

Original Article

Association between the polygenic liabilities for prostate cancer and breast cancer with biochemical recurrence after radical prostatectomy for localized prostate cancer

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Abstract: Prostate and breast cancers are hormone-related malignancies and are characterized by a complex interplay of hundreds of susceptibility loci throughout the genome. Prostate cancer could be inhibited by eliminating androgens through castration or estrogen administration, thus facilitating long-term treatment of prostate cancer; however, the role of estrogen in prostate cancer remains unclear. This study aimed to determine whether polygenic risk scores (PRSs) comprising combinations of genome-wide susceptibility variants influence the clinical outcomes of prostate cancer patients. The study subjects were recruited from four medical centers in Taiwan, and genome-wide genotyping data were obtained from 643 prostate cancer patients. We derived the PRS for prostate cancer (PRS-PC) and for breast cancer (PRS-BC) for each patient. The association between the PRS-PC/PRS-BC at the age of prostate cancer onset and recurrence within seven years was evaluated using a regression model adjusted for population stratification components. A higher PRS-PC was associated with an earlier onset age for prostate cancer (beta in per SD increase in PRS = -0.89, $P = 0.0008$). In contrast, a higher PRS-BC was associated with an older onset age for prostate cancer (beta = 0.59, $P = 0.02$). PRS-PC was not associated with the risk of recurrence (hazard ratio = 1.03, $P = 0.67$), whereas a higher PRS-BC was associated with a low recurrence risk (hazard ratio = 0.86, $P = 0.03$). These results indicate that the genetic predisposition to breast cancer is associated with a low risk of prostate cancer recurrence. Further studies are warranted to explore the role of breast cancer susceptibility variants and estrogen signaling in prostate cancer progression.

Keywords: Polygenic risk score, prostate cancer, breast cancer, radical prostatectomy, biochemical recurrence

Introduction

Prostate cancer is one of the most common malignancies among men, with an estimated

prevalence of 191,930 new cases and 33,330 deaths in the United States in 2020 [1]. Epidemiological evidence indicates that ethnicity and family history are significant genetic

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contributors to prostate cancer pathogenesis. The Nordic Twin Study of Cancer estimated that genetic factors account for 57% of the variation in the risk of prostate cancer, and that prostate cancer is one of the most heritable cancers [2]. Recent genome-wide association studies (GWAS) have reported a substantial (34.4%) familial relative risk of prostate cancer [3]. Post-GWAS pathway analysis through a meta-analysis of association summary statistics have identified programmed cell death 1, DNA damage response, DNA repair, and cell cycle pathways as putative pathomechanisms for prostate cancer [3]. Most susceptibility variants identified through GWAS have low relative risks, usually ranging from 1.1 to 1.3; hence, their clinical utility is limited [4]. Converging genome-wide susceptibility genomic loci into a polygenic risk score (PRS) could lead to better clinical prediction [5]. By retrieving the summary data from a GWAS of a discovery sample, the selection of susceptibility variants and its corresponding weight was preserved. Then, the cumulative additive effect of thousands of susceptibility variants could be assessed in another independent target sample. A previous study reported that the relative risk of prostate cancer among men in the top 1% of the PRS distribution was 5.71 [95% confidence interval (CI), 5.04-6.48] relative to those in the 25th-75th percentile (baseline group) [3]. The PRS potentially provides information to facilitate better screening procedures for breast cancer by targeting individuals at a high genetic risk [6]. However, the prognostic roles of these cancer susceptibility loci and their combinations on prostate cancer progression remain to be elucidated.

Since Huggins and Hodges reported that metastatic prostate cancer can be inhibited by eliminating androgens through castration or estrogen administration [7], hormonal therapy has remained the principal treatment modality among advanced prostate cancer patients. Androgens and estrogens are sex steroid hormones that penetrate the plasma membrane into prostate cells. After binding to the hormones, steroid receptors form dimers, translocate into the nucleus, bind to the DNA and coregulators, mediate target gene transcription, and regulate prostate development [8]. Numerous studies have reported the importance of androgen signaling in prostate cancer

pathogenesis, leading to life-prolonging treatments; however, the role of estrogens in prostate cancer remains unclear.

Breast and prostate cancers are hormone-related cancers and may have shared a common genetic basis. Prostate cancers often progress through androgen signaling, and breast cancers rely on estrogens. Hormonal therapy for prostate and breast cancers are initially effective; however, endocrine hormone-resistant disease recurrence is observed in numerous patients [9, 10]. Increasing evidence has indicated that estrogen signaling plays a critical role in not only breast cancer but also prostate cancer pathogenesis [11]. National Comprehensive Cancer Network guidelines have acknowledged the efficacy of oral estrogens as second-line hormonal therapy for metastatic prostate cancer patients [12]. Estrogen therapies have consistently shown a clinically significant response in 70-80% of patients with metastatic castration-resistant prostate cancer [7, 13, 14]. Furthermore, family studies have found a higher incidence of prostate cancer among the relatives of breast cancer patients [15]. Evidence has emerged that rare and high penetrance cancer susceptibility variants of *BRCA1* and *BRCA2* are associated with prostate and breast cancer risks [16, 17]. A GWAS meta-analysis also reported two loci (1p34/*NSUN4* and 6q23/*L3MBTL3*) jointly associated with the risks of prostate and breast cancers [18].

Given the critical functions of estrogen/androgen signaling in breast and prostate cancers, we hypothesized that the genetic predisposition to breast cancer might influence prostate cancer prognosis. To test our hypothesis, we evaluate whether the PRS derived through GWAS on prostate and breast cancer helps predict biochemical recurrence among patients with localized prostate cancer undergoing radical prostatectomy (RP).

Materials and methods

Patient recruitment

The study population comprised 648 patients, who underwent RP as initial therapy for localized prostate cancer, from four medical centers in Taiwan: National Taiwan University Hospital, Kaohsiung Medical University Hospital, E-Da

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Hospital, and Kaohsiung Veterans General Hospital [19]. The demographic, clinical, and follow-up data were obtained from their medical records. Biochemical recurrence was defined as two consecutive prostate-specific antigen (PSA) values of > 0.2 ng/mL after RP [20-23]. This study was approved by the Institutional Review Boards of Kaohsiung Medical University Hospital (KMUHIRB-2013132). Written informed consent was obtained from each patient, and the study was carried out in accordance with the tenets of the Declaration of Helsinki.

Genetic analysis and quality control

Genome-wide genotyping was performed using the custom Taiwan Biobank chips and run on the Axiom Genome-Wide Array Plate System (Affymetrix, Santa Clara, CA, USA), including ~600 k common variants. For quality control process, we excluded patients with > 5% missing variants, and variants with a call rate of < 5%, a minor allele frequency of < 0.001, and deviation from Hardy-Weinberg equilibrium with $P < 1 \times 10^{-6}$. We used the 1,000 Genomes Project Phase 1 East Asian reference haplotypes (Genomes Project Consortium 2015) as the reference panel to impute genotypes using MaCH [24]. Variants with imputation info > 0.7 were retained. Consequently, 643 individuals and ~5.6 million variants were recruited.

Data from existing meta-analyses were used as the discovery sample to identify susceptibility variants for prostate cancer [3] from among 79,194 and 61,112 individuals of European ancestry as cases and controls, respectively, and for breast cancer [25] from among 122,977 and 105,974 individuals of European ancestry and 14,068 and 13,104 individuals of East Asian ancestry as cases and controls, respectively. To exclude variants in linkage disequilibrium, variants were clumped with a pairwise R^2 threshold of 0.5 and a sliding window size of 500 kb. Sets of variants with P -values less than different thresholds for association tests for prostate or breast cancer were defined: 1, 0.5, 0.1, 0.05, and 0.005. To explore the role of candidate susceptibility loci for prostate or breast cancer, genome-wide significant variants (P -value < 5×10^{-8}) were selected additionally. For a set with m susceptibility loci, we calculated the PRS as: $PRS_i = \sum_{j=1}^m \hat{\beta}_j g_{ij}$, where $\hat{\beta}_j$ is the reported effect size (log odds ratio) of j th loci

from the public GWAS results [3, 25], g_{ij} is the allele count of the mutant allele for i th individual at j th loci. For each individual, the PRS derived from established susceptibility loci for prostate cancer (PRS-PC) [3] and breast cancer (PRS-BC) [25] was determined using PLINK and normalized to a Z score. Furthermore, the PRS-PC and PRS-BC were categorized into deciles for easy interpretation. We adjusted the first five population stratification dimensions during PRS association analyses.

Statistical analysis

Patient clinicopathological characteristics are expressed as numbers and percentages of patients or as mean \pm standard deviation (SD). We constructed Kaplan-Meier survival curves to determine the cumulative probabilities of recurrence stratified by PRS-PC/PRS-BC. Considering recurrence as time-to-event data, we also analyzed recurrence at different follow-up periods including 1, 3, 5, and 7 years after initial therapy. We analyzed the association between PRS-PC/PRS-BC and recurrence and with other clinical outcomes including onset age for prostate cancer, PSA, pathologic Gleason score, pathologic stage, and surgical margin. Significant associations of the PRS-PC and PRS-BC were determined through regression models adjusted for population stratification components. A linear regression model was used for continuous outcome variables, a logistic regression model was used for dichotomous outcome variables, and a Cox proportional hazards regression model was used for time-to-event data. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using the SAS statistical package (version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA).

Results

The clinicopathological characteristics of patients are summarized in **Table 1**. The (mean \pm SD) age at diagnosis was (65.6 \pm 6.6) years; (mean \pm SD) follow-up duration was (38.3 \pm 31.3) months.

The associations between PRS-PC and onset age and between PRS-BC and onset age were showed in **Tables 2** and **3**, respectively. A higher PRS-PC was associated with an earlier onset age for prostate cancer across different P -value

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Table 1. Clinical characteristics of the study cohort (n = 643)

Variables	Mean (SD)
Age at diagnosis, years	65.6 (6.6)
PSA at diagnosis, ng/mL	18.9 (56.7)
Pathologic Gleason score, n (%)	
≤ 7	531 (82.6)
> 7	112 (17.4)
Pathologic stage, n (%) ^a	
T1/T2	364 (57.1)
T3/T4	274 (42.9)
Surgical margin, n (%)	
Negative	459 (71.4)
Positive	184 (28.6)
Follow-up time, months	38.3 (31.3)

^aSubtotal does not sum to 643 due to missing data. SD, standard deviation.

thresholds, and the signal was most enriched at a *P*-value threshold of 1 (beta = -0.89, *P* = 0.0008). In contrast, a higher PRS-BC was associated with an older onset age for prostate cancer at a *P*-value threshold of 0.005 (beta = 0.59, *P* = 0.02, **Table 3**). The results for PRS-PC/PRS-BC at a *P*-value threshold of 5×10^{-8} showed a similar pattern, but not reached significant (beta = -0.31, *P* = 0.24 for PRS-PC in **Table 2**; beta = 0.49, *P* = 0.06 for PRS-BC in **Table 3**).

The association between PRS-PC and prostate cancer recurrence is summarized in **Table 4**. A higher PRS-PC at a *P*-value threshold of 0.005 was associated with a higher risk of 1-year recurrence [odds ratio (OR) = 1.23, *P* = 0.05] but was not associated with subsequent recurrence and the recurrence risk [hazard ratio (HR) = 1.03, *P* = 0.67]. The association between PRS-BC and prostate cancer recurrence is summarized in **Table 5**. A higher PRS-BC at a *P*-value threshold of 0.005 was associated with a lower risk of 1-year recurrence (OR = 0.78, *P* = 0.02), 3-year recurrence (OR = 0.78, *P* = 0.005), 5-year recurrence (OR = 0.83, *P* = 0.03), 7-year recurrence (OR = 0.85, *P* = 0.06), and recurrence risk (HR = 0.86, *P* = 0.03). At a *P*-value threshold of 5×10^{-8} , neither PRS-PC nor PRS-BC were associated with prostate cancer recurrence.

The cumulative incidence for prostate cancer recurrence stratified by deciles of PRS-PC/PRS-

Table 2. Association between polygenic risk scores for prostate cancer and onset age of prostate cancer

Threshold	Number of loci included	beta	<i>P</i> -value
<i>P</i> < 1	451,431	-0.89	0.0008
<i>P</i> < 0.5	306,098	-0.88	0.0009
<i>P</i> < 0.1	94,748	-0.81	0.002
<i>P</i> < 0.05	56,266	-0.62	0.02
<i>P</i> < 0.005	11,915	-0.53	0.04
<i>P</i> < 5×10^{-8}	906	-0.31	0.24

Adjustment for first five principle components for population stratification.

Table 3. Association between polygenic risk scores for breast cancer and onset age of prostate cancer

Threshold	Number of loci included	beta	<i>P</i> -value
<i>P</i> < 1	323,919	-0.06	0.82
<i>P</i> < 0.5	231,015	-0.06	0.82
<i>P</i> < 0.1	81,108	0.21	0.43
<i>P</i> < 0.05	51,150	0.44	0.09
<i>P</i> < 0.005	12,779	0.59	0.02
<i>P</i> < 5×10^{-8}	799	0.49	0.06

Adjustment for first five principle components for population stratification.

BC at a *P*-value threshold of 0.005 is summarized in **Figure 1**. Compared to the lowest decile of PRS-PC, the highest decile of PRS-PC had a higher incidence of recurrence in the initial year but not in the subsequent six years. The highest decile of PRS-BC had a lower cumulative incidence of recurrence than the lowest decile of PRS-BC.

The associations between PRS-PC or PRS-BC and patient clinicopathological characteristics were showed in **Tables 6** and **7**, respectively. A higher PRS-PC at a *P*-value threshold of 0.005 was associated with lower pathologic stage (OR = 0.85, *P* = 0.04). A higher PRS-BC at a *P*-value threshold of 5×10^{-8} was associated with higher pathologic Gleason score (OR = 1.19, *P* = 0.02). No significant association was observed for PSA at diagnosis and for surgical margin.

Discussion

This study used the PRS method to investigate the association between genome-wide suscep-

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Table 4. Association between polygenic risk scores for prostate cancer and biochemical recurrence

Threshold	1 year recurrence		3 year recurrence		5 year recurrence		7 year recurrence		Recurrence	
	OR	P-value	OR	P-value	OR	P-value	OR	P-value	HR	P-value
$P < 1$	1.10	0.36	1.02	0.85	1.00	0.99	0.99	0.90	1.01	0.97
$P < 0.5$	1.10	0.38	1.01	0.94	1.00	0.97	0.99	0.87	1.00	0.99
$P < 0.1$	1.03	0.80	0.99	0.89	0.93	0.37	0.95	0.54	0.95	0.44
$P < 0.05$	1.06	0.58	1.08	0.40	0.98	0.80	0.98	0.78	0.97	0.68
$P < 0.005$	1.23	0.05	1.13	0.16	1.05	0.57	1.06	0.48	1.03	0.67
$P < 5 \times 10^{-8}$	0.93	0.50	0.90	0.25	0.90	0.20	0.97	0.70	0.98	0.80

Adjustment for first five principle components for population stratification. OR, odds ratio.

Table 5. Association between polygenic risk scores for breast cancer and biochemical recurrence

Threshold	1 year recurrence		3 year recurrence		5 year recurrence		7 year recurrence		Recurrence	
	OR	P-value	OR	P-value	OR	P-value	OR	P-value	HR	P-value
$P < 1$	0.87	0.19	0.87	0.11	0.87	0.12	0.89	0.19	0.90	0.11
$P < 0.5$	0.85	0.12	0.85	0.08	0.86	0.08	0.89	0.15	0.89	0.08
$P < 0.1$	0.84	0.09	0.88	0.15	0.89	0.17	0.91	0.28	0.91	0.14
$P < 0.05$	0.92	0.41	0.90	0.24	0.93	0.40	0.96	0.63	0.94	0.36
$P < 0.005$	0.78	0.02	0.78	0.005	0.83	0.03	0.85	0.06	0.86	0.03
$P < 5 \times 10^{-8}$	0.90	0.30	0.86	0.10	0.87	0.11	0.87	0.09	0.91	0.13

Adjustment for first five principle components for population stratification. OR, odds ratio.

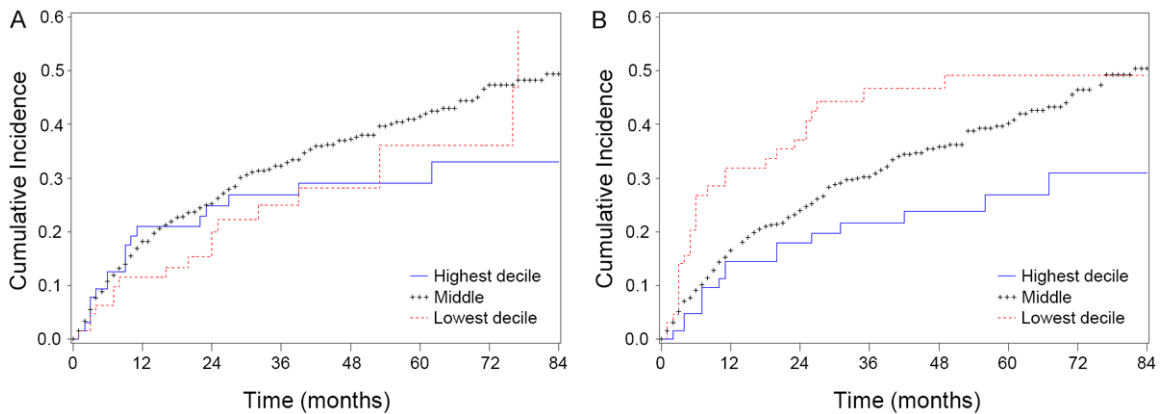


Figure 1. Cumulative incidence of biochemical recurrence by polygenic risk for (A) prostate cancer and (B) breast cancer, derived at a P -value threshold of 0.005.

Table 6. Association between polygenic risk scores for prostate cancer and patient clinicopathological characteristics

Threshold	PSA at diagnosis		Pathologic Gleason score		Pathologic stage		Surgical margin	
	beta	P-value	OR	P-value	OR	P-value	OR	P-value
$P < 1$	-0.48	0.83	1.08	0.35	1.03	0.75	0.97	0.76
$P < 0.5$	-0.49	0.83	1.08	0.32	1.02	0.79	0.96	0.68
$P < 0.1$	-2.52	0.27	1.05	0.54	0.97	0.74	1.01	0.94
$P < 0.05$	-1.73	0.46	1.01	0.94	0.94	0.43	0.93	0.44
$P < 0.005$	-0.67	0.77	1.01	0.95	0.85	0.04	1.02	0.86
$P < 5 \times 10^{-8}$	2.61	0.26	1.01	0.86	0.90	0.16	1.05	0.59

Adjustment for first five principle components for population stratification. OR, odds ratio.

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Table 7. Association between polygenic risk scores for breast cancer and patient clinicopathological characteristics

Threshold	PSA at diagnosis		Pathologic Gleason score		Pathologic stage		Surgical margin	
	beta	P-value	OR	P-value	OR	P-value	OR	P-value
$P < 1$	-0.53	0.82	1.07	0.41	0.94	0.40	0.87	0.12
$P < 0.5$	-0.92	0.69	1.07	0.40	0.94	0.40	0.89	0.18
$P < 0.1$	1.41	0.54	1.03	0.72	0.93	0.34	0.95	0.55
$P < 0.05$	2.19	0.34	1.03	0.67	0.90	0.17	0.96	0.61
$P < 0.005$	-0.86	0.71	1.14	0.09	0.94	0.43	0.95	0.55
$P < 5 \times 10^{-8}$	-0.43	0.85	1.19	0.02	0.97	0.72	0.88	0.16

Adjustment for first five principle components for population stratification. OR, odds ratio.

tibility loci and the recurrence and clinical outcomes in prostate cancer using a moderately sized patient cohort from four medical centers in Taiwan and a recent well-powered GWAS for prostate cancer and breast cancer. The present results indicate that a high genetic risk of prostate cancer is associated with an early onset age; in contrast, a high genetic risk of breast cancer is associated with a late onset age for prostate cancer and a low recurrence risk.

GWAS have identified hundreds of susceptibility loci associated with the risk of prostate cancer, suggesting that genetic factors serve as promising candidates in improving the outcomes of clinical risk assessment. PRS-based risk assessment for prostate cancer was first carried out by simply enumerating the risk alleles in five common susceptibility variants, and it was revealed that men harboring the five SNPs and had a family history had an OR of 9.46 for prostate cancer in comparison with those not harboring these factors [26]. In this study, PRS-PC using meta-GWAS summary statistics revealed that high PRSs are significantly associated with an early onset age for prostate cancer, concurrent with previous reports [27]. However, we obtained limited evidence of a high PRS-PC being able to predict disease recurrence or progression. Similarly, men with a higher PRS-PC are at a greater risk of prostate cancer; however, these scores could not predict their clinical outcomes [28]. These results suggest that these prostate cancer susceptibility loci function at an early stage of tumorigenesis and may have a different etiology from that of advanced-stage disease.

Prostate and breast cancers are hormone-dependent; thus hormone therapy is widely used in treatment of these cancers. Despite

infrequently used, estrogen-based therapies were one of the earliest treatments for advanced prostate cancer, suggesting the clinical relevance of estrogen signaling in prostate cancer. The functions of estrogen are primarily mediated through estrogen receptor α (ER α) and β (ER β). Immunohistochemical studies have reported that prostate tissues express both ER α and ER β with differential distributions. ER α is primarily expressed in the stroma of the non-malignant prostate, and its expression is associated with a high Gleason score and poor survival [29]. In contrast, ER β is primarily confined to basal-epithelial cells and is reportedly downregulated in prostate cancers [30]. In a previous study, prostate cancer did not occur in ER α -knockout (KO) mice after androgen and estrogen treatment; however, premalignant transformation occurred in ER β -KO mice prostate, suggesting that ER α potentially mediates the effects of estrogen to stimulate prostate carcinogenesis, and ER β potentially protects against prostate carcinogenesis [31]. Furthermore, several genetic variants in the ER binding elements are associated with prostate cancer progression and survival, indicating that ER target genes potentially influence disease progression [32]. A selective ER α antagonist, toremifene, has recently demonstrated some favorable results in treating prostate cancer. Toremifene decreased tumor incidence and prolonged survival in a prostate cancer transgenic mice model [33]. Clinically, patients treated with toremifene had a lower rate of prostate cancer in men with prostatic intraepithelial neoplasia compared to placebo [34]. Toremifene plus androgen deprivation therapy was also shown to delay disease recurrence in patients with bone metastatic prostate cancer compared to androgen deprivation ther-

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apy alone [35]. Pathway analysis of breast cancer GWAS highlights mitogen activated protein kinases, immune, DNA damage response, cell cycle, and growth factor pathways containing Wnt, fibroblast growth factor, platelet derived growth factor signaling, to be involved in genetic predisposition to breast cancer [25]. Many of these pathways are also responsible for causing susceptibility to prostate cancer [3], suggesting shared mechanisms in the development of these hormone-related cancers. Considering the role of estrogens and their antagonistic effects on androgens in the prostate, the aforementioned factors may explain why a high PRS-BC is associated with an older onset age of prostate cancer and a lower risk of disease recurrence herein. However, the mechanisms underlying the protective effect of PRS-BC in prostate cancer are largely unknown, thus requiring further investigation.

In the present study, the PRS at a P -value threshold of 5×10^{-8} did not lead to a better prediction for biochemical recurrence and onset age of prostate cancer. Since the variants kept for calculating PRS include true-associated and null variants of a disease, the prediction maximizes when the PRS at a P -value threshold reached a good balance between true and null signals. It has been suggested that the PRS at a non-conservative P -value threshold is usually the most enriched to maximum capture the variances of a disease [36].

The applicability and limitations of the PRS approach has been reviewed [37], and the power and predictive accuracy of PRS has also been demonstrated [38]. The variants in higher linkage disequilibrium (LD) regions may capture more variance associated with a causal variant, and hence result in a lower P -value in association tests [39]. LD score regression has been proposed to distinguish confounding bias from polygenicity [40]. Deriving genetic correlations across traits based on GWAS summary only, LD regression can be performed without individual genotype data. However, LD regression requires larger sample sizes to achieve equivalent efficacy. Otherwise, LD regression will not be suitable if study population was admixed. Clumping for LD in polygenic profiling may result in loss of power as informative markers may be lost. LD pred accounting for the effects of variants in LD has been proposed to

increase the heritability estimates [41]; the difficulty was that LD information from an external reference panel in addition to discovery sample and target sample is required. PRS-CS, a recently proposed polygenic prediction method that infers posterior effect sizes of variants using summary data from GWAS and an external LD reference panel, utilizes a high-dimensional Bayesian regression framework and leads to a better prediction generally [42]. However, ethnic heterogeneity between the discovery sample, LD reference, and target sample may reduce prediction accuracy.

This study has several limitations. First, the patient cohort is relatively smaller than that of those of previous case-control GWAS. Though large sample size for existing meta-analyses (discovery sample) provided sufficient power to detect small effect size for a loci and thus sufficient predictive accuracy of PRS, the small sample size for current target sample limited the power to detect the association of PRS with other phenotypes. Nevertheless, this study provides valuable information regarding the clinical characteristics and follow-up data regarding disease recurrence among such patients. Second, the study population comprised individuals of only Taiwanese ancestry; hence, our results may not be generalized to other populations. Third, single nucleotide polymorphism-based PRS did not completely represent the genetic susceptibility to the disease [43]. Furthermore, this study used cross-population GWAS results to determine the PRS, thus potentially decreasing the predictive variance [44]. Most existing GWAS have focused on European individuals, thus facilitating better prediction of the genetic risk in comparison with that among individuals of non-European ancestry. More GWAS studies including non-European individuals are required to elucidate the clinical application of the PRS across diverse populations [45]. Fourth, breast cancer is a heterogeneous disease with different hormonal subtypes, and has disparate response to therapeutics. The GWAS meta-analyses for generating PRS-BC included all breast cancers. However, most (about 80%) breast cancer tumors are ER-positive, we still think that the PRS-BC generated from the large scale GWAS meta-analyses provides good genome-wide heritability estimates for overall breast cancer. Finally, multiple hypothesis tests were conduct-

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ed to assess various associations between PRS-PC/PRS-BC and several outcomes; hence, the probability for false-positive results would have been relatively high. Therefore, the present findings can be considered preliminary rather than confirmatory.

To our knowledge, our study is the first to report the inverse association between the PRS-BC with onset age and disease recurrence for prostate cancer. Although the practical applications of these polygenic risk data warrant further investigation, our findings indicate that estrogen signaling significantly contributes to prostate cancer progression. Few studies have focused on estrogen-based therapies for prostate cancer; however, further studies may provide detailed insights into novel therapeutic targets for treating prostate cancer.

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Disclosure of conflict of interest

None.

Abbreviations

GWAS, genome-wide association study; PRS, polygenic risk score; CI, confidence interval; RP, radical prostatectomy; PSA, prostate-specific antigen; SD, standard deviation; OR, odds ratio; HR, hazard ratio; ER, estrogen receptor; KO, knockout; LD, linkage disequilibrium.

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