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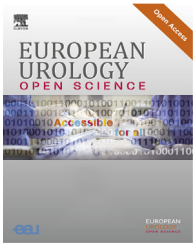

Benign Prostatic Hyperplasia

Shared Inherited Genetics of Benign Prostatic Hyperplasia and Prostate Cancer

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Abstract

Background: The association between benign prostatic hyperplasia (BPH) and prostate cancer (PCa) remains controversial, largely due to a detection bias in traditional observational studies.
Objective: To assess the association between BPH and PCa using inherited single nucleotide polymorphisms (SNPs).
Design, setting, and participants: The participants were White men from the population-based UK Biobank (UKB).
Outcome measurements and statistical analysis: The association between BPH and PCa was tested for (1) phenotypic correlation using chi-square, (2) genetic correlation (r_g) based on genome-wide SNPs using linkage disequilibrium score regression, and (3) cross-disease genetic associations based on known risk-associated SNPs (15 for BPH and 239 for PCa), individually and cumulatively using genetic risk score (GRS).
Results and limitations: Among 214 717 White men in the UKB, 24 623 (11%) and 14 311 (6.7%) had a diagnosis of BPH and PCa, respectively. Diagnoses of these two diseases were significantly correlated (χ^2 = 1862.80, p < 0.001). A significant genetic correlation was found (r_g = 0.16; 95% confidence interval 0.03–0.28, p = 0.01). In addition, significant cross-disease genetic associations for established risk-associated SNPs were also found. Among the 250 established genome-wide association study–significant SNPs of PCa or BPH, 49 were significantly associated with the risk of the other disease at p < 0.05, significantly more than expected by chance (N = 12, p < 0.001; χ^2 test). Furthermore, significant cross-disease GRS associations were also found; GRS_{BPH} was significantly associated with PCa risk (odds ratio [OR] = 1.26 [1.18–1.36], p < 0.001), and GRS_{PCa} was significantly associated

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with BPH risk (OR = 1.03 [1.02–1.04], $p < 0.001$). Moreover, GRS_{BPH} was significantly and inversely associated with lethal PCa risk in a PCa case-case analysis (OR = 0.58 [0.41–0.81], $p = 0.002$). Only White men were studied.

Conclusions: BPH and PCa share common inherited genetics, which suggests that the phenotypic association of these two diseases in observational studies is not entirely caused by the detection bias.

Patient summary: For the first time, we found that benign prostatic hyperplasia and prostate cancer are genetically related. This finding may have implications in disease etiology and risk stratification.

1. Introduction

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are two of the most common diseases in men, and the incidence for both conditions increases considerably with age [1,2]. These two pathological processes negatively impact quality of life and result in considerable healthcare expense. BPH is a histological diagnosis characterized by a proliferation of both stromal and epithelial cells in the transitional zone of the prostate [3]. This proliferation can lead to bladder outlet obstruction and subsequent lower urinary tract symptoms (LUTS). PCa, on the contrary, is a malignant adenocarcinoma primarily found in the peripheral zone of the prostate and, prior to metastasis, is typically asymptomatic, being primarily detected by prostate-specific antigen (PSA) screening [4].

Despite the major differences in cellular growth patterns and stereotyped locations within the prostate, a link between BPH and PCa has been hypothesized, studied, and reported [5,6]. Their co-occurrence was first documented from autopsy studies in 1957 and 1992 [7,8]. Since then, conflicting results were reported in many studies [9–15]. To date, no consensus has been reached on their association and causal relationship [6]. Consequently, the current National Cancer Institute website states that "BPH is not linked to cancer and does not increase your risk of getting PCa" [16].

A major cause for the inconclusive findings is the inherent detection bias of observational studies in diagnosing these two diseases. Patients treated by urologists for one of these diseases are more likely to be examined thoroughly and are therefore more likely to be diagnosed for the other disease [17]. This detection bias is particularly prominent because the likelihood of diagnosing BPH and PCa increases with heightened prostate examinations and diagnostic evaluations that include PSA measurements [18,19]. Conversely, patients diagnosed with PCa on initial evaluation who are subsequently treated for PCa may never be given a diagnosis of symptomatic BPH, even though histological BPH may be present in the transition zone at the time of prostatectomy. Furthermore, patients treated with androgen deprivation therapy and/or radiation are unlikely to be given a diagnosis of BPH as the cause of any subsequent LUTS.

Inherited single nucleotide polymorphisms (SNPs) offer an alternative approach to assess the association between BPH and PCa. Genome-wide SNPs can be used to estimate the polygenic heritability of each disease and the genetic correlation between the two diseases [20]. This alternative approach does not directly test phenotypic co-occurrence of the two diseases. Instead, it tests the correlation between heritability of individual diseases, which is estimated only from the respective diseases and is therefore not susceptible to the detection bias. Furthermore, established risk-associated SNPs for each disease make it possible to perform a cross-disease association [21,22].

The primary hypothesis of this study is that BPH and PCa are linked, and that this association is partially contributed by shared inherited genetics via the same genes (causal or pleotropic effects) and/or different genes in linkage disequilibrium (LD). This hypothesis was tested in a large population-based cohort.

2. Patients and methods

2.1. Participants

The participants were from the UK Biobank (UKB), a population-based study with genetic and phenotypic data for approximately 500 000 individuals from across the UK, aged 40–69 yr at recruitment (accessed under application number: 50295) [23]. Extensive phenotypic and genomic information, including disease diagnosis, questionnaire, and biomarkers, is available for each participant in the UKB. Diagnoses of BPH (Data-Field 132073) and the procedure for transurethral resection of the prostate (TURP; Data-Field 41200, 41210, and 41272), as well as diagnosis of PCa (Data-Field 40001, 40002, 40006, 41202, 41204, and 41270) were provided by the UKB based on the ICD-10 code and/or self-reports (released on July 9, 2021). Information on PCa-specific death (lethal PCa) was based on death registries (Supplementary Fig. 1). Genome-wide SNP data are available for all participants.

2.2. SNPs and polygenic risk score

Independent risk-associated SNPs for BPH and PCa included in this study were established using an evidence-based review of published genome-wide association studies (GWASs; defined as $p < 5 \times 10^{-8}$ and pairwise LD [$r^2 < 0.2$]) and are available in the UKB, including 15 for BPH and 239 for PCa. Their SNP ID, risk and reference alleles, odds ratio (OR), allele frequency, and references are described in Supplementary Table 1.

The cumulative effect of SNPs on each disease was measured by genetic risk score (GRS), a population-standardized polygenic risk score. GRS was calculated by multiplying the per-allele OR with the number of

risk alleles of each SNP and normalizing the risk by the average risk expected in the population [24]. Specifically, GRS was calculated for each disease as follows:

$$\mathrm{GRS} = \prod_{i=1}^{n} \frac{OR_i^{g_i}}{W_i}$$

$$W_i = f_i^2 OR_i^2 + 2f_i(1-f_i)OR_i + (1-f_i)^2$$

where g_i stands for the number of risk alleles (0, 1, or 2) of genotype for SNP i in an individual, OR_i stands for the OR of an SNP i estimated from external studies, and f_i stands for the risk allele frequency of SNP i based on gnomAD (NFE population). As such, GRS value can be interpreted as a relative risk to the general population regardless of the number of risk-associated SNPs used in GRS calculation.

2.3. Statistical analysis

The phenotypic correlation between BPH and PCa diagnosis was assessed using a chi-square test. The strength of association (OR and 95% confidence interval [CI]) between the two diseases was estimated using multivariable logistic regression adjusting for age at recruitment and genetic background (top ten principal components provided by the UKB).

SNP-based heritability (h^2) for BPH and PCa, and the genetic correlation (r_g) between BPH and PCa were estimated based on polymorphic SNPs (minor allele frequency >0.01) in the genome using a linkage disequilibrium score regression analysis [20]. Briefly, GWASs of BPH and PCa were first performed using individual-level data adjusting for age at recruitment and genetic background (top ten principal components), as well as the other disease (to reduce the impact of the detection bias on estimating SNP effect for disease association; Supplementary Fig. 1). GWAS summary statistics of BPH and PCa were then matched to the precomputed LD scores of the 1000 Genomes European reference to estimate h^2 for BPH and PCa and r_g between BPH and PCa, respectively. SNP heritability estimates were converted to the liability scale based on the observed prevalence in the UKB.

The cross-disease genetic association for BPH and PCa was tested based on known risk-associated SNPs (individually and cumulatively, as measured by GRS) of these two diseases. The association of individual SNPs and GRS with cross-disease risk was tested, adjusting for age at recruitment and genetic background.

3. Results

Among 214 717 White men in the UKB, 24 623 (11%) and 14 311 (6.7%) had a diagnosis of BPH and PCa, respectively (Table 1). Diagnoses of these two diseases were significantly correlated (χ^2 = 1862.80, p < 0.001). Specifically, 3231 (1.5%) men had a diagnosis of both BPH and PCa, which was significantly higher than the expected number of 1332 (0.62%) men, assuming that the diagnosis of these diseases were independent (χ^2 = 797.96, p < 0.001). Having a diagnosis of PCa was associated with an OR (95% CI) of 1.58 (1.51–1.65) for also having a diagnosis of BPH (p < 0.001). Conversely, having a diagnosis of BPH was associated with an OR (95% CI) of 1.57 (1.50–1.64) for PCa diagnosis (p < 0.001). These ORs were estimated adjusting for age at recruitment and genetic background.

Genetic susceptibility to BPH and PCa was estimated based on polymorphic SNPs across the genome (minor allele frequency >1%). SNP-based heritability or h^2 (95% CI) was 0.09 (0.07–0.11) for BPH (p < 0.001) and 0.16 (0.12–0.20) for PCa (p < 0.001; Fig. 1 and Supplementary Fig. 1). Furthermore, a significant and positive genetic correlation between the two diseases was found (r_g [95% CI]: 0.16 [0.03–0.28], p = 0.01).

When examining established risk-associated SNPs for BPH and PCa, significant cross-disease genetic associations were found. Among the 250 risk-associated SNPs of PCa or BPH from previous GWAS studies, 49 were significantly associated with the risk of the other disease at p < 0.05, which was significantly more than expected by chance (N = 12, p < 0.001 [χ^2 test]). Specifically, among the 239 established independent PCa risk–associated SNPs, 43 were associated with BPH diagnosis at p < 0.05 (Fig. 1 and Supplementary Table 1). Reciprocally, among the 15 established independent BPH risk–associated SNPs, ten were associated with PCa diagnosis at p < 0.05. Four established GWAS-significant risk-associated SNPs of PCa and BPH overlapped.

Table 1 – Diagnosis of BPH and PCa among White men in the UKB (N = 214 717)

Diagnosis	No. (%) of men	Age (yr), median (IQR)	
		At recruitment	Age at diagnosis
BPH			
Any BPH	24 623 (11)	63.5 (60.5–66.5)	62.3 (57.31–67.19)
TURP [a]	5704 (27)	64.5 (61.5–67.5)	61.58 (57.07–66.31)
Non-TURP [a]	15 833 (73)	63.5 (59.5–66.5)	62.57 (57.4–67.41)
PCa			
Any PCa	14 311 (6.7)	63.5 (59.5–66.5)	65.35 (60.08–69.16)
Lethal PCa	692 (4.8)	65.5 (62.5–68.5)	65.5 (61.02–69.46)
Nonlethal PCa	13 619 (95)	63.5 (59.5–66.5)	65.33 (60.8–69.12)
Both BPH and PCa	3231 (1.5)	64.5 (61.5–67.5)	62.57 (58.06–67.12) [b]
Neither BPH or PCa	179 014 (83)	57.5 (49.5–63.5)	–

BPH = benign prostatic hyperplasia; IQR = interquartile range; PCa = prostate cancer; TURP = transurethral resection of the prostate; UKB = UK Biobank.
[a] Number of patients with missing data for TURP: N = 49 817.
[b] Based on earlier age at diagnosis of BPH and PCa.

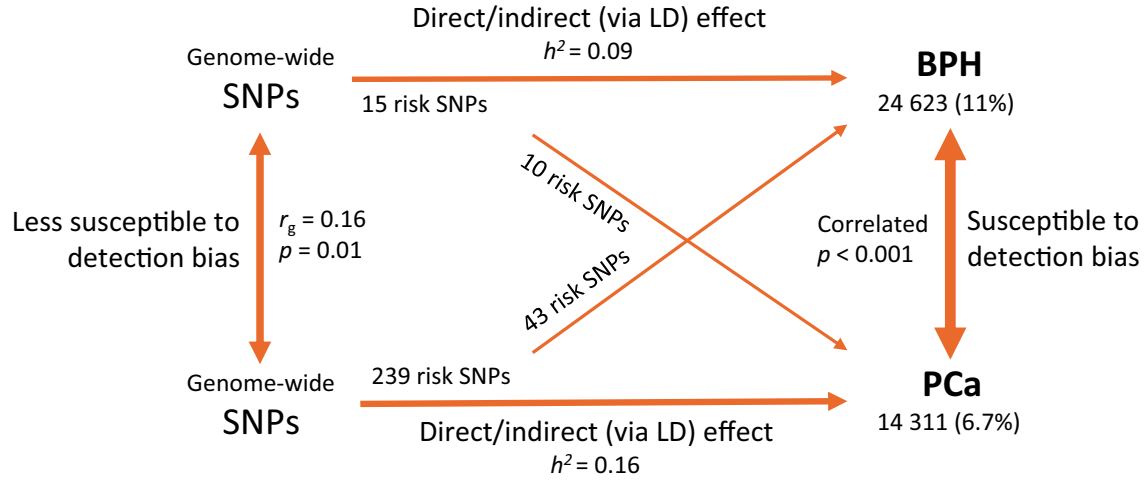

Fig. 1 – Summary of findings for the phenotypic and genetic link between BPH and PCa in White men of the UKB. First, diagnoses of BPH and PCa were significantly correlated (bidirectional arrows on the right side, $p < 0.001$). Second, inherited polygenic background contributed to the diagnosis of each disease (horizontal arrows, h^2 of 0.09 and 0.16 for BPH and PCa, respectively). Third, polygenic backgrounds for BPH and PCa were significantly correlated (bidirectional arrows on the left side, $r_g = 0.27$, $p < 0.001$). Last, cross-disease association of established risk-associated SNPs for BPH and PCa was found (diagonal arrows). These findings provide strong statistical evidence that diagnoses of BPH and PCa are linked, and the excessed co-occurrence of these two diseases was in part contributed by inherited genetics and not entirely driven by the detection bias. BPH = benign prostatic hyperplasia; LD = linkage disequilibrium; PCa = prostate cancer; SNP = single nucleotide polymorphism; UKB = UK Biobank.

Table 2 – Performance of GRS for predicting disease risk in the UK Biobank (N = 214 717)

GRS (no. of risk SNPs)	Comparison	Sample size	Association test [a]	
			OR (95% CI)	p value
GRS_{BPH} (15 SNPs)	BPH cases vs controls	24 623 vs 190 094	2.39 (2.26–2.52)	<0.001
	BPH-TURP cases vs controls	5704 vs 205 927	3.61 (3.26–3.98)	<0.001
	BPH-TURP cases vs BPH non-TURP cases	,704 vs 15 833	2.01 (1.78–2.26)	<0.001
	PCa cases vs controls	14 311 vs 200 406	1.26 (1.18–1.36)	<0.001
	Lethal PCa cases vs controls	692 vs 214 025	0.74 (0.53–1.02)	0.07
	Lethal PCa cases vs nonlethal PCa cases	692 vs 13 619	0.58 (0.41–0.81)	0.002
GRS_{PCa} (239 SNPs)	BPH cases vs controls	24 623 vs 190 094	1.03 (1.02–1.04)	<0.001
	BPH-TURP cases vs controls	5704 vs 205 927	1.04 (1.02–1.07)	0.001
	BPH-TURP cases vs BPH non-TURP cases	5704 vs 15 833	1.02 (0.99–1.06)	0.1
	PCa cases vs controls	14 311 vs 200 406	1.53 (1.51–1.55)	<0.001
	Lethal PCa cases vs controls	692 vs 214 025	1.25 (1.21–1.29)	<0.001
	Lethal PCa cases vs nonlethal PCa cases	692 vs 13 619	0.99 (0.94–1.04)	0.8

BPH = benign prostatic hyperplasia; CI = confidence interval; GRS = genetic risk score; OR = odds ratio; PCa = prostate cancer; SNP = single nucleotide polymorphism; TURP = transurethral resection of the prostate.
[a] Adjusting for age at recruitment and genetic background (top ten principal components).

We also evaluated the cumulative effect of SNPs on disease risk. In addition to highly significant associations between disease-specific GRS and their respective disease risks, significant cross-disease associations were also found (Table 2). GRS based on the 15 established BPH risk–associated SNPs was positively associated with PCa diagnosis (OR = 1.26, $p < 0.001$). Similarly, GRS based on the 239 established PCa risk–associated SNPs (GRS_{PCa}) was significantly associated with BPH diagnosis (OR = 1.03, $p < 0.001$).

Furthermore, GRS was also associated with specific phenotypes of BPH and PCa (Table 2). Notably, GRS_{BPH} was inversely associated with lethal PCa risk when comparing lethal PCa cases versus nonlethal PCa cases (any PCa patients who did not die from the disease, OR = 0.58, $p = 0.002$). Upon examining the results by GRS_{BPH} deciles (Supplementary Table 2), while no trend of lethal PCa prevalence with GRS_{BPH} deciles was found ($p = 0.1$), the prevalence of lethal PCa in men of the highest GRS_{BPH} decile was 0.23%, noticeably lower than that of the remaining deciles (0.33%, $p = 0.02$). In contrast, the prevalence of nonlethal PCa increased slightly with higher GRS_{BPH} deciles ($p_{trend} = 0.01$), with the highest rate (6.6%) found in men of the top GRS_{BPH} decile. As for GRS_{PCa}, no association with lethal PCa was found in a case-case analysis (OR = 0.99, $p = 0.8$). The prevalence of both lethal and nonlethal PCa increased by each decile at a similar scale (Supplementary Table 2).

In light of the genetic correlation and cross-disease association of GRS between these two diseases, we next explored the clinical utility of using two GRS values for predicting the diagnosis of BPH, PCa, and both diseases (Table 3 and Fig. 2). For example, using a GRS of 1.5 as a cutoff value (ie, a 1.5-fold increased risk over the general population), men with both high GRS_{BPH} and high GRS_{PCa} had a considerably higher prevalence of these two diseases than men with both low

Table 3 – Strategy for identifying high-risk men for BPH and PCa using GRS_{BPH} and GRS_{PCa}

GRS strategy for risk stratification			Prevalence, no. (%)				
GRS_{BPH}	GRS_{PCa}	No. (%) of men[a]	Any BPH	Any PCa	BPH and PCa	BPH TURP[a]	PCa lethal
<1.5	<1.5	158 857 (80)	17 753 (11)	8138 (5.1)	1894 (1.2)	4026 (3.3)	400 (0.25)
<1.5	≥1.5	32 021 (16)	3739 (12)	4502 (14)	916 (2.9)	885 (3.6)	218 (0.68)
≥1.5	<1.5	5612 (2.8)	973 (17)	328 (5.8)	122 (2.2)	283 (6.5)	6 (0.11)
≥1.5	≥1.5	1304 (0.66)	220 (17)	204 (16)	49 (3.8)	75 (7.4)	6 (0.46)

BPH = benign prostatic hyperplasia; GRS = genetic risk score; PCa = prostate cancer; TURP = transurethral resection of the prostate.
[a] Number of patients with missing data: 16 907 for GRS_{BPH}, 5331 GRS_{PCa}, and 49 817 for TURP.

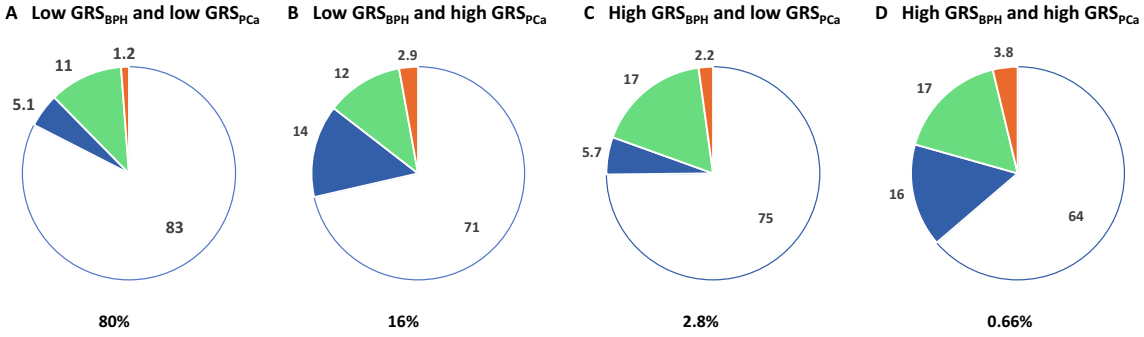

Fig. 2 – Pie charts of the prevalence for BPH and PCa diagnoses in four groups of men with low (<1.5) and high (≥1.5) GRS_{BPH} and GRS_{PCa}: (A) both low, (B) low GRS_{BPH} and high GRS_{PCa}, (C) high GRS_{BPH} and low GRS_{PCa}, and (D) both high. The percentage of men in each GRS group is indicated under each pie chart. Blue, green, and red slices represent the prevalence of PCa, BPH, and both diseases, respectively. BPH = benign prostatic hyperplasia; GRS = genetic risk score; PCa = prostate cancer.

GRS_{BPH} and low GRS_{PCa} (16% vs 5.1% for PCa, 17% vs 11% for BPH, and 3.8% vs 1.2% for both BPH and PCa). Similarly, men with either high GRS_{BPH} or high GRS_{PCa} had a higher prevalence of these two diseases. Men with low GRS_{BPH} and high GRS_{PCa} had a higher prevalence of lethal PCa (0.68%) than those with both low GRS_{BPH} and low GRS_{PCa} (0.25%) and especially those with high GRS_{BPH} but low GRS_{PCa} (0.11%). Regarding surgical intervention for BPH, men with high GRS_{BPH} underwent TURP more frequently than those with low GRS_{BPH}, regardless of GRS_{PCa} status (6.5–7.4% for high GRS_{BPH} vs 3.3–3.6% for low GRS_{BPH}).

4. Discussion

The primary goal of this study is to address the longstanding controversy surrounding the association between BPH and PCa [5–15]. This clinically important question has been complicated by an inherent detection bias in epidemiological studies where patients diagnosed with one disease are typically examined more thoroughly by urologists and therefore have a higher chance of being diagnosed with the other disease [17]. It is practically impossible to estimate the degree (partially or total) of the detection bias contributing to the observed association of BPH and PCa in traditional studies. Utilizing a large population-based cohort of over 200 000 men with diagnostic information for both diseases and genome-wide SNP data, we tested the association using both traditional epidemiological and alternative inherited genetic approaches (Fig. 1). We (1) demonstrated a statistical association of phenotypic diagnoses of BPH and PCa ($p < 0.001$) and (2) revealed a polygenic inherited basis for each of these two diseases (h^2 of 0.09 and 0.16 for BPH and PCa, respectively), and (3) more importantly, the present analysis suggests that these two diseases are genetically correlated and that they share part of a polygenic background (r_g = 0.16) and risk-associated SNPs. These findings provide strong statistical evidence that diagnoses of BPH and PCa are linked, and the excess concurrence of these two diseases was in part contributed by inherited genetics and not entirely driven by the detection bias.

A shared inherited risk between BPH and PCa may arise from several potential sources, including (1) LD of different genes for BPH and PCa in the same chromosomal region; (2) pleiotropy where same genes or variants affect both BPH and PCa; (3) causal effect where genes cause a disease first, which in turn cause the other disease; and (4) biases from population stratification. While the likelihood for the last source is low because this study was based on White men from a population-based cohort and the analysis adjusted for population stratification, we cannot differentiate between the sources of LD, pleiotropy, and causality. Therefore, we can only conclude that the shared inherited risk is directly or indirectly associated with both BPH and PCa, but does not necessarily cause these two diseases directly.

Although a Mendelian randomization (MR) analysis is a well-established method to interrogate the causal effect of an exposure to an outcome [25], the validity of key assumptions underlying an MR analysis (independent and exclusion) in our study is difficult to justify [26]. The independent assumption states that there are no unmeasured confounders of the associations between genetic vari-

ants and outcome. The exclusion restriction assumption requires that the genetic variants affect the outcome only through their effect on the risk factor of interest. Therefore, it is difficult to interpret MR results even if these are statistically significant. However, as an exploratory effort, we performed two MR analyses to assess a possible causal relationship between BPH and PCa using 32 BPH risk–associated SNPs, and between PCa and BPH using 100 PCa risk–associated SNPs (Supplementary Table 3). The causal association was first tested based on a one-sample MR analysis using the inverse-variance weighted method. Although a significant causal association was found in both MR analyses, significant heterogeneity was also found in both analyses. Results from additional robust methods for sensitivity analysis (weighted median and MR-Egger) were inconsistent. Therefore, the interpretation of the causal relationship between the two diseases via MR remains inconclusive.

Furthermore, as a comparison, we performed a similar analysis to assess the association and genetic correlation between BPH and another urological cancer (bladder cancer). While the diagnoses of these two diseases were highly correlated ($\chi^2 = 1615.00$, $p < 0.001$), there was no significant genetic correlation between the two diseases ($r_g = 0.01$, $p = 0.93$). These results suggest that unlike BPH and PCa, where the observed link is partially explained by shared inherited risk, there is no evidence that BPH and bladder cancer share an inherited genetic risk; instead, the observed link between BPH and bladder cancer may be caused largely or completely by the detection bias.

The finding of a shared inherited risk between BPH and PCa from this study may have clinical utility and implications for understanding the etiology. For example, identifying commonality of genes in the chromosomal regions that are associated with both BPH and PCa may help better understand the etiology for these two diseases. Toward this effort, we performed a preliminary pathway analysis for the 65 nearest genes in the 51 independent regions associated with both BPH and PCa using the Kyoto Encyclopedia of Genes and Genomes (Supplementary Table 4). These genes are significantly enriched in only one biological pathway, the PCa pathway ($p = 0.007$, Benjamini correction; Supplementary Table 5). A major caveat of this analysis is that the nearest genes may or may not account for the observed genetic associations, a common challenge for understanding the biological mechanisms of GWAS findings.

The genetic correlation between the two diseases, especially the cross-disease genetic association, also suggests that GRS_{BPH} and GRS_{PCa} may be used in the clinic to stratify the risk for these two diseases. For example, men with either high GRS_{BPH} or GRS_{PCa}, or both have higher risks for these two diseases, alone or both, and men with high GRS_{BPH} are more likely to undergo surgical intervention. Men identified to have a high risk for PCa may benefit from more aggressive screening, while men at a high risk of BPH may warrant earlier referral to urological subspecialists and consideration of early intervention for LUTS with surgery or minimally invasive procedures [27–30].

While confirming the previous null result that GRS_{PCa} does not differentiate aggressiveness of the disease in PCa patients [21,31,32], we obtained a novel finding that GRS_{BPH} is inversely associated with lethal PCa in a case-case analysis. Specifically, men with the highest GRS_{BPH} decile have a lower risk for lethal PCa but a similar risk for nonlethal PCa when comparing with men in the remaining deciles. This finding is important and plausible considering that (1) GRS_{BPH} is positively associated with prostate volume [22] and (2) prostate volume is inversely associated with aggressive PCa [33]. However, additional studies are needed to confirm this novel finding before exploring its clinical utility. Furthermore, more studies are warranted to understand specific SNPs and genes underlying this association and their biological effects on lethal PCa. Large PCa patient cohorts with germline data, PSA measurements, magnetic resonance imaging findings, prostate volume, Gleason grade at the time of biopsy and prostatectomy, location of tumor and/or histological BPH in peripheral and transition zones, as well as long-term disease follow-up are crucial to confirm and understand the association.

Several limitations of this study are noted. First, because ~95% of patients in the UKB are White, our analyses and conclusions were limited to this group only. The generalizability of our finding in other ethnic and racial populations needs to be evaluated. Second, it is recognized that the UKB cohort was included in a previous GWAS that identified BPH risk–associated SNPs [22]. Although this may inflate the performance of GRS_{BPH} for predicting BPH risk, it has limited impact on the key findings of genetic correlation. Third, the lack of detailed clinical variables relevant to BPH and PCa in this population-based biobank, such as PSA, prostate volume, Gleason grade, and quantification of LUTS, hinders more granular analysis and understanding of clinical and genetic associations. Some findings from this study, especially the inverse association between GRS_{BPH} and lethal PCa, should be considered preliminary. A comprehensive analysis in large and clinically well-characterized urological patient cohorts is needed. Finally, we did not perform a functional analysis to investigate the biological mechanism of the genetic associations for both BPH and PCa. This is in part due to the nature of this genetic study where the primary goal is to identify chromosomal regions with statistical evidence for association. More importantly, we recognize the substantial challenges in these functional studies. The chromosomal region for each genetic association is typically large (>500 kb) and many of these regions are outside of coding genes. Nevertheless, we feel that genetic association studies provide critical data relevant to human diseases. Geneticists and biologists can collaborate to understand biological mechanisms of genetic associations.

5. Conclusions

In conclusion, utilizing genome-wide SNP data from a large population-based cohort, we demonstrated that BPH and PCa share common polygenic inherited risk. This novel genetic result suggests that the excess of co-occurrence of these two diseases is not completely driven by the detection bias. The current conclusion that BPH and PCa are not

related, as stated by the National Cancer Institute and other authoritative agencies, may be reconsidered.

***Author contributions*:** Jianfeng Xu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Xu, Helfand, Glaser.
Acquisition of data: Xu.
Analysis and interpretation of data: Shi, Wei, Lanman, Xu, Helfand, Glaser.
Drafting of the manuscript: Xu, Helfand, Glaser.
Critical revision of the manuscript for important intellectual content: Glaser, Shi, Wei, Lanman, Ladson-Gary, Vickman, Franco, Crawford, Zheng, Hayward, Isaacs, Helfand, Xu.
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***Data sharing*:** The data used in this study are available in the UK Biobank, a publicly available repository. Data were accessed through a Material Transfer Agreement under application reference number 50295. For additional information, please feel free to contact the corresponding author Jianfeng Xu, DrPH.

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Appendix A. Supplementary data

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References

[1] Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984;132:474–9.
[2] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
[3] Roehrborn CG. Pathology of benign prostatic hyperplasia. Int J Impot Res 2008;20(Suppl 3):S11–8.
[4] McNeal JE, Redwine EA, Freiha FS, Stamey TA. Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. Am J Surg Pathol 1988;12:897–906.
[5] Alcaraz A, Hammerer P, Tubaro A, Schroder FH, Castro R. Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. Eur Urol 2009;55:864–73.
[6] Orsted DD, Bojesen SE. The link between benign prostatic hyperplasia and prostate cancer. Nat Rev Urol 2013;10:49–54.
[7] Sommers SC. Endocrine changes with prostatic carcinoma. Cancer 1957;10:345–58.
[8] Bostwick DG, Cooner WH, Denis L, Jones GW, Scardino PT, Murphy GP. The association of benign prostatic hyperplasia and cancer of the prostate. Cancer 1992;70(1 Suppl):291–301.
[9] Greenwald P, Kirmss V, Polan AK, Dick VS. Cancer of the prostate among men with benign prostatic hyperplasia. J Natl Cancer Inst 1974;53:335–40.
[10] Armenian HK, Lilienfeld AM, Diamond EL, Bross ID. Relation between benign prostatic hyperplasia and cancer of the prostate. A prospective and retrospective study. Lancet 1974;2:115–7.
[11] Thompson IM, Coltman Jr CA, Crowley J. Chemoprevention of prostate cancer: the Prostate Cancer Prevention Trial. Prostate 1997;33:217–21.
[12] Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192–202.
[13] Chokkalingam AP, Nyren O, Johansson JE, et al. Prostate carcinoma risk subsequent to diagnosis of benign prostatic hyperplasia: a population-based cohort study in Sweden. Cancer 2003;98:1727–34.
[14] Orsted DD, Bojesen SE, Nielsen SF, Nordestgaard BG. Association of clinical benign prostate hyperplasia with prostate cancer incidence and mortality revisited: a nationwide cohort study of 3,009,258 men. Eur Urol 2011;60:691–8.
[15] Zhang L, Wang Y, Qin Z, et al. Correlation between prostatitis, benign prostatic hyperplasia and prostate cancer: a systematic review and meta-analysis. J Cancer 2020;11:177–89.
[16] National Cancer Institute. Understanding prostate changes: a health guide for men. https://www.cancer.gov/types/prostate/understanding-prostate-changes.
[17] Meigs JB, Barry MJ, Giovannucci E, Rimm EB, Stampfer MJ, Kawachi I. High rates of prostate-specific antigen testing in men with evidence of benign prostatic hyperplasia. Am J Med 1998;104:517–25.
[18] Lerner LB, McVary KT, Barry MJ, et al. Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline part I—initial work-up and medical management. J Urol 2021;206:806–17.
[19] Carroll PR, Parsons JK, Andriole G, et al. NCCN guidelines insights: prostate cancer early detection, version 2.2016. J Natl Compr Canc Netw 2016;14:509–19.
[20] Ni G, Moser G. Schizophrenia Working Group of the Psychiatric Genomics C, Wray NR, Lee SH. Estimation of genetic correlation via linkage disequilibrium score regression and genomic restricted maximum likelihood. Am J Hum Genet 2018;102:1185–94.
[21] Conti DV, Darst BF, Moss LC, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. Nat Genet 2021;53:65–75.
[22] Gudmundsson J, Sigurdsson JK, Stefansdottir L, et al. Genome-wide associations for benign prostatic hyperplasia reveal a genetic correlation with serum levels of PSA. Nat Commun 2018;9:4568.
[23] Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203–9.
[24] Yu H, Shi Z, Wu Y, et al. Concept and benchmarks for assessing narrow-sense validity of genetic risk score values. Prostate 2019;79:1099–105.
[25] Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013;37:658–65.
[26] Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations. Wellcome Open Res 2019;4:186.

[27] Flanigan RC, Reda DJ, Wasson JH, Anderson RJ, Abdellatif M, Bruskewitz RC. 5-Year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. J Urol 1998;160:12–6, discussion 16–7.
[28] Izard J, Nickel JC. Impact of medical therapy on transurethral resection of the prostate: two decades of change. BJU Int 2011;108:89–93.
[29] Bulut S, Ozden C, Aktas BK, et al. Effects of medical therapy or surgery on prostatic and bladder resistive indices in patients with benign prostatic hyperplasia. Urol Int 2015;94:181–6.
[30] Krambeck AE, Jacobson DJ, McGree ME, et al. Effectiveness of medical and surgical therapies for lower urinary tract symptoms in the community setting. BJU Int 2012;110:1332–7.
[31] Shi Z, Platz EA, Wei J, et al. Performance of three inherited risk measures for predicting prostate cancer incidence and mortality: a population-based prospective analysis. Eur Urol 2021;79:419–26.
[32] Xu J, Isaacs SD, Sun J, et al. Association of prostate cancer risk variants with clinicopathologic characteristics of the disease. Clin Cancer Res 2008;14:5819–24.
[33] Yamashiro JR, de Riese WTW. Any correlation between prostate volume and incidence of prostate cancer: a review of reported data for the last thirty years. Res Rep Urol 2021;13:749–57.