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Possible clinical implications of peripheral zone changes depending on prostate size

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Abstract

Purpose Although numerous studies have observed an inverse relationship between the size of benign prostate hypertrophy (BPH) and the incidence of prostate cancer (PCa), few studies have explored specific mechanisms by which BPH and PCa may influence one another. In a recent study, one possibility has been brought up that growth in the transition zone due to BPH may cause pressure-induced fibrotic changes in the peripheral zone, an area where 80% of cancer occurs, leading to gland atrophy and the thickening of the prostatic capsule. To shed more light on this phenomenon, we conducted a pilot study examining the quantitative and qualitative histo-anatomical changes that occur in the peripheral zone associated with BPH.

Methods Thirty-nine prostate specimens of various sizes were selected from patients who had undergone radical prostatectomies. Each prostate was evaluated in six different locations along the dorsal aspect of the peripheral zone by measuring the thickness of the peripheral fibrotic zone (prostate capsule) and its association with gland atrophy. Multiple regression analysis was performed to determine the relationship between prostate size and the average thickness of the prostate capsule.

Results Multiple regression analysis revealed a strong, positive relationship between prostate size and average capsule thickness with a Pearson coefficient of 0.707 ($p < 0.05$). Fibrotic histo-anatomical changes were spatially associated with gland atrophy: glands found within the peripheral fibrotic zone appeared elongated and atrophic.

Conclusion The results suggest that BPH may be associated with the development of fibrotic material and atrophy of glands within the peripheral zone. Because this atrophy involves glands where 80% of prostate cancer originates, this potentially explains the inverse relationship between PCa and BPH.

Keywords Prostate cancer · Benign prostate hypertrophy · Peripheral zone · Gland atrophy

Abbreviations

BPH	Benign prostate hypertrophy
Cz	Central zone
PCa	Prostate cancer
Pz	Peripheral zone
Tz	Transitional zone

Introduction

Prostate cancer (PCa) and benign prostate hyperplasia (BPH) are two of the most common urological disorders found within older men. Recent studies showed an inverse correlation of BPH size and incidence of PCa [1–12]. Despite numerous studies supporting this observation, the exact cause of this clinical phenomenon remains unclear. Alcaraz et al. suggested "anatomic, pathologic, and genetic interactions" between BPH and PCa [1]. Both BPH and PCa are characterized by growth within the prostate; however, extensive search of the literature only reveals few studies describing possible mechanisms whereby BPH potentially inhibits the development of PCa [1].

One hypothesis is based on the histo-anatomical changes in BPH that occur in the prostate as a result of BPH. As well known to clinicians, the prostate consists of different zones, which include the anterior stroma or central zone (Cz), the transitional zone (Tz), and the peripheral zone (Pz), each one with unique features [13, 14]. In BPH, pressure from the

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growing Tz can compress cells within the other zones and cause changes in tissue organization, particularly in the Pz [13]. One of the observed changes is the development of a peripheral fibrotic layer immediately adjacent to the prostatic anatomical capsule [15, 16]. The anatomic prostate capsule in younger patients without BPH is a thin fibro-muscular band that surrounds the posterior and lateral parts of the prostate, but not the anterior/ventral aspect of the prostate; therefore, it is not considered a 'true' organ capsule [17]. This capsule is described as an "inner layer of smooth muscle fibers, mainly oriented transversely, and an outer collagenous membrane" [17]. In prostates with BPH, fibrotic material (with a linear organization similar to the anatomical capsule) can begin to develop immediately adjacent to this collagenous membrane, giving the appearance of a thickening of the capsule. Often, this thickened layer creates a plain of dissection that makes it surgically easier to peel out the BPH component when performing open or laparoscopic BPH prostatectomy. Because of this, the additional peripheral fibrotic layer is sometimes referred to by experienced urologists as the 'surgical capsule' [16, 18]. Although this technical term of 'surgical capsule' is established in the literature by urological surgeons, controversies about its specific characteristics and nature still remain, and only few studies try to provide some clarification of its properties.

The hypothesis has risen in the literature that the development of the surgical capsule may lead to pressure-induced atrophy of the adeno-glands in the Pz [19, 20, 22]. One recent study found that large prostates had significantly less adeno-gland density in the Pz than small prostates [19]. Another study, using computer simulations, suggested that hypertrophy in the Tz (due to BPH) was associated with changes in the Pz that mechanically impeded the development of PCa [20]. The purpose of this pilot study is to shed more light on this clinically important question. Using specimens from completely removed prostates of different sizes, we examined the correlation between prostate size and the thickness of the peripheral fibrotic layer in the peripheral zone, as well as the spatial relationship between the fibrotic tissue and gland atrophy.

Methodology

To examine the relationship between BPH and changes in the Pz, a retrospective study was conducted comparing the overall volume of the prostate with the thickness of the peripheral fibrotic layer, sometimes called the surgical capsule. After obtaining IRB approval, 39 patients were selected who had underwent a radical prostatectomy between 2005 and 2016. Patient selection was based on two factors: first, easy reconstruction of the prostate anatomy by the anatomical slides to identify the exact location of measurements. Grossing techniques vary greatly among pathologists, with some using coronal cuts; while others use sagittal or transverse cuts, leading to differences in the orientation of the different portions. In an effort to measure the prostate in consistent areas each time, patients were selected from a group of two pathologists who made their cuts in a consistent coronal manner and provided clear diagrams of the locations of those cuts in relation to its position within the prostate. Second, patients were selected based on the size of the prostate. To reflect all prostate sizes in this study, specimens were chosen that represented small (≤ 35 g), medium (> 35 g and < 80 g), and large prostates (≥ 80 g).

Once selected, H&E slides of each prostate were examined using light microscopy. To obtain comparable results, a protocol was developed to examine each prostate in the same corresponding areas. Using the diagrams/descriptions made by the pathologists, slides were chosen that represented the two most equatorial slices (halfway between the apex and the base of the prostate, see Fig. 1a). Not all prostate specimens are useable because of an inability to reconstruct them to find their anatomical position within the prostate. Once selected, each of the two slides were studied and measured at the 4:00, 6:00, and 8:00 positions of the posterior portion of the prostate (see diagram in Fig. 1b) resulting in six measurements per case. Measurements were taken from the inked outside boundary of the prostate to the first tissue that gave the appearance of normal Pz glands and tissue organization. This measured area included the original, anatomical capsule and the developed "surgical capsule." From this point on, the combination of the anatomical capsule and the surgical capsule will be referred to as simply the capsule. Measurements were done under $25\times$ magnification using a transparent ruler. The overall average thickness of the capsule was determined by averaging the six measurements.

Statistical analysis

Sample characteristics were summarized using frequency (%) and median (interquartile range, IQR) for categorical and continuous data, respectively. Continuous values were tested for normal distribution by using the Shapiro–Francia test.

Average prostate thickness was calculated from the six measurements. Generalized linear models were used to determine the statistically significant predicting factors for average thickness. Multiple stepwise linear regression analyses were performed to test for the independence of respective associations. Main effects and an intercept were included in the model. A threshold of $p < 0.05$ and a backward stepwise elimination procedure were used to build reduced generalized linear models until only significant ($p < 0.05$) factors and/or variables remained in the model. Heteroskedasticity, multicollinearity, normal distribution of residuals, specification, functional form, and influential

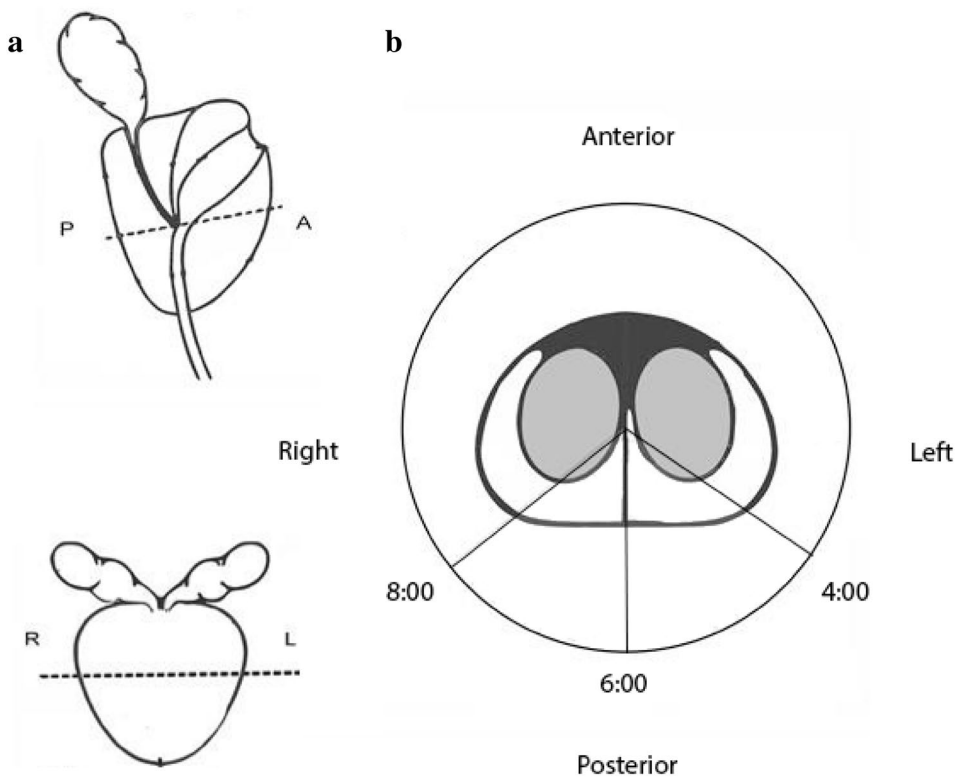

Fig. 1 **a** Schematic diagram of prostate showing location of equatorial position. **b** Measurements were taken at the 4:00, 6:00, and 8:00 positions of the schematic

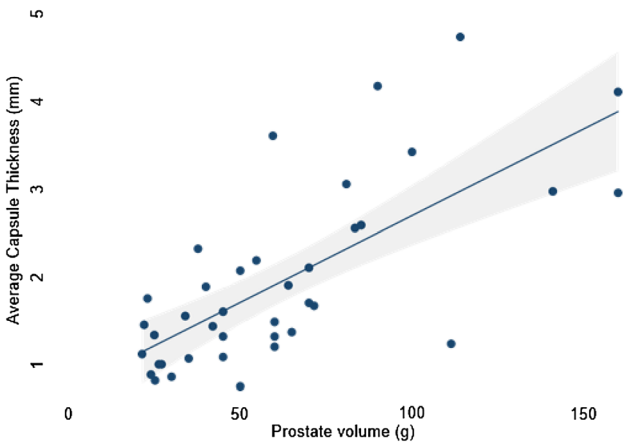

Fig. 2 Average capsule thickness against prostate volume with linear prediction and 95% confidence interval

observations tests were used to check the quality of the regression models. Bivariate relationships between the other variables were assessed by calculating Pearson's correlation coefficients (Fig. 2).

The goodness of fit was assessed using the Akaike information criterion (AIC) and Bayesian information criterion (BIC), and Chi-squared ($\chi 2$) tests. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station TX).

Results

Patient characteristics, including prostate sizes, are listed in Table 1. Results from the study suggested two key findings. First, capsule thickness was associated with prostate size. The first stepwise regression model included average thickness as criterion, prostate volume as main predictor, and potential confounders, such as age, height, weight, BMI, final Gleason score, seminal vesicle invasion, pathologic nodal stage, and pre-surgical treatment (such as treatment with hormones, finasteride and a-blockers). Using the multimodality statistical approach as outlined above, predictors such as height, BMI, body weight, Gleason score, tumor stage, and seminal vesicle invasion, were sequentially removed. Only prostate volume was found to be a significant predictor of average capsule thickness with a Pearson correlation value of 0.707 ($p < 0.05$). Table 2 presents the results of a regression model for prostate volume. Based on determination coefficients, prostate volume alone could explain 50% of variation in average capsule thickness.

Second, examination of the slides suggested that development of fibrotic material, or surgical capsule, was spatially associated with the atrophy of glands within the Pz. An important difference between the anatomical capsule and the surgical capsule is the presence of glands. No glands were observed in the anatomic capsule. However, in many of the specimens, atrophic glands were observed within areas of fibrosis, or the area we defined as

Table 1 Patient characteristics

Characteristic	
N	39
Age, median in years (IQR)	66 (59, 71)
Race, *n* (%)	
White	27 (69.2)
Black	5 (12.8)
Hispanic	7 (17.9)
Height (in), median (IQR)	70 (67, 72)
Weight (lb), median (IQR)	195 (170, 230)
BMI, median (IQR)	28.5 (25.7, 32.9)
Charlson comorbidity index, median (IQR)	5 (4, 6)
Smoker, *n* (%)	
Non-smoker	22 (61.1)
Prior smoker	10 (27.8)
Current smoker	4 (11.1)
Pathologic nodal stage, *n* (%)	
NX	10 (27.8)
N0	23 (63.9)
N1	3 (8.3)
Prostate size in grams, *n* (%)	
Small (≤ 35 g)	11 (28.2)
Medium (> 35 g and < 80 g)	18 (46.2)
Large prostates (≥ 80 g)	10 (25.6)
Pre-treatment with	
Neoadjuvant hormones, *n* (%)	2 (5.1)
Alpha-blockers, *n* (%)	2 (5.1)
Finasteride, *n* (%)	1 (2.6)
Radiation therapy, *n* (%)	0 (0)

Table 2 Linear regression model predicting average thickness (mm) from prostate volume

	Model
N	39
Intercept	0.71
95% CI	0.24–1.18
p	0.004
Prostate volume Pearson coefficient	0.707
95% CI	0.01–0.03
p	0
R^2	0.50
Prostate volume	0.50
Deg. freedom	2
AIC	88.18
BIC	91.50

the surgical capsule. In contrast to the round, full glands found within normal areas of the Pz (i.e., where no fibrosis had developed) glands in areas of fibrosis appeared significantly elongated and atrophied. In many of the prostates with larger capsules, a clear transition was observed from normal, round appearing glands in the Pz to the atrophic, elongated glands of the capsule area, with the transition of the glands occurring in the same area as the transition to the fibrotic areas did (Fig. 3). In smaller prostates with little fibrotic changes, few atrophic glands were observed (Fig. 4).

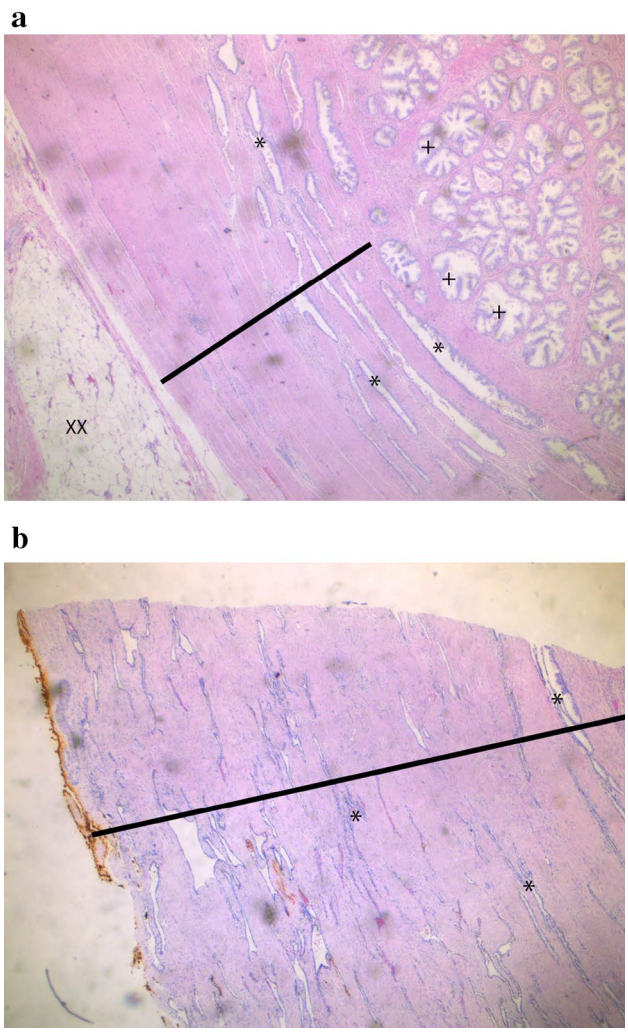

Fig. 3 H&E histological staining of larger prostate capsules. Thick lines indicate the capsule. Normal glands are indicated by plus symbol and atrophic glands are indicated by asterisk symbol. XX indicates extra-capsular fat. In comparison to smaller prostates (see in Fig. 4), larger prostates were observed to have thicker capsules with greater numbers of atrophic and elongated glands. **a** Large prostate (114 g) with a visible transition from normal appearing glands of the Pz to the scarce, atrophic and longitudinal glands within the capsule. **b** Another example of a large prostate (160 g) with a thick capsule and the atrophic glands within. (Both slides shown at ×25 magnification)

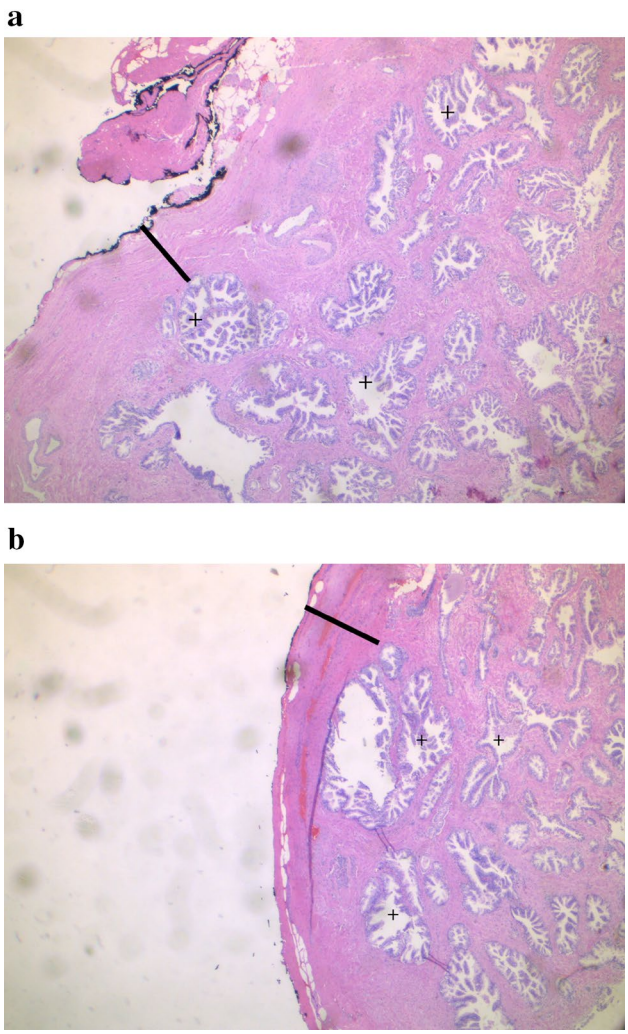

Fig. 4 H&E histological staining of two smaller prostates (**a** 30 g, **b** 31 g) with less development of fibrotic like tissue and significantly less atrophic glands. Thick line demonstrates the capsule. Plus symbol indicates normal glands. There are barely any atrophic glands found within the capsule when compared to the slides in Fig. 3 (both slides shown at ×25 magnification)

Discussion

Numerous clinical studies have demonstrated an inverse relationship between prostate volume and the incidence and aggressiveness of PCa: as prostate volume increases, incidence of PCa decreases and patients with large prostates showing a better prognosis [2–5, 21–23]. F.H. Schroeder and an international group of co-authors published an extensive literature review concerning this phenomenon [1]. These findings are barely challenged in the literature.

In one recent study, the incidence of PCa was reduced by 40% in large prostates with a volume > 65 cc when compared to smaller prostates with a volume < 35 cc [22]. The authors brought up the hypothesis that the adeno-glands of the Pz in large prostates may be exposed to pressure-induced atrophy caused by the increased growth of the Tz, which may lead to the demise of the adeno-glands in the Pz, the zone were about 80% of all adeno-carcinomas of the prostate originate [22]. This possible explanation sounds logical, and therefore it is interesting to notice that the literature is lacking any histo-anatomical studies looking into this specific question. To our knowledge, this is one of the first studies to directly analyze and compare the Tz and Pz in prostates of different sizes.

The results of our study suggest several assumptions. The observation of glands within areas of the fibrosis, whether healthy or atrophied, suggests that the histo-anatomical changes involve a transformation of tissue in the Pz rather than hypertrophy of the anatomical capsule. The significant, positive relationship between prostate size and capsule thickness as well as the spatial association of fibrotic changes and gland atrophy leads to the assumption that BPH-related Tz enlargement is causing wide-spread atrophy, apoptosis and scarring of the epithelial cells in the Pz, and as a response forming a thicker collagen-rich layer, observed as a thickening of the prostate capsule. This disease process in large BPH prostates may significantly reduce the risk of developing adenocarcinoma in the remaining epithelial glands of the Pz. This would explain the reduced incidence for PCa in large BPH prostates, a phenomenon well documented in the literature as outlined above.

Accumulating evidence in the literature suggests that BPH and PCa share important anatomic, pathologic, and genetic links in addition to the well-established epidemiologic association between these conditions [22]. Although many of these findings published over the recent years are preliminary and require further research, they offer new insight into the mechanisms of disease process underlying the development of BPH and PCa. A recent study used a mathematical model that demonstrated that "BPH produces the volumetric expansion of the prostate in the perpendicular direction" to the area of the Pz. This expansion was predicted to interfere directly with PCa growth [20]. A possible explanation for this atrophy is pressure-induced apoptosis resulting from reduced blood flow, which leads to the scar-like development of the capsule [16]. Another possible reason may be that pressure on the glands initiates signaling cascades leading to apoptosis.

Limitation of our study is the relative small sample size and its single-center design. Another limitation is the nature of the prostate where the precise boundaries between the different zones, the surgical/anatomical capsule, and extra capsular tissue are in some cases not well defined. The transition between the zones often occurs gradually and it can be difficult to make pin point measurements. Furthermore, the thickness of the capsule varies considerably within a single prostate, some areas appearing considerably thicker

than others. We did our best to take multiple measurements at the same representative locations on each prostate. Also the presence of seminal vesicle tissue can make measurements of the capsule in small prostates difficult by distorting the shape of the capsule. In this study, seminal vesicles were identified by their difference in shape and by the presence of lipofuscin pigments.

Due to the relatively small sample size, we consider this study as a pilot study. We want to encourage other institutions to look into this phenomenon, analyze and evaluate their cases as well. If the hypothesis of interaction between BPH and PCa is correct, it will have significant implications how we urologists see and treat patients with BPH.

Conclusion

The results of this histo-anatomical study of prostates in different sizes provide possible explanations for the well-documented inverse association between prostate volume and the incidence of prostate cancer. Data from this study and the outlined discussion should encourage other clinicians and investigators to further explore the relationship between prostate volume and the incidence and aggressiveness of prostate cancer, in order to better understand this phenomenon. If confirmed, this may have relevant future clinical implications in diagnostics and treatment for BPH.

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Compliance with ethical standards

Conflict of interest The authors have no financial relationships or conflicts of interest to disclose.

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