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Hypothesis

Evolving Hypothesis that Prostate/BPH Size Matters in Protection against Prostate Cancer

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Abstract

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are the two predominant urologic diseases affecting aging men. As a matter of fact, 95–98% of elderly men with prostate as their "primary organ disease" for consulting urologists have either the clinical diagnosis of BPH, PCa or both. Other primary diagnoses of the prostate such as sarcoma, lymphoma or isolated bacterial prostatitis (not in the context of a systemic urinary tract infection) are rare entities. Although BPH and PCa are very common, their interaction is currently not well understood. Numerous clinical studies and meta-analysis reviews have demonstrated a negative correlation between prostate BPH size and the probability of PCa presence, but little is known to explain this clinical phenomenon. Recent histo-anatomical and magnetic resonance imaging studies have revealed data leading to a hypothesis indicating the expanding transition zone (TZ) in a growing BPH prostate causes mechanical stress within the peripheral zone (PZ) with secondary fibrosis and atrophy of the glands within the PZ. This dynamic interaction of the TZ against the PZ in a growing BPH-prostate could explain the negative correlation between BPH size and PCa incidence. The purpose of this review is to present and discuss the evolving hypothesis that prostate size may matter and be protective against prostate cancer.

Introduction

The two predominant urological diseases impacting aging men are benign prostatic hyperplasia (BPH) and prostate cancer (PCa). Over half of men aged over 50 years old show histological findings of BPH, and PCa remains a highly aggressive malignancy with still rising rates in the United States.[1,2] Both BPH and PCa are associated with tissue proliferation and often coincide with each other, but, until recently, their specific interaction has not been well understood.[3] A negative/inverse association between BPH size and PCa incidence has been well documented in various clinical studies, a relationship barely challenged in the literature.[4,5]

Investigating the anatomical and histological zonal changes in a growing prostate may provide further insight into this association. In this context it should be mentioned that a prostate can be visualized as containing three main zones: the central zone (CZ), transition zone (TZ), and peripheral zone (PZ). These zones are distinguished by their embryologic origin, biological function, and pathological susceptibility.[6] It is well accepted in the literature that TZ proliferation provides the main contribution to a BPH prostate as it grows, and that 80–85% of PCa arises from the PZ.[1,7,8] Additionally, studies have shown that large BPH prostates develop enhanced capsule thickness and PZ glandular tissue atrophy.[9–12] This review presents studies that apply different technologies and methodologies focusing on the interaction between BPH and development/incidence of PCa. As far as we know, this is the first paper summarizing the data and study results leading to the hypothesis on the protective effects of BPH against PCa.

Hypothesis

During BPH growth, the TZ expands, applying pressure directly on the PZ against the prostatic capsule. This pressure leads to the accumulation of collagen causing fibrosis and glandular tissue atrophy within the PZ, where over 80–85% of PCa arises.[13] This dynamic interaction of the TZ against the PZ in a growing BPH-prostate could explain the negative correlation between BP-size and PCa incidence. In recent years, there have been different studies using

Keywords: Prostate; Benign prostatic hyperplasia; Prostate cancer.

Abbreviations: BPH, benign prostatic hyperplasia; CZ, central zone; MRI, magnetic resonance imaging; PCa, prostate cancer; PCPT, prostate cancer prevention trial; PZ, peripheral zone; TZ, transition zone.

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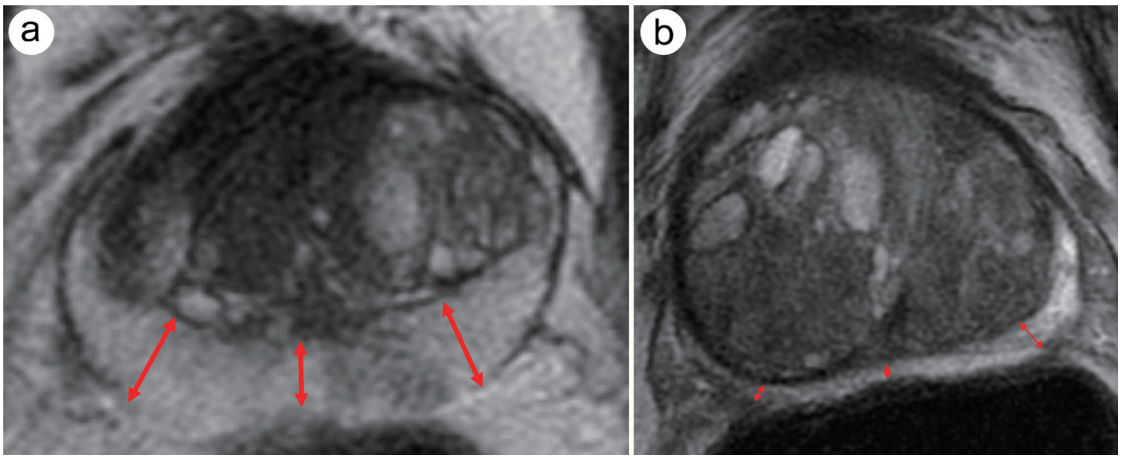

Fig. 1. The 'compression effect' on the PZ in large prostates. (a) MRI example of a small prostate (21 cc): Axial T2 image of the mid-gland region of a prostate showing a thick relative peripheral zone (relative to (b)) delineated by the red arrows; (b) MRI example of a large prostate (124 cc): Axial T2 image of the prostate gland within the mid-gland region of a prostate showing a thin relative peripheral zone (relative to (a)) delineated by the red arrows. MRI, magnetic resonance imaging; PZ, peripheral zone.

different technologies and methodologies all supporting this idea that BPH size matters and may be protective against prostate cancer.

Evaluation of hypothesis

Meta-analysis of prostate size and incidence of PCa in transrectal ultrasound studies

A meta-analysis published in 2021 using PubMed and PRISMA guidelines reviewed the literature over the last 24 years regarding the correlation between prostate size and biopsy-proven PCa incidence. The results indicated that more than 90% of published studies demonstrate a highly significant statistical negative correlation between prostate size and PCa incidence, and the remaining studies lacked adequate statistical power. In this meta-analysis, there were no studies indicating a positive association between prostate size and incidence of PCa.[14]

Study of prostate volume association with pathological features and recurrence

A clinical study published in 2019 examined the association between prostate volume and pathological features as well as biochemical recurrence during follow up. This study revealed that patients with a prostate volume >60 cc were less likely to have high-risk local or node positive disease, or biochemical recurrence post local treatment. Furthermore, this study also confirmed a negative relationship between prostate volume and tumor volume.[15] Additionally, the literature shows a decrease in incidence of tumor upgrading on radical prostatectomy with larger prostate volume (>50 cc), indicating reduced invasiveness.[16]

Mathematical model

In 2019, Lorenzo *et al*. performed computer-based mathematical simulation studies on BPH and development of PCa and found that TZ growth in BPH-prostates mechanically impedes prostate cancer growth within the PZ. These simulation studies indicate that BPH growth in the TZ builds up mechanical stress fields within the prostate leading to deformational states, especially in the PZ, that obstruct tumor growth and limit invasiveness of developing PCa.[13]

MRI study

Magnetic resonance imaging (MRI) is a precise, non-operator dependent and noninvasive imagining technique that allows excellent visualization and measurement of the PZ anatomy within the prostate.[17,18] A recent multiparametric MRI study on biopsy naïve patients investigated the anatomical changes of the PZ in relation to total prostate size. The findings revealed a 'compression effect' on the PZ in large prostates. This phenomenon is presented in Figure 1: (a) shows a small prostate (21 cc) with a thick PZ, whereas (b) shows a large prostate (124 cc) with a much thinner PZ. According to the data of this study, small and midsized prostates presented with a large range and variation of PZ thickness readings. Once the prostate volume reached a volume near 90 cc and above, PZ thickness and volume dropped noticeably, as shown in Figure 2. This MRI study data suggests that the PZ can withstand the mechanical stress of an expanding TZ in a growing BPH prostate to a certain extent only; beyond this level of prostate size the PZ gets compressed.[19]

Histo-anatomical studies

Histo-anatomical studies have examined the impact of prostate volume on capsule thickness and cell density of the glands within the PZ. In this context, it is important to state that the prostatic capsule found in younger males is a so-called 'false capsule' that is located on the posterior and lateral sides around the prostate. However, it is largely absent on the prostate anterior aspect. This 'incomplete' capsule originates from the periprostatic pelvic fascia and includes smooth muscle cell layers and a collagenous outer layer.[20] Large BPH-prostates in elderly men develop additional fibrotic and collagenous layers adjacent and inwardly from the anatomical capsule, causing the anatomical capsule to thicken. Experienced urologists often consider this fibrotic layer in a large BPH prostate the 'surgical capsule'. This nomenclature is due to a common phenomenon oc-

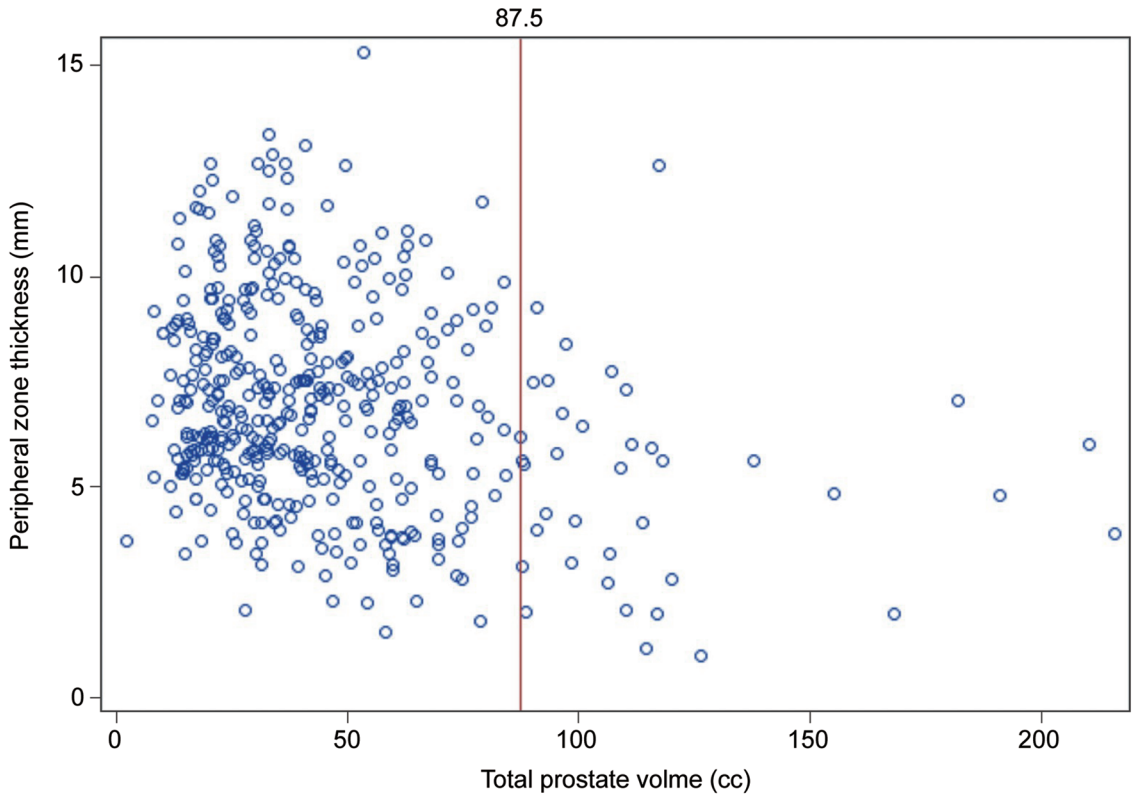

Fig. 2. Scatterplot of total prostate volume (cc) and peripheral zone thickness (mm): Patient measurements are represented by blue dots. The stratification line (87.5 cc) is denoted in red where average PZT appeared significantly lower after 87.5 cc.

curring in large prostates (>80 cc) where BPH and adenoma can be easily removed due to the overlying surgical capsule.[19–21] Additionally, in smaller prostates this occurrence is much less pronounced.

Two recent histo-anatomical studies showed significant structural changes associated with BPH size: not only an increased capsule thickness, but also decreased glandular cell density within the PZ, specifically in large prostates when compared to small prostates.[12,22] These histo-anatomical changes have been well illustrated by Guzman *et al*.[23] As 80–85% of PCa originate in the PZ and as the PZ glandular tissue is vanishing in larger prostates, these findings support the hypothesis that BPH size might have a protective effect against PCa.

Prostate cancer prevention trial

The results found in the Prostate Cancer Prevention Trial (PCPT) can additionally be explained by the previous studies and hypothesis mentioned above. In the PCPT nearly 1,900 patients received continuous Finasteride, a 5-alpha reductase inhibitor (5ARI). The treatment arm showed an over twofold increase in aggressive PCa which contradicted the prestudy idea that Finasteride may be useful as a 'chemoprophylaxis' against PCa. Finasteride as a 5ARI is known to shrink the TZ (the BPH component of the prostate). The bigger the prostate the more pronounced the shrinkage effect. This decrease in TZ volume reduces the mechanical stress on the PZ, thus allowing more space for the growth and recovery of the glandular epithelial tissue within the PZ which leads to increased chances for developing PCa.[24] The PCPT results support the hypothesis that growing and thus more PZ glandular epithelium likely leads to higher chances for developing PCa. The PCPT data was also used by Lorenzo *et al*. in their mathematical model study showing that "the shrinkage of the prostate induced by Finasteride reduces the hydrostatic/mechanical stress on the PZ layer that otherwise would have accumulated over years in the BPH tissue; this leads to a state favoring the development of PCa".[13]

Future directions

At least six different study technologies and methodologies (as listed above) support the hypothesis that BPH-size is providing a protective effect against PCa. Despite extensive review of the literature we could not find any studies contradicting the presented hypothesis. However, we are well aware of deficiencies and shortcomings which should be addressed in future studies:

1. This hypothesis is based on the assumption that BPH initiates earlier in a growing and aging prostate than PCa (and not the other way around).
2. In the mentioned histo-anatomical papers the non-cancerous BPH area in radical prostatectomies was analyzed. This is the only way to study the changes of BPH within the entire prostate as BPH-prostatectomies do not include the prostate capsule, and the TUR tissue chips cannot anatomically be relocated within the prostate gland. Therefore, only low-volume PCa cases are suitable in histo-anatomical studies. Routine autopsies also do not include the entire prostate gland, and prospective autopsy studies for this purpose will take years to collect enough BPH prostates of all different sizes. Furthermore, severe morbidities

causing end of life may also affect the histo-anatomical features of BPH prostates when compared to earlier years in life.
3. Furthermore, in histo-anatomical studies, reconstructing the anatomy from numerous slides of radical prostatectomy specimens can be challenging. Different pathologists use different techniques of sample acquisition which may affect the reconstruction of prostate anatomy. Additionally, slides of interest that are altered by PCa need to be excluded because cancerous tissue leads to disruption of the natural PZ and capsule architecture. Also, capsule thickness can vary between prostate specimens, and the boundary separating prostate capsule and BPH tissue can be challenging to determine.
4. The histo-anatomical studies were all single institutional studies. Multi-institutional study groups using a more diversified population would provide more generalized findings.

Despite these limitations, there are sufficient data and reports that support the hypothesis that BPH size may have a protective effect against PCa. This hypothesis paper should encourage others to examine the relationship between both disease entities. If the outlined hypothesis is correct, it could influence future diagnosis and treatment of both diseases.

Conclusions

The presented hypothesis provides explanations for the negative association between BPH size and PCa incidence, a clinical phenomenon well documented in the literature. The presented studies, different in design, techniques, and methodologies, all support the idea that as the TZ expands in a growing BPH prostate, the PZ gets compressed and thinned, a dynamic biological process leading to fibrosis and atrophy of the PZ glandular tissue where 80–85% of PCa arises. The presented data are barely challenged in the current literature. As BPH and PCa are by far the two most common urological diseases in elderly men, future research should focus on this interaction between both entities. This hypothesis paper should encourage subsequent analysis of this phenomenon by other researchers and clinicians. If the proposed hypothesis of BPH-related protective features against PCa is correct, it could influence future diagnosis and treatment of both diseases.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study conception and design (JS, WD), IRB approval, material preparation, data collection, and analysis (JS, WD), first draft of the manuscript (JS), revisions of the manuscript (JS, WD). Both authors have made a significant contribution and have approved the final manuscript.

Ethical statement

The written informed consent for publication of Figure 1 was exempted by the Institutional Review Board (IRB) of Texas Tech University Health Sciences Center under the approved number L20-147.

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