the finasteride arm of the PCPT study. Finally, since volume reduction did not increase the overall rate of PCa on needle biopsy, it appears safe to state that finasteride substantially decreases the overall prevalence of PCa, as was indeed reported by the authors of the PCPT trial.

A number of limitations may apply to our study and to the interpretation of our results. Our data originate from a single European referral institution. Nonetheless, it could be postulated that the relationship between gland volume and PCa characteristics may be specific to our patient cohort. We believe that such postulate may be safely rejected base on several previous analyses that confirmed similarity between our cohort and PCa patients from other countries and continents. Besides these limitations that are inherent to our study, limitations also apply to our attempt at extrapolating our findings to the PCPT cohort. For example, there might be other explanations for the observed higher prevalence of HGPCa in finasteride exposed men, such as suboptimal detection of PCa in men with large glands. However, if such was indeed the case then Freedland's[5] and our data would demonstrate no relationship between gland size and unfavorable PCa at RP. Another argument against our and Freedland's[5] observations may claim that men with large prostates might be subjected to more vigorous detection, given higher PSA levels. This in turn might introduce a lead-time bias. The latter would result in detection of PCa at an earlier age and at an earlier pathological stage. We believe that this limitation was not operational in our analyses, as we adjusted for age and PSA.

In conclusion, our findings demonstrated that the rate of HGPCa, extra capsular extension and seminal vesicle invasion were higher in small prostates. Moreover, small prostates harbored larger tumors. Our observations corroborate the findings of Freedland et al.[5] Extrapolation of the findings from both series to the PCPT data suggest that men with small prostates were à *priori* predisposed to higher rates of HGPCa.

Conflict of interest statement

Alberto Briganti: none declared.
Felix K-H Chun: none declared.
Andrea Gallina: none declared.
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