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Review – Prostatic Disease

Is There Evidence of a Relationship between Benign Prostatic Hyperplasia and Prostate Cancer? Findings of a Literature Review

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Abstract

Context: More than half the male population aged >50 yr have histologic evidence of benign prostatic hyperplasia (BPH), while prostate cancer (PCa) is among the most common male cancers according to recent registry data. Understanding the aetiologies of both conditions is crucial to reduce the resulting burden of mortality and morbidity.
Objective: This review aims to examine the available data on the epidemiology, pathology, risk factors, and genetic markers involved in BPH and PCa; to discuss their clinical implications for management of both conditions; and to discuss their implications for PCa prevention. Our primary objective was to clarify the relationship between BPH and PCa by bringing together evidence from diverse areas of research.
Evidence acquisition: The primary source of data was PubMed, which was searched using Boolean strategies and by scanning lists of related articles. We also examined secondary sources from reference lists of retrieved articles and data presented at recent congresses.
Evidence synthesis: Accumulating evidence suggests that BPH and PCa share important anatomic, pathologic, and genetic links in addition to the well-established epidemiologic association between these conditions. We also found data that suggest interactions between apparently diverse factors, such as dihydrotestosterone levels and inflammation. Recent publications support the hypothesis that both BPH and PCa are part of the metabolic syndrome, while inflammation is emerging as a major contributor to the development of both BPH and PCa. Although many of the findings are preliminary and require further research, they offer new insight into the mechanisms of disease underlying the development of BPH and PCa.
Conclusions: Available data suggest that epidemiologic and pathologic links exist between BPH and PCa. Evidence of links between the conditions and contributory factors may offer common preventative strategies for BPH and PCa and common therapeutic approaches to their management.

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1. Introduction

Both benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are major health concerns that are likely to have an increasing impact in line with the gradual aging of the population. European national registry data show that the prostate is now the most common site of cancer in men (excluding nonmelanoma skin cancers), while BPH affects as many as 62% of men aged >50 yr [1–3]. Lower urinary tract symptoms (LUTS) associated with BPH can seriously impair quality of life, but therapies such as α-blockers and 5-α reductase inhibitors (5-ARIs) offer significant benefits [4–7]. There has also been substantial progress in PCa survival in recent years: the overall 5-yr, age-adjusted, survival rate was 78% for men diagnosed with PCa in 2000–2002, compared with 67% for men who were diagnosed in 1990–1994 [8,9]. It is, however, unclear whether this improved survival rates stems from improvements in the management of PCa or from stage migration to less advanced disease at diagnosis due to more widespread screening and prostate-specific antigen (PSA) measurement.

Effective management of either condition first requires an accurate diagnosis, however, and much research has aimed to help clinicians to distinguish PCa from BPH. At the same time, the similarities between the two conditions and their frequent coexistence raise the question of whether they are linked. Epidemiologic studies have shown that the incidence and prevalence of PCa and BPH rise with increasing age. Both conditions are hormone-dependent, and an expanding body of evidence supports an important role for inflammation. Nevertheless, there is no proven causal relationship between BPH and PCa. PCa arising in the transition zone may be related to BPH (perhaps in association with certain forms of hyperplasia), but BPH is not considered to be a premalignant lesion or a precursor of prostate carcinoma [10].

Further consideration of the potential links between BPH and PCa is warranted in the light of recent advances in our understanding of these diseases. Elucidating these links could prove valuable to inform the management of both conditions in clinical practice. This review aims to contribute to this process by examining current data on the shared characteristics of BPH and PCa, and discussing the potential clinical implications of this evidence.

2. Evidence acquisition

We applied Boolean searches of PubMed using the following search terms: prostate cancer, benign prostatic hyperplasia, inflammation, epidemiology, incidence, prevalence, metabolic syndrome, survival, marker, gene, Asian, oestrogen, and phytoestrogen. All searches were commenced from the year 1980 and restricted to publications in English. We also searched related articles on PubMed, and we identified further relevant articles by manually searching reference lists of identified papers and data presented at recent congresses.

3. Evidence synthesis

Our literature searches identified evidence that supports several links between BPH and PCa. Currently available data confirm that androgens play a central role in the development of both conditions, but inflammation is increasingly emerging as a major causative factor. The metabolic syndrome may also play a role in the development of BPH and PCa, while a number of genetic factors have been implicated.

3.1. *Epidemiologic associations between benign prostatic hyperplasia and prostate cancer*

Both BPH and PCa are increasingly common with advancing age, although evidence suggests that BPH develops earlier than PCa. About 8% of men aged 31–40 yr show histological evidence of BPH, and this rate increases sharply to 50% in men aged 51–60 yr, to 70% in men aged 61–70 yr, and to 90% in men aged 81–90 yr [11]. Clinical BPH, characterised by the occurrence of moderate-to-severe LUTS, occurs in approximately 25% of men aged 50 –59, in 33% of men aged 60 –69, and in 50% of men aged ≥80 yr [11]. Prostate cancer incidence also rises with advancing age, although this increase occurs about 15 yr later than for BPH: a Swiss cancer registry study reported an incidence of 8 prostate cancer cases per 100 000 population in the age range 45–54 yr, compared with 110 cases per 100 000 men aged 55–64 yr. An incidence of 424 prostate cancer cases per 100 000 was shown in men aged 65–74 yr, and an incidence of 883 cases per 100 000 was shown in men aged ≥75 yr [12]. It is possible that current incidence data for PCa underestimates this trend, however, because improved diagnosis and increased attention has boosted detection rates, particularly in the younger age groups. In addition, it remains uncertain how many cancers detected very early would actually progress to become clinically relevant. The Swiss registry study found that the overall age-standardised rate per 100 000 population increased between 1974–1979 and 1990–1994 by 47%, but incidence in

the group aged 45–54 yr increased by 77% over the same time period [12]. A Canadian study reported a 72% increase in age-standardised PCa incidence rates between 1959 and 1989, without a correspondingly rapid climb in mortality [13].

Autopsy data suggest that most prostate cancers (83%) develop in men who also have BPH elsewhere in the prostate, and that this association is consistent across all age ranges [14]. In the pre-PSA era, incidental PCa was found in a significant proportion (>15%) of men undergoing transurethral resection of the prostate (TURP) for symptomatic BPH [15]. However, the rate of PCa newly identified during TURP has decreased substantially in the era of PSA screening, probably because occult disease is now identified earlier, before TURP is necessary [16]. The concurrent development of both conditions gained further support from the baseline data for the Reduction by Dutasteride in Prostate Cancer Events (REDUCE) study, which revealed a 67% prevalence of BPH in men whose PSA levels met the entry criteria as indicators of increased PCa risk [17].

Another study has identified fast-growing BPH as a risk factor for PCa [18]. This analysis of 220 men with recently diagnosed PCa (PSA < 50 ng/ml) revealed a significant link between BPH growth rate (assessed using prostate volume) and both clinical PCa grade and PSA level ($p = 0.018$ and $p = 0.002$, respectively) [18]. More recent reports by the same authors linked fast-growing BPH with advanced stage disease (T3 vs T2) and death from PCa (both $p < 0.001$) [19,20]. Other studies have, however, reported that larger prostate volume may be protective against aggressive PCa. For example, a retrospective study assessed the association between prostate size and PCa grade and stage in a single-centre radical prostatectomy cohort ($n = 3412$) [21]. Prostate volumes of up to 45 cm^3 were associated with higher rates of high-grade cancer, extracapsular extension, seminal vesicle invasion, and larger tumour volume. Above 45 cm^3, the association of prostate volume with these PCa features was in the opposite direction.

3.2. Anatomic relationships

It appears that most PCa originates in the peripheral zone, but one in four arise in the transition zone: histological examination of radical prostatectomy specimens revealed that 68% of adenocarcinomas had arisen in the peripheral zone, and 24% had arisen in the transition zone [22]. The transition zone is also where most BPH originates; it may extend into the peripheral zone and occasionally originate from the peripheral zone [23]. Interestingly, a histologic investigation has reported that about one-third of transition-zone PCas actually originate within BPH nodules [14].

3.3. The role of hormones, inflammation, the metabolic syndrome, and genetics in benign prostatic hyperplasia and prostate cancer

3.3.1. Role of dihydrotestosterone

Androgens are crucial for normal prostate growth and development, as well as the development of BPH and PCa [24,25]. The two isozymes of 5-α reductase (type 1 and type 2) convert testosterone to dihydrotestosterone (DHT), which binds to the androgen receptor and promotes cellular differentiation and proliferation within the prostate [24]. The development of abnormal prostate growth is thought to involve disruption of DHT-supported homeostasis between cell proliferation and cell death, and, as a result, proliferative processes predominate and apoptotic processes are inhibited [24,25]. For PCa, emerging data support a model in which enhanced androgen receptor activity is involved in the early stages of the disease [26]; in well-differentiated tumours, the androgen receptor activates growth-promoting genes, growth-inhibiting genes, and cell-differentiation genes, and, as a result, the growth rate is low. Progression to high-grade disease and metastases involves selective down-regulation of androgen-receptor target genes that inhibit proliferation, induce differentiation, or regulate apoptosis [26].

The key role of DHT in the development of both PCa and BPH prompted the development of 5-ARIs as a treatment for BPH, and potentially, for the prevention of PCa. Large-scale randomised, controlled trials have confirmed the value of dutasteride and finasteride for improving LUTS and for reducing the risk of disease progression in men with BPH [6,7]. The Prostate Cancer Prevention Trial (PCPT) similarly linked finasteride treatment with improved BPH symptoms, and also found a 25% relative risk reduction for PCa detection after 7 yr ($p < 0.001$ vs placebo) [27].

3.3.2. Role of oestrogen

Prostate growth depends on synergistic interactions between oestrogen and androgens. Inducing BPH or PCa in vivo requires a combination of androgen and oestrogen, illustrating the important role of oestrogen in the pathogenesis of prostate disease. The ratio of oestrogen to androgen in the prostate increases by 40% in ageing men, and this may influence the natural history of both BPH and PCa [28].

Oestrogen's role in pathogenic prostate growth may explain, at least in part, why Asian men who follow a traditional diet (which provides a rich supply of phytoestrogens) have a lower prevalence of BPH and PCa than men following a modern Western diet [29] and why PCa incidence among Asian immigrants to the United States is higher than in their respective native populations [30]. Case-control studies have linked a high intake of soy-based foods with a reduced risk of PCa: one such study in 398 Chinese men reported an odds ratio of 0.58 (95% CI: 0.35–0.96) for the highest versus the lowest tertile of tofu consumption [31]. The influence of diet on PCa is complex, however, and other studies have identified fat intake, fish consumption, or well-done meats as risk factors [32–34].

The evidence for a protective role of phytoestrogens has prompted research into using either dietary modification or supplementation with therapeutic extracts, and preliminary studies have yielded promising results [35,36]. Interestingly, a prospective study in a population of 49 509 Japanese men linked soy consumption with a reduced risk of being diagnosed with localised PCa but also with an increased risk of a diagnosis of advanced cancer, suggesting that the protective effect might be specific to certain PCa subtypes [37]. Further studies are required to clarify the role of oestrogens in the development of BPH and different grades of PCa.

3.3.3. *Role of inflammation*

Epidemiologic data reveal a considerable overlap between inflammation (prostatitis) and BPH. The USA Health Professionals Study found that men with BPH were 7.7 times more likely to have a history of prostatitis than men without BPH, and that men with a history of prostatitis were 3.3-fold more likely to have BPH than those without prostatitis [38]. Similarly, another large-scale study found that men with BPH had an odds ratio of 8.0 for a history of prostatitis, while men with a history of prostatitis were twice as likely to have BPH as those without prostatitis [39]. Prostatitis was also linked with worsened urologic symptoms in this study ($p < 0.0001$ vs men without prostatitis).

A biopsy substudy of the Medical Therapy of Prostate Symptoms (MTOPS) trial has yielded some valuable insights into the link between inflammation and BPH [40]. About 40% of baseline biopsy specimens had chronic inflammatory infiltrates; these samples came from men with higher serum PSA levels (3.1 ng/ml vs 2.3 ng/ml) and larger prostate volumes (41 ml vs 37 ml) compared with samples without evidence of inflammation [40] (Table 1). In addition, men in the placebo group with inflammatory infiltrates were more likely to suffer BPH progression than those without inflammation (21% and 13.2%, respectively; $p = 0.08$); similar nonsignificant trends were observed for increased symptom scores and invasive treatments [40]. Acute urinary retention only occurred in men with inflammation at baseline (5.6% vs 0%, $p = 0.003$).

These data suggest that inflammation contributes to the development of BPH, rather than occurring in response to the altered tissue architecture resulting from BPH. Prospective studies with predefined end points and power to detect such a causative link would be useful to confirm this finding.

Emerging evidence also suggests a role for inflammation in the pathogenesis of PCa. In one study, needle biopsy specimens from men with clinical signs to suggest malignancy revealed a significant link between inflammation and serum PSA [41]. Repeat biopsies after 5 yr detected new cases of PCa in 20% of men with inflammation at baseline, compared with just 6% of men without inflammation. Studies of genetic polymorphisms provide further support for a link between inflammation and PCa. For example, the genes *MSR1* (macrophage scavenger receptor 1) and *RNASEL* (RNAse L), which encode proteins involved in host response to infection, have both been implicated in susceptibility to PCa [42–46].

Table 1 – Inflammation at baseline and benign prostatic hyperplasia (BPH) severity in the Medical Therapy of Prostate Symptoms (MTOPS) study [40]

	Baseline prostate size, ml	Baseline PSA level, ng/ml	Progression, %	Increase in IPSS, %	Invasive therapy, %	AUR, %
Chronic inflammatory infiltrates at baseline	41	3.1	21	13.7	7.3	5.6
No chronic inflammatory infiltrates detected at baseline	37	2.3	13.2	11.2	11.2	0

PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; AUR = acute urinary retention.

Table 2 – Benign prostatic hyperplasia (BPH) disease characteristics (a) and prostate cancer risk (b) according to body mass index (BMI).

	BMI, kg/m^2					*p* value
	<25	≥25–<27.5	≥27.5–<30	≥30–<35	≥35	
(a) Baseline parameters according to BMI categories in the CombAT study [59]						
Fasting insulin, pmol/l	57.0	63.4	81.8	100	120.9	<0.001
IPSS (screening)	19.1	18.6	19.3	19.4	19.9	<0.02
PV, cm^3	51.5	53.0	57.3	59.1	65.2	<0.001
TZV, cm^3	25.8	26.9	31.1	35.7	32.0	<0.001

	BMI, kg/m^2					*p* value (for trend)
	<25	≥25–<27.5	≥27.5–<30	≥30–<35	≥35	
(b) Relative risk (RR)* of prostate cancer incidence according to BMI categories in the Cancer Prevention Study II nutrition cohort [61]						
All cases	1.00 (reference)	1.02	0.98	0.94	0.91	0.14
Nonmetastatic low grade	1.00 (reference)	1.03	0.92	0.86	0.84	0.002
Nonmetastatic high grade	1.00 (reference)	0.87	1.23	1.22	–	0.03
Stage D or fatal cases	1.00 (reference)	1.41	1.14	1.54	–	0.05

IPSS = International Prostate Symptom Score; PV = prostate volume; TZV = transition zone volume.
RR adjusted for age at interview, race, education, smoking status, family history of prostate cancer, total calorie intake, history of prostate-specific antigen testing, history of diabetes, and physical activity.

Another gene, *GSTpi* (coding for glutathione S-transferase), seems to protect against carcinogenesis and is downregulated in PCa [34,47]. *GSTpi* is upregulated, however, in proliferative inflammatory atrophy (PIA; discrete foci with simple atrophy or postatrophic hyperplasia associated with inflammation), possibly in response to oxidative stress due to inflammation [48]. A subset of PIA foci demonstrate *GSTpi* hypermethylation, offering a putative mechanism for progression to PCa either directly or via prostatic intraepithelial neoplasia (PIN) [49]. Further evidence comes from histological examination of 629 high-grade PIN (HGPIN) lesions from 14 radical prostatectomy samples, which revealed frequent morphological transitions between HGPIN and PIA [50]. This study also documented frequent occurrences of small carcinoma lesions in the vicinity of focal atrophy. Interestingly, immunohistochemical data indicate that *GSTpi* is upregulated in benign prostate ducts and the secretory acinar epithelium following long-term finasteride treatment [51]; these authors speculate that the chemopreventive effect of this drug could be mediated, in part, by upregulation of *GSTpi* expression.

Further studies are required to fully define the role of inflammation in the development of both BPH and PCa, but accumulating evidence suggests that inflammation and prostatic growth (both benign and malignant) may be closely interrelated in a continuum of progressive disease. In vivo studies have also linked raised androgen levels with inflammatory carcinogenesis, and demonstrated a beneficial effect of androgen blockade using a 5-ARI [52,53].

3.3.4. *Metabolic syndrome*

There is evidence that both BPH and PCa are components of the metabolic syndrome. The term metabolic syndrome is used to describe the coexistence of a cluster of atherosclerotic risk factors including visceral obesity, insulin resistance, dyslipidaemia, and hypertension [54]. Hyperinsulinaemia, dyslipidaemia, elevated blood pressure, and obesity have all been identified as risk factors for the development of both BPH and PCa [19,20,55–58].

Analysis of screening and baseline data from 4820 men who entered the Combination of Avodart and Tamsulosin (CombAT) trial revealed a significant correlation between higher body mass index (BMI) categories and LUTS severity, prostate volume, and transition zone volume ($p < 0.02$, $p < 0.001$, $p < 0.001$, respectively) [59] (Table 2a). Several studies have also linked the metabolic syndrome with fast-growing BPH, which as described previously may be a stronger risk factor for the development of PCa than slow-growing BPH [18,55,60].

Data have also revealed an association between metabolic syndrome and PCa progression, severity or outcome. In a study of 299 men with recently diagnosed PCa, those who had hyperinsulinaemia, hypertriglyceridaemia, or were obese were more likely to have high-grade than low-grade PCa ($p = 0.019$, $p = 0.019$, and $p = 0.044$, respectively) [20]. Type 2 diabetes, hyperinsulinaemia, and treated

hypertension have also been associated with fatal PCa ($p < 0.035$, $p = 0.004$, $p < 0.023$, respectively, vs survivors with PCa) [19].

Increasing BMI has been associated with an increased risk of aggressive PCa in the Cancer Prevention Study II nutrition cohort ($n = 69\ 991$ men); obese men (BMI $\geq$30 kg/m^2) had a 1.54 relative risk of metastatic or fatal cancer compared with men whose BMI was $<$ 25 kg/m^2 [61] (Table 2b). This finding is consistent with some previous reports that obesity is a risk factor for more aggressive PCa [62,63]. Changes in testosterone or insulin levels associated with obesity might explain the increased risk of aggressive PCa with increasing BMI [61]. Of interest, the risk of nonmetastatic low-grade PCa in the Cancer Prevention Study II cohort decreased with increasing BMI [61].

3.3.5. *Genetic alterations*

Malignancy is characterised by genomic alterations that allow proliferation, while BPH may be viewed as an overgrowth of ''normal'' epithelium, suggesting that genetic and/or protein alterations can distinguish between these conditions. Indeed, considerable research efforts are dedicated to identifying the genetic and/or protein alterations that may help to distinguish malignant from benign prostate growth [64]. However, a number of genetic alterations common to both conditions have also been identified. A microarray study including a nonredundant set of 511 genes has revealed genetic overlap between BPH and PCa [65]. A cluster of genes of unknown function distinguished asymptomatic BPH from all other samples, while a cluster of proliferation genes identified symptomatic BPH, and oncogenes identified BPH that had coexisted with PCa [65]. Symptomatic BPH and BPH with cancer also shared two gene clusters (designated cytokines and inflammation), suggesting that symptomatic BPH is linked more closely to PCa than to asymptomatic BPH [65].

Genes that encode enzymes involved in steroid hormone synthesis or function, such as *CYP17* (which encodes the cytochrome P450c17α enzyme involved in the genesis of human sex steroid hormones) and *SRDAR2* (which encodes steroid alpha reductase type II) have attracted attention as potential markers of PCa and BPH [66,67]. A genotyping analysis study, using blood samples from Japanese men with PCa ($n = 252$), BPH ($n = 202$), or male controls ($n = 131$), found that a polymorphism in the promoter region of the *CYP17* gene distinguished both BPH and PCa from controls [66]. There was no difference in genotype frequency according to tumour grade or stage, or the presence of metastases [66]. Another study, in Turkish men, found no association between this same polymorphism and PCa, although an association with BPH was identified ($p = 0.004$) [68]. In the same study, a polymorphism in the promoter region of the PSA gene was found to be associated with both PCa and BPH.

The associations between *SRDAR2* polymorphisms (*V89L*, *A49T*) and BPH or PCa have been examined in a multiethnic population of 606 men ($n = 100$ with PCa, $n = 393$ with BPH, $n = 113$ with normal prostates) [67]. The presence of the *L89L* genotype had an overall odds ratio for PCa of 4.47 (95% CI: 1.24–16.18) compared with the *VV* genotype [67]. This association was stronger in Hispanics (OR = 7.26; 95% CI: 1.49–35.47). Although *V89L* was nonsignificantly associated with BPH in the overall population, BPH risk increased significantly with the number of L alleles in Hispanics (p for trend = 0.03). Prostate cancer and BPH were not associated with the *A49T* polymorphism. In another study of 357 Swedish men, *SRD5A2* high-activity allele variants *A49T AT* and *V89L LL* were more frequent in patients with PCa compared with the general population ($p = 0.026$ and $p = 0.05$, respectively). Prostate cancer progression was, however, independent of *SRD5A2* variants [69].

Gene rearrangements have been implicated in a number of cancers, and have recently been uncovered in patients with PCa. One such rearrangement involves the androgen-regulated *TMPRSS2* gene and the ets-related genes (*ERG*) that encode transcription factors. The fusion of these genes has been reported in 40–80% of patients with PCa, approximately 20% of PIN cases, but rarely in benign prostatic tissue [70,71]. In a study of 252 men with stage T1a/b PCa who were followed for a median of 9 yr, *TMPRSS2-ERG* gene fusion was significantly associated with tumours with a Gleason score $>$7 and also with PCa mortality and/or metastatic disease [72]. *TMPRSS2-ERG* rearrangement leads to androgenic induction of *ERG* expression. The biological functions of *ERG* overexpression in PCa are not completely understood. A recent study suggests that *ERG* overexpression in prostate tumour cells may activate the oncogene *C-MYC* and also abrogate prostate epithelial differentiation [73].

Epigenetic processes, such as DNA methylation, represent another mechanism of gene regulation. A number of genes have been identified that are commonly hypermethylated, and therefore inactivated, during PCa progression [74]. Some of these are thought to be tumour suppressor genes (eg, *APC*, *RASSF1A*), while others have a role in cell-cycle regulation (*14-3-3σ*) or heavy metal binding (*MT1G*),

or encode for proteins such as ABC transporters (*MDR1*), glutathione S-transferase (*GSTpi*), and glutathione peroxidase (*GPX3*). Some of these genes (eg, *RASSF1A*, *14-3-3σ*, *MT1G*, and *MDR1*) have also been found to be hypermethylated in BPH tissues, indicating a role for this epigenetic alteration in benign prostatic growth [74–77].

4. Conclusions

Evidence is accumulating to support pathologic links between BPH and PCa in addition to the well-established epidemiologic associations. Anatomic and genetic data also suggest that many prostate cancers are associated with preexisting BPH.

The rate of BPH growth is gaining increasing support as both a predictive and prognostic factor for PCa: fast-growing BPH is linked with an increased risk of developing PCa, and an increased likelihood that such cancer will be high-stage or grade. This is interesting given the knowledge that 5-ARIs arrest the underlying disease in BPH by reducing, and maintaining reductions in, prostate volume and that the PCPT study showed that treatment with a 5-ARI can also significantly reduce the risk of PCa development.

Inflammation is also becoming well-established as a risk factor for both benign and malignant prostate growth, and possibly for progression from BPH to PCa. Microarray studies have indicated overlap of clusters of genes involved in inflammation between BPH and PCa. In addition, raised androgen levels have been implicated in inflammation associated with PCa.

Accumulating data also suggest that we should view BPH and clinical PCa as part of the metabolic syndrome, with interesting implications for clinical management. Physicians should consider the possible presence of type 2 diabetes, hyperinsulinaemia, and dyslipidaemia in any patient who presents with BPH or PCa. Conversely, patients with metabolic syndrome characteristics may be at elevated risk of PCa or BPH. Raised insulin levels have been particularly strongly connected with PCa development and could potentially be used as a marker of tumour aggressiveness and prognosis.

A major limitation of these findings is that studies conducted to date are largely hypothesis-generating rather than hypothesis-confirming. Consequently, further research is required before firm conclusions can be drawn on the precise nature, and clinical significance, of these links. As our knowledge grows and underlying pathologies involved in both BPH and PCa are further characterised, common preventative strategies and therapeutic approaches may emerge. New and upcoming data offer the potential to optimise both treatment and prevention of these commonly coexisting diseases.

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Study concept and design: Alcaraz, Castro.
Acquisition of data: Alcaraz, Hammerer, Tubaro, Schröder, Castro.
Analysis and interpretation of data: Alcaraz, Hammerer, Tubaro, Schröder, Castro.
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Editorial Comment on: Is There Evidence of a Relationship between Benign Prostatic Hyperplasia and Prostate Cancer? Findings of a Literature Review

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Prostate cancer and benign prostatic hyperplasia (BPH) are two highly prevalent diseases affecting adult and elderly men. Although both are the subject of intense preclinical and clinical research, their etiologies are not completely understood. Traditionally, the two conditions are considered as two distinguished and unrelated diseases, although several issues suggest possible linkages. Specifically, both are hormone-dependent diseases, their incidence increases with age, and they often coexist in the same patients. Moreover, inhibitors of 5-α reductase, which are quite an effective treatment for patients with lower urinary tract symptoms due to benign prostatic enlargement and BPH, have been shown to prevent the occurrence of prostate cancer in the Prostate Cancer Prevention Trial (PCPT); another similar trial, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, is ongoing with dutasteride [1,2].

Alcaraz et al reported an interesting nonsystematic review of the literature on the relationship between prostate cancer and BPH [3]. The purposes of the review were quite ambitious, although the available literature probably does not justify a review. On the whole, the authors concluded that the published studies generated more hypotheses than they could confirm.

In my opinion, the possible role of inflammation [4] and the correlations among BPH, prostate cancer, and metabolic syndrome [5] are the most appealing and promising field of research. To date, however, as correctly stated by the authors, no causal relationships have been proven among those conditions, and further studies are much needed.

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Editorial Comment on: Is There Evidence of a Relationship between Benign Prostatic Hyperplasia and Prostate Cancer? Findings of a Literature Review

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Well-known risk factors for prostate cancer (PCa) include age, androgens, and environmental and genetic factors [1–3]. Benign prostatic hyperplasia (BPH) is a disease of the aging male and is frequently coexistent with PCa. The current review paper from Alcaraz et al emphasizes recent work indicating that PCa is associated with BPH and gives new insights and help understanding the etiologies of BPH and PCa [4]. The authors refer to anatomic, pathologic, and genetic links but also stress the common influence of steroid hormones, inflammation, and metabolic syndrome on both conditions. One has to appreciate that the authors try to cover many aspects of potential relationship between BPH and PCa, but this comprehensive approach leaves little space for more detailed discussion, including conflicting articles or data. Available epidemiologic data suggesting a relationship between BPH and PCa or possible *pathomechanisms* like inflammation or metabolic disorders are limited by significant detection and selection bias. They could often just describe a simple coincidence of these conditions. The real incidence of PCa, BPH, or inflammation is uncertain, and often, the diagnosis of BPH or inflammation is only clinical. Men with symptoms or elevated prostate-specific antigen (PSA) due to BPH or prostatitis are more likely to undergo biopsies. Furthermore, BPH causing urinary retention may facilitate prostatic inflammation.

In our own series of 364 consecutive radical prostatectomies, just 7% of cancers were found only in the transition zone [5], where most of BPH originates. Sometimes well-differentiated cancer in the transition zone seems to emerge directly from BPH nodules. The current concept of preneoplastic lesions of the prostate is still incomplete, and nowadays, most pathologists negate a relevant role of the only morphological link between BPH and PCA, termed *atypical adenomatous hyperplasia* (AAH). Probably the most promising approach for revealing a common origin of BPH and PCa is to compare the genetic fingerprint of both diseases. Several studies, however, have produced conflicting results, and due to the common prostatic origin of BPH and PCa, a huge natural molecular overlap can be expected.

Taken together, despite the similarities and the high coincidence of BPH and PCa, we are still far from proving a causal link between these conditions.

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