Review

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How Well do Polygenic Risk Scores Identify Men at High Risk for Prostate Cancer? Systematic Review and Meta-Analysis

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Abstract

Objectives: Genome-wide association studies have revealed over 200 genetic susceptibility loci for prostate cancer (PCa). By combining them, polygenic risk scores (PRS) can be generated to predict risk of PCa. We summarize the published evidence and conduct meta-analyses of PRS as a predictor of PCa risk in Caucasian men. **Patients and methods:** Data were extracted from 59 studies, with 16 studies including 17 separate analyses used in the main meta-analysis with a total of 20,786 cases and 69,106 controls identified through a systematic search of ten databases. Random effects meta-analysis was used to obtain pooled estimates of area under the receiver-operating characteristic curve (AUC). Meta-regression was used to assess the impact of number of single-nucleotide polymorphisms (SNPs) incorporated in PRS on AUC. Heterogeneity is expressed as I^2 scores. Publication bias was evaluated using funnel plots and Egger tests. **Results:** The ability of PRS to identify men with PCa was modest (pooled AUC 0.63, 95% CI 0.62-0.64) with moderate consistency (I^2 64%). Combining PRS with clinical variables increased the pooled AUC to 0.74 (0.68-0.81). Meta-regression showed only negligible increase in AUC for adding incremental SNPs. Despite moderate heterogeneity, publication bias was not evident. **Conclusion:** Typically, PRS accuracy is comparable to PSA or family history with a pooled AUC value 0.63 indicating mediocre performance for PRS alone.

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Abbreviations: PRS, Polygenic risk score; PCa, Prostate cancer; AUC, Area under the ROC curve; SNP, Single-nucleotide polymorphisms.

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Introduction

In 2020, prostate cancer (PCa) was the second most commonly diagnosed cancer in men globally with over 1,400,000 new cases and caused more than 375,000 deaths world-wide[1]. Even though PCa incidence and mortality have declined or stabilized in high-income countries during the past 1-2 decades, prevalence of PCa is predicted to increase in the future due to increasing life expectancy among patients with PCa, very likely primarily men with low-risk disease[1,2].

Prostate cancer has very high heritability compared to most other cancers, up to 57% according to twin studies[3]. In genome-wide association studies (GWAS), over two hundred susceptibility loci for PCa have been found, though most make only a small contribution to overall susceptibility[4-6]. Polygenic risk scores (PRS) integrating the effect across single nucleotide polymorphisms have potential as a tool for identifying high-risk men and hence allow development of a personalized, risk-stratified screening strategy. One modelling study suggested that screening based on PRS and age, compared to age alone, decreased the number of screened men by 16%[7]. However, it also decreased screen-based cases by 3%[7]. Interestingly, in the same study, the PRS-based approach did increase detection of PCa cases in younger age groups. Currently there is no sufficient evidence to evaluate whether using genetic predisposition as a criterion for targeting screening affects detection of aggressive versus non-aggressive PCa.

The aim of this systematic review and meta-analysis was to summarize the evidence on the accuracy of PRS in predicting risk of PCa. To our knowledge, this is the first meta-analysis investigating this topic.

Patients and MethodsWe performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations[8]. This study was registered in the PROSPERO database (CRD42020201345). Ethical review was not required since this study does not use any primary data, but only summary results.

Electronic and manual search strategy

Ten electronic databases (Medline (Ovid), Web of Science, the Cochrane Library, PubMed, Google Scholar, Medline (STN), Embase, Biosis, SciSearch and Drugu) were screened using selected search terms (provided in Supplement Table 1). Publication language was limited to English and publication dates from Jan 2009 to Sep 2021. To our knowledge, the first article using a PRS approach to evaluate the risk of PCa was published in 2009. Study identification included both electronic searching strategies combined with manual search of the reference lists of the eligible publications.

Study selection

The inclusion criteria were as follows: 1) cohort studies, case-cohort studies, nested case-control studies; 2) studies using a polygenic risk score to evaluate risk of PCa; and 3) studies that have been conducted in Caucasian men (to avoid population stratification, studies with mixed ethnicities including Caucasian men were included, however). The exclusion criteria were: 1) abstracts, letters/commentaries to the editor, conference proceedings and systematic reviews; 2) studies conducted exclusively in non-Caucasian subjects; 3) studies using only narrow subset of all cases (e.g., limited to early-onset or metastatic cases); 4) studies conducted in animals; 5) studies published after Sep 2021; 6) outcome is not PCa diagnosis (e.g., reports on PCa progression); and 7) studies assessing role of only individual single-nucleotide polymorphisms (SNPs) or gene variants without combining their effects into a score.

Data extraction and quality assessment

Three reviewers independently screened the titles and abstracts of all studies initially identified using the selection criteria to identify studies for full text screening. In case of discrepancy, a consensus was reached by a discussion. If a consensus could not be attained by the original three reviewers, an additional reviewer (AA) was brought in to make the final decision. Three authors (RL, KP, KS) independently extracted the data from one third of the publications and one author (AS) extracted the data from all the publications using a pre-designed data extraction form to collect the following items: number of cases and controls overall; number of cases and controls by PRS subgroups; age groups covered; ethnicity; source of the subjects; number of SNPs used for the PRS; method for PRS construction; and reported area under the receiver operating curve (AUC) with 95% confidence intervals (CI). We used the AUC values reported in the original publications instead of calculating those from numbers of cases and controls, because an accurate AUC estimate cannot be calculated from grouped data but needs to be generated over full range of sensitivity and (one minus) specificity (for all cutoff values). In cases with missing data, the corresponding authors of original publications were contacted by email.

Risk of bias in individual studies was independently evaluated by two authors (AS and AA) and in case of disagreement, an additional author assessed the risk of bias and made the final decision. The following characteristics were used to evaluate bias based on reporting guidelines for case-control studies: sources of the cases and controls; matching of cases and controls; exposure assessment and outcome definition consistent with the CLARITY criteria (Evidence Partners/McMaster). This was chosen because only case selection was appropriate form the quality assessment tool for diagnostic accuracy studies (QUADAS-2)[36], while those pertaining to the reference test were not (histological confirmation based on biopsy prior to enrolment used in all studies). Extent of covariates included in estimation of AUC was not regarded as control of confounding, but as different approaches to estimating the contribution of PRS.

Data synthesis and analysis

In the main analysis, area under the receiver-operating characteristic curves (AUC) values were meta-analyzed. Random effects modelling was used to obtain meta-analytic AUC estimates with inverse variance weighting. The results are illustrated as forest plots. As a subgroup

Table 1 Studies included to pooled meta-analysis which reported area under the ROC curve (AUC) values. Analysis included studies where only polygenic risk score was used to evaluate AUC values.

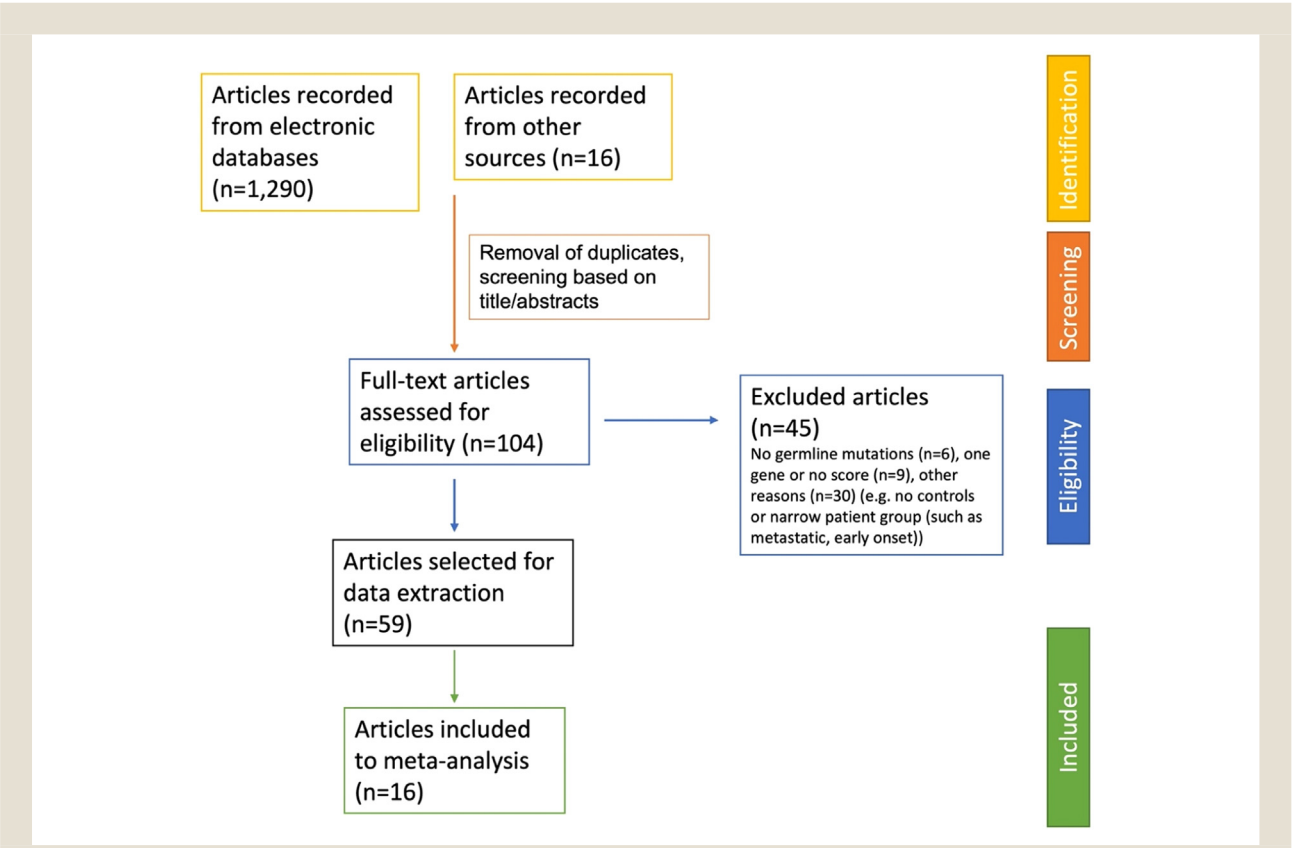
Study	Number of subjects		Age, years		Ethnicity/source of the subjects		SNPs used in PRS	AUC (95% CI) when only PRS was added to the model	AUC+95% CI when PRS and clinical variables were added to the model	Clinical variables added to the model
	Cases	Controls	Cases	Controls	Cases	Controls				
Aly et al. 2011[19]	2135	3106	66.0 (6.9)	64.2 (6.8)	Caucasian/data from Stocholm-1 study		36 SNPs	0.610 (0.590-0.630)	0.67 (0.65-0.7)	Age, PSA, free-to-total PSA, FH
Xu et al. 2011[20]	455	1687	40-79	dns	Caucasian/ data from the North Carolina-Louisiana prostate cancer project (PCaP)	Caucasian/ Data from Illumina's iControlDB	32 SNPs	0.600 (0.571-0.631)		
Johansson et al. 2012[21]	520	988	59 (49-60)	59 (49-60)	Caucasian/Subjects from the Northern Sweden Health and Disease Cohort (NSHDC)		33 SNPs	0.643 (0.614-0.672)	0.87 (0.85-0.89)	tPSA, %fPSA
Cybulski et al. 2013[23]	Altogether n=208		dns	dns	Caucasian/Data from Polish men in Szczecina and West Pomerania area		9 SNPs and 9 rare mutations	0.590 (0.524-0.665)	0.72 (0.66-0.78)	Digital rectum examination
Butoescu et al. 2014[24]	170	146	68 (55-82)	66 (54-78)	Caucasian/Study group from Belgia		9 SNPs	0.611 (0.549-0.673)	0.78 (0.73–0.83)	PSA, prostate volume, digital rectal examination, transrectal ultrasound results
Cremers et al. 2015[25]	169	587	<=75	<=75	Caucasian/Dutch		74 SNPs	0.640 (0.616–0.665)		
Grönberg et al. 2015[26]	4947	18870	50-69	50-69	Caucasian/Data from Stocholm-3 cohort		232 SNPs	0.640 (0.597-0.686)	0.69 (0.68-0.71)	STHLM3 model (a combination of plasma protein biomarkers [PSA, free PSA, intact PSA, hK2, MSMB, MIC1], genetic polymorphisms [232 SNPs], and clinical variables [age, family, history, previous prostate biopsy, prostate exam]), and PSA concentration)
Szulkin et al. 2015[27]	1370	1239	<70	<70	Caucasian/Data from Epidemiology and Risk factors in Cancer Heredity (SEARCH)		65 SNPs	0.680 (0.660–0.700)		
Conran et al. 2016[28]	410	1244	63.52 (+/- 5.99)	62.22 (+/-6.01)	Caucasian/ Data from Placebo arm of REDUCE trial		59 SNPs	0.62 (0.59–0.65)		
Gomes-Acebo et al. 2017[29]	818	1006	<65 years n=342, 65=> n=476	<65 years n=410, 65=> n=596	Caucasian/Spanish, two Arabic individuals (one case and one control)		56 SNPs	0.660 (0.635-0.686)		

(*continued on next page*)

Table 1 (*continued*)

Study	Number of subjects		Age, years		Ethnicity/source of the subjects		SNPs used in PRS	AUC (95% CI) when only PRS was added to the model	AUC+95% CI when PRS and clinical variables were added to the model	Clinical variables added to the model
	Cases	Controls	Cases	Controls	Cases	Controls				
Lecarpentier et al. 2017[30]	212	1313	dns	dns	Caucasian/Data from the Surveillance, Epidemiology, and End Results (SEER) database (U.S. Cancer registries)		103 SNPs	0.620 (0.581-0.661)		
Lello et al. 2019[9]	379	24733	dns	dns	Caucasian/UK biobank		448 SNPs	0.640 (0.625-0.655)		
Sipeky et al. 2020[32]	2738	2400	dns	dns	Caucasian/Data from FinRSPC and Tampere University Hospital cohort	Caucasian/ Data from FinRSPC	55 SNPs	0.600 (0.571-0.631)	0.62 (0.61-0.63)	PSA, age
Black et al. 2020[33]	1972	1919	59.5 ± 7.2	57.2 ± 13.0	Caucasian/ Data from Johns Hopkins University Hospital, Ambry Genetics, and NorthShore University HealthSystem's Genomic Health Initiative		72 SNPs	0.640 (0.620-0.660)		
Zhang et al. 2021a[34]	1172	1157	dns	dns	Caucasian/ Data from CGEMS (The Cancer Genetic Markers of Susceptibility)		61 SNPs	0.621 (0.578–0.655)		
Zhang et al. 2021b[34]	2758	4482	dns	dns	Caucasian/ Data from BPC3 (The Breast and Prostate Cancer Cohort Consortium)		61 SNPs	0.629 (0.596-0.656)		
Wang et al 2021[35]	457	4125	dns	dns	Caucasian/ The Penn Medicine BioBank at University of Pennsylvania		116 SNPs	0.633 (0.606-0.659)	0.75 (0.73-0.77)	Age and the first 10 within-ancestry principal components as covariates

Figure 1 Selection procedure of the study. Altogether 1,290 articles were recorded from electronic databases. 16 additional articles were found from reference list of selected articles. Data was extracted from 59 articles and 16 was used in meta-analysis.



analysis, pooled AUC values were analyzed separately to studies where PRS was calculated by 1) summing the number of risk alleles for each subject; and 2) summing the number of risk alleles with weighting by the estimated per-allele log OR. Separate analysis was also performed with AUC values where PRS was combined with some clinical characteristics. Analyses of studies divided by their risk of bias score were also carried out. Finally, a leave one out analysis was performed to assess the influence of any single study.

Publication bias across trials was evaluated using Egger tests and examined graphically using funnel plots. Heterogeneity in results is expressed as inconsistency index (I^2). Meta-regression was used to assess the impact of number of SNPs on AUC. All analyses were performed using Stata statistical software (Version 16).

ResultsStudy selection

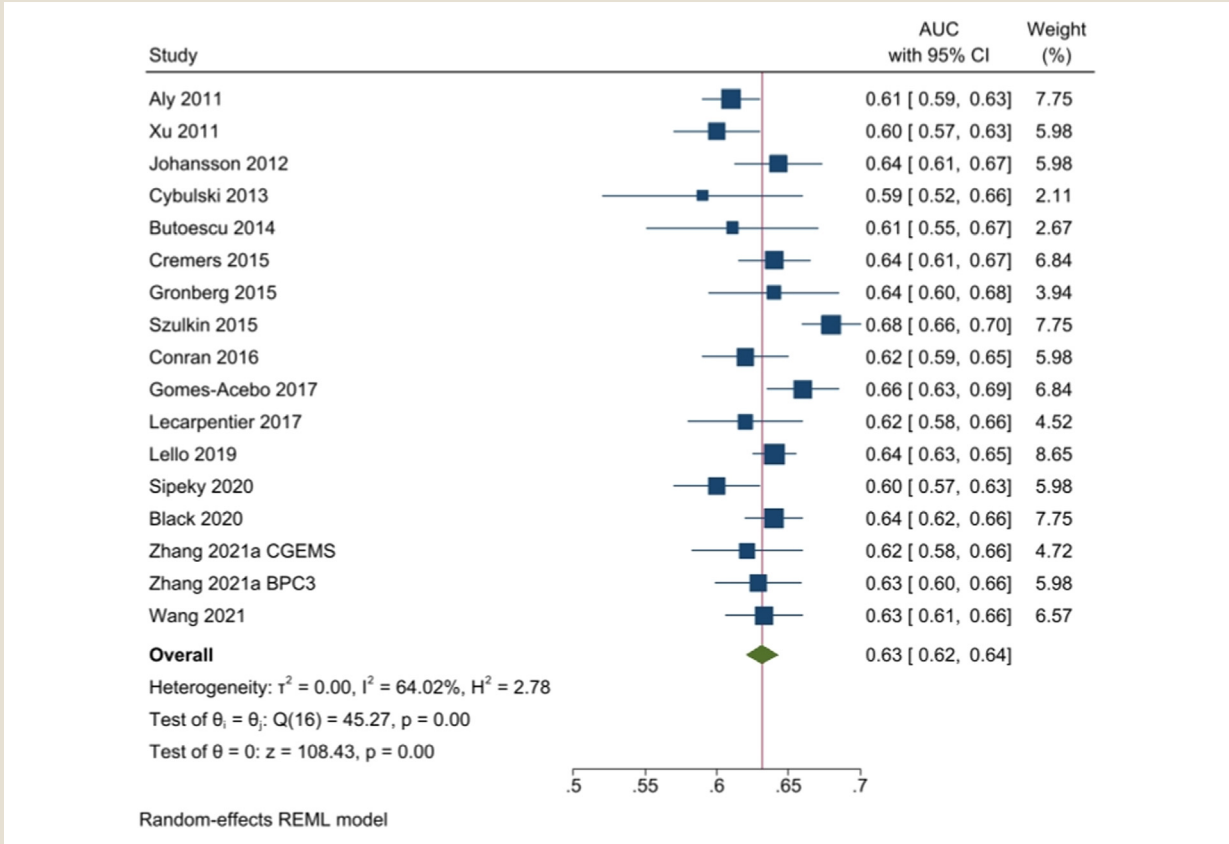
Altogether 1,290 publications were identified from the 10 databases searched with addition of 16 articles from manual search (Fig. 1). After removal of duplicates and selection based on the predefined criteria, 104 articles were entered for full-text screening. Forty-five articles were excluded for the following reasons: did not evaluate germline mutations (n=6); evaluated only a single SNP or did not report PRS (n=27); did not use controls free of prostate cancer (n=3); too narrow patient group such as only metastatic cases or early onset cases (n=7); and did not evaluate PCa risk (n=2).

Data was extracted from 59 publications (Supplemental Table 3), of which 16 studies were included in the meta-analysis (Fig. 1, Table 1).

Study characteristics

All 16 publications included in the meta-analysis were case-control studies with a total of 20,786 cases and 69,106 controls (Table 1). The number of SNPs incorporated for PRS varied from 9 to 448 and almost all studies used SNPs selected based on previous association with PCa risk. Two different methods, with minor modification between studies, were employed to construct PRS: 1) summing the number of risk alleles for each subject; and 2) summing the number of risk alleles with weighting by the estimated per-allele log OR (Supplemental Table 2). Analysis of the association between PRS was evaluated using logistic regression in all studies, except in study by Lello et al. 2019[9] where

Figure 2 Forest plot of analyses of AUC. Analyses included 16 studies with 17 original analyses. Heterogeneity of the analyses is expressed as I2 score.



L1-penalized regression was used. Of the clinical factors, six studies also included PSA, five family history, three prostate volume and three DRE results, though all but two[22,31] also reported AUC results for the PRS alone. Two studies reporting only analysis with PRS combined with clinical variables[22,31] (but not for PRS alone) were excluded from the main analysis.

No material differences in risk of bias assessment were found between the included studies, with scores ranging 7-8 (with one study scored at 6 points) (Supplemental Table 4). The main difference in risk of bias scores was between population-based (five studies) versus hospital-based case series (eight studies), with four reports pooling cases from several studies. Only one study did not use the same source population for controls as cases (scored at 6), and none of the studies clearly reported participation separately for cases and controls (nine studies identified cases and controls within a previously established study population such as REDUCE, FinRSPC, UK Biobank). No score was assigned to a publication combining material from 20 different studies and reporting only pooled results.

Main meta-analysis of AUC

Pooled data from the 16 studies including 17 risk estimates showed a combined estimate of AUC=0.63, 95% CI 0.62-0.64 (Fig. 2). This analysis involved a moderate level of heterogeneity (I^2=64%).

The average increment in the AUC from adding PRS to a risk model with other risk indicators was 0.037 (SD 0.026), based on 10 studies. However, a confidence interval could not be obtained for the increase in AUC from PRS, as few studies reported a confidence interval for the increment.

Subgroup and sensitivity analyses

We evaluated the influence of number of SNPs on AUC for the PRS using meta-regression. The regression coefficient for the increase in AUC with number of SNPs was 1.00004 (95% CI 0.9999-1.0001, p=0.47) indicating only negligible increase with increasing number of SNPs. When meta-regression was conducted evaluating number of SNPs for PRS incorporating also clinical variables such as PSA or prostate volume, a comparable result was obtained (RR 1.0003, 95% CI 0.9911-1.0014).

Figure 3 Forest plot of analyses of AUC based on the construction method of PRS in the original analysis: A) simply summing the number of risk alleles for each subject (n=8); or B) summing the number of risk alleles with weighting by the estimated per-allele log OR (n=6). Heterogeneity is expressed as I^2 score.

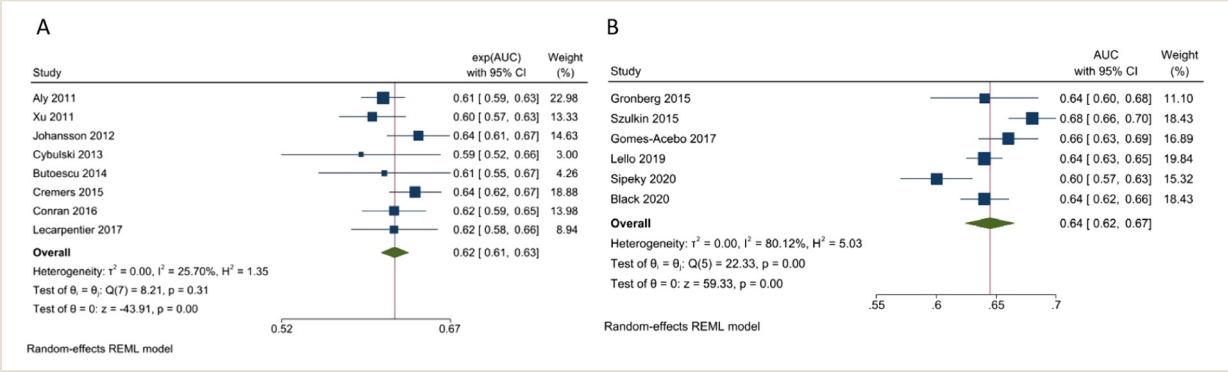
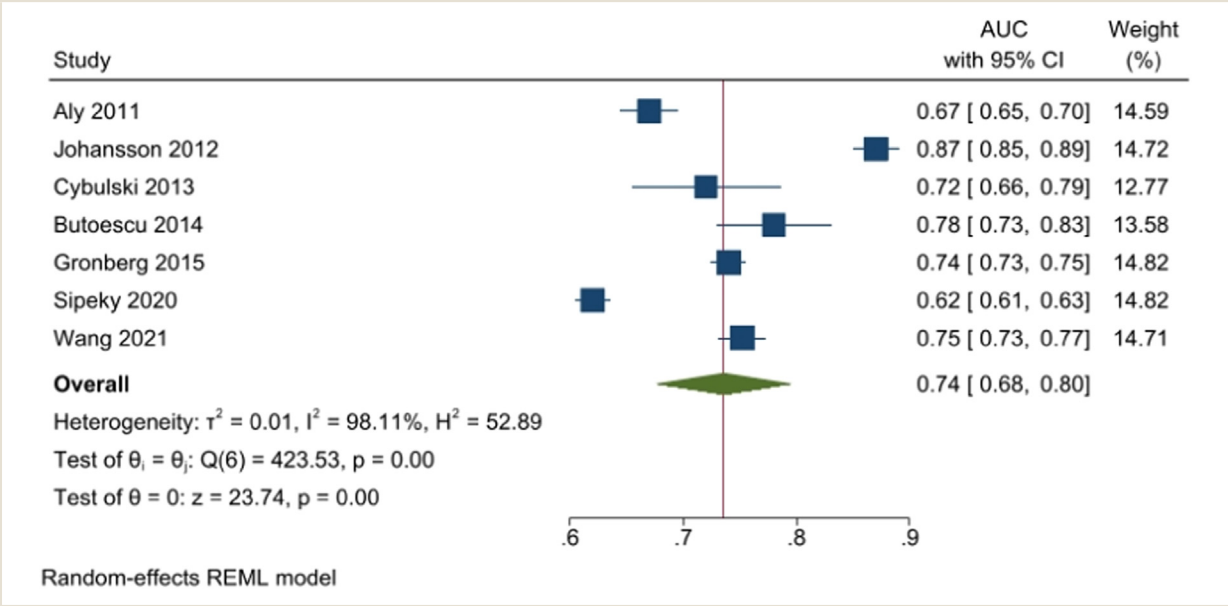


Figure 4 Forest plot of analyses of AUC when analysis was done by combining PRS and clinical variables (e.g. PSA, prostate volume, and digital rectum examination). The analysis included 7 original studies.

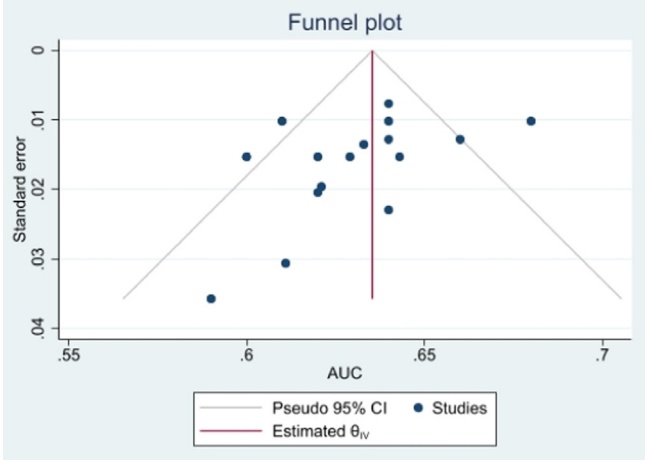


As a subgroup analysis, pooled estimates were calculated based on the method used for constructing the PRS; 1) simply summing the number of risk alleles for each subject (n=8); or 2) summing the number of risk alleles with weighting by the estimated per-allele log OR (n=6). In studies using the simple SNP count, the pooled AUC was 0.62, 95% CI 0.61-0.63 (I^2 25.7%) (Fig 3A), and for the risk-weighted method, the AUC was 0.64, 95% CI 0.62-0.67 (I^2 80.12%) (Fig 3B).

When studies were excluded one by one (leave one out analysis), the pooled estimate was hardly affected (summary AUC remained 0.63 with 95% CI 0.62-0.64 in each case).

In an analysis including the seven studies, which reported AUC for PRS combined with clinical variables (e.g. PSA, prostate volume, digital rectal examination, and transrectal ultrasound results), the pooled AUC estimate was 0.74, 95% CI 0.68-0.80 showing substantial heterogeneity (I^2 98%) (Fig. 4). There was no clear indication of publication bias (Egger test 0.83 and a symmetric funnel plot). There were no major differences based on which clinical factors were included (though the number of studies compared was small). The number of SNPs used for the PRS had only a trivial effect in this analysis (p=0.96), and the regression coefficient was comparable to the main analysis. When

Figure 5 Funnel plots of analysis of AUC analyses with all original analysis. As seen from the funnel, analysis with original studies indicate no evidence of publication bias.



the analysis of PRS including clinical variables was conducted based on the method PRS was calculated, AUC for simple PRS (n=4) was 0.76, 95% CI 0.67-0.85 (I^2 96%) and for weighted PRS (n=2) 0.68, 95% CI 0.56-0.80 (I^2 99%), again with high heterogeneity.

The risk of bias score was not associated with the AUC estimate (p=0.39, pooled AUC values 0.63 for 11 studies with scores 6-7 and 0.64 for the six studies with score 8).

Publication bias

Publication bias was evaluated using funnel plots (Fig. 5, Supplemental Figure 1) and Egger's test. Funnel plots were created including all studies (Fig. 5) to visualize the apparently symmetrical distribution. Egger's test for the main analysis including 16 studies was non-significant (p=0.079) suggesting no material publication bias. A similar study distribution can be seen in funnel plot of analysis of PRS including SNPs and clinical variables (Supplemental Figure 1).

When Egger's tests were performed in a subgroup analysis based on how the PRS was constructed in the original analysis, test results were non-significant for both studies using a simple PRS (p=0.53) and those with weighted PRS (p=0.52).

DiscussionThis meta-analysis investigated the current evidence of PRS performance in identifying men at high risk of PCa. In the ROC analysis, the pooled AUC estimate including 16 studies was 0.63 (95% CI 0.62-0.64), with some increment in discriminative capacity in addition to PSA, age, and family history[11-13]. In an analysis including PRS combined with clinical predictor variables, such as PSA, with 7 studies, the AUC increased to 0.74 (95% CI 0.68-0.81). Heterogeneity in between the studies was moderate in the main analysis. However, in the analysis including also clinical predictor variables heterogeneity was high.

A meta-analysis by Louie et al. (2015) analyzed whether accuracy of PSA screening could be increased using risk models[13]. The risk models were mainly based on clinical parameters and compared to PCa risk evaluation based only PSA values. The analysis showed that AUC for PCa risk based only PSA is 0.66 and with risk models varied from 0.74 to 0.79. Compared to these values, typical risk estimation using PRS is comparable to PSA in terms of predictive capacity. Furthermore, PSA testing is widely available, involves little cost and is well standardized, whereas PRS requires genotyping (besides availability of applicable risk estimates for SNP scoring), reducing its feasibility and affordability compared to PSA. Also, there are no standardized procedures for estimating PRS. Compared with various clinical risk indicators (PSA, free/total PSA ratio, DRE, prostate volume) the contribution of PRS was limited, with an increase in AUC <0.05 in most studies.

We performed sensitivity analyses by dividing the studies based on how the PRS was constructed and found no material differences. The study populations varied from international randomized trials to case-control analyses nested within large cohorts and single-institution case series, but the controls generally represented men at average risk of PCa without biopsies to exclude latent PCa. There was some overlap between materials used in the publications, with several reports using cases and controls for example from the REDUCE and PLCO trials.

The findings were not influenced by publication bias, as the dispersion in the funnel plots was symmetrical, although recent meta-analysis of the topic suggested mild publication bias in the field of medicine[14]. Also, Egger's tests showed no significant results in sensitivity and subgroup analysis, indicating no evident of small study effects in our analysis.

Despite the fact that almost all studies in our meta-analysis used SNPs selected based on their association with PCa risk, the number of SNPs incorporated for calculation of PRS exerted only a trivial impact on the PRS performance. One potential explanation is that the genetic

variants with the largest impact on PCa risk were identified early and are covered by most PRS algorithms, whereas the additional variants added to later studies using the most extensive PRS algorithms have incorporated mainly SNPs with minor influence.

Study quality was not associated with the reported AUC values. There was only limited variation in risk of bias scores, but the AUC estimates were nearly identical for those with higher versus lower scores.

Even though this is a comprehensive analysis, one possible limitation in our analysis was the variability in results across studies, indicated by the moderate to high heterogeneity in the main analysis and analysis including clinical variables. This is most likely attributable to differences in methods used for construction of the PRS such as selection of SNPs and clinical variables, as well as analyses and reporting. For example, the study with the highest predictive value (0.86)[10] was excluded from the meta-analysis as it reported the c-index from a Cox regression and not an actual AUC as the included studies. The AUC compares whether men with an event have a higher predicted score compared to men without the event. The c-index is the concordance in predicted probability taking into account the event-time. Thus, the two metrics cannot be compared directly.

We did not aim to identify an optimal cut-off value for decision-making as is often done in evaluations of diagnostic tests using AUC. Also, we decided not to analyze odds ratios as effect measures, because they were calculated in highly inconsistent fashion in terms of subject grouping (definitions of both high-risk groups and reference groups representing populations at low or average risk). Some studies reported their results only as odds ratios, hazard ratios or risk ratios and those were not included in the analysis. The measures with the highest utility for decision-making include absolute risks and positive predictive values, but those were reported in only a few studies, which did not allow pooling across studies.

Besides AUC, another measure of PRS is positive predictive values (PPV), which indicates the absolute risk of PCa among men with a PRS results indicating an elevated likelihood of the disease. PPV cannot be directly estimated from our data, as case-control sampling cannot yield the probability of true positive results in the population. PV can be estimated also from case-control data, but it requires estimates of test specificity, sensitivity, and disease prevalence, which were not available for the studies included in this analysis. In other studies, PPV for PRS in the highest 5% was 0.26 and for the highest 20% 0.19 in the ProtecT trial, compared with PPV of 0.12 for PSA alone[37]. Comparable PPV estimates were also reported for the highest PRS groups for aggressive PCa in the same trial[38].

Another limitation in our study was that analyses were restricted to studies conducted with Caucasian subjects, as this has been the focus of most published analyses. Furthermore, there are some indications of differences in genetic predictors of prostate cancer by ethnic background (population stratification) and hence similar performance of a PRS across ethnic groups could not be assumed, but use of more ethnically diverse study populations would likely increase heterogeneity[15]. Thus, future studies should also focus on other races and ethnicities. To date, it is not fully understood to what extent genetic susceptibility explains differences of PCa rates between races and ethnicity groups[25].

Prostate cancer screening with PSA has been shown to decrease PCa mortality in the ERSPC trial – however, with the disadvantage of overdiagnosis and overtreatment of indolent disease[16]. The potential of more tailored, risk-adapted, or personalized screening utilizing genetic susceptibility or clinical parameters to target screening is of major scientific interest[17,18]. Furthermore, there is emerging consensus that screening should target aggressive PCa to reduce overdiagnosis and overtreatment. Utility of genetic predictors for clinically significant PCa could not be assessed with the current data, but remains an important research question. Only two studies[21,32] in our analyses reported AUC for aggressive and non-aggressive cases, and both showed marginally lower estimates for aggressive PCa. BARCODE1 pilot study evaluated the usability of PRS in selection of men for PCa screening[39]. Men in the highest PRS decile were invited to screening and underwent magnetic resonance imaging resulting in 39% (7/18) being diagnosed with PCa. All cases were low-risk PCa, which suggests that selection of target population through PRS may increase primarily detection of low-risk disease and therefore may not effectively reduce mortality. However, these are only preliminary results based on small numbers and hence involve substantial uncertainty.

As a conclusion, even though polygenic risk scores allow detection of men at increased risk for PCa, the accuracy or PRS-based risk prediction is comparable to PSA or family history. Thus, the utility of PRS alone for identifying high-risk men is uncertain based on the current data. However, combining PRS with clinical variables increased AUC to some extent. Furthermore, it remains uncertain whether PRS can be used for targeting a subgroup of men with high genetic risk for screening. The optimal method for calculating PRS remains unclear, though the substantial increase in the number of variants or tailored genetic variants selected by genetic ancestry (e.g. European *vs* African ancestry) may improve the results.

Author contributions

Aino Siltari 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

Anders Bjartell, Anssi Auvinen, Susan Evans-Axelsson, Amit Kiran, Teemu J. Murtola, Alex Asiimwe, and Billy Franks

Acquisition of data

Aino Siltari, Ragnar Lönnerbro, Karl Pang, Kirill Shiranov, and Alex Asiimwe

Analysis and interpretation of data

Aino Siltari, Ragnar Lönnerbro, Karl Pang, Kirill Shiranov, and Alex Asiimwe

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Supplementary materials
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References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249.
2. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. *Eur Urol*. 2020;77:38–52.
3. Mucci LA, Hjelmborg JB, Harris JRNordic Twin Study of Cancer (NorTwinCan) Collaboration. Familial risk and heritability of cancer among twins in Nordic Countries. *JAMA*. 2016;315:68–76.
4. Al Olama AA, Kote-Jarai Z, Berndt SI, et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet*. 2014;46:1103–1109.
5. Eeles RA, Al Olama AA, Benlloch S, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet*. 2013;45:385–391.
6. 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.
7. Pashayan N, Duffy SW, Chowdhury S, et al. Polygenic susceptibility to prostate and breast cancer: implications for personalised screening. *Br J Cancer*. 2011;104:1656–1663.
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62:e1–34.
9. Lello L, Raben TG, Yong SY, Tellier LCAM, Hsu SDH. Genomic prediction of 16 complex disease risks including heart attack, diabetes, breast and prostate cancer. [published correction appears in Sci Rep. 2019;9(1):17515]. *Sci Rep*. 2019;9:15286. doi:10.1038/s41598-019-51258-x.
10. Mars N, Koskela JT, Ripatti P, et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat Med*. 2020;26:549–557.
11. Thompson IM, Ankerst DP, Chi C, et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. *JAMA*. 2005;294:66–70.
12. Zheng SL, Sun J, Wiklund F, et al. Genetic variants and family history predict prostate cancer similar to prostate-specific antigen. *Clin Cancer Res*. 2009;15:1105–1111.
13. Louie KS, Seigneurin A, Cathcatr P, Sasieni P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. *Annals of Oncol*. 2015;26:848–864.
14. van Aert RCM, Wicherts JM, van Assen MALM. Publication bias examined in meta-analyses from psychology and medicine: A meta-meta-analysis. *PLoS One*. 2019;14:e0215052. doi:10.1371/journal.pone.0215052.
15. Rebbeck TR. Prostate Cancer Genetics: Variation by Race, Ethnicity, and Geography. *Semin Radiat Oncol*. 2017;27:3–10.
16. Hugosson J, Roobol MJ, Månsson M, et al. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. *Eur Urol*. 2019;76:43–51.
17. Benafif S, Ni Raghallaigh H, McGrowder E, et al. The BARCODE1 Pilot: a feasibility study of using germline single nucleotide polymorphisms to target prostate cancer screening. *BJU Int*. 2021. doi:10.1111/bju.15535.
18. Seibert TM, Fan CC, Wang Y, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts. *BMJ*. 2018;360:j5757. doi:10.1136/bmj.j5757.
19. Aly M, Wiklund F, Xu J, et al. Polygenic risk score improves prostate cancer risk prediction: results from the Stockholm-1 cohort study. *Eur Urol*. 2011;60:21–28.
20. Xu Z, Bensen JT, Smith GJ, Mohler JL, Taylor JA. GWAS SNP Replication among African American and European American men in the North Carolina-Louisiana prostate cancer project (PCaP). *Prostate*. 2011;71:881–891.
21. Johansson M, Holmström B, Hinchliffe SR, et al. Combining 33 genetic variants with prostate-specific antigen for prediction of prostate cancer: longitudinal study. *Int J Cancer*. 2012;130:129–137.
22. Newcombe PJ, Reck BH, Sun J, et al. A comparison of Bayesian and frequentist approaches to incorporating external information for the prediction of prostate cancer risk. *Genet Epidemiol*. 2012;36:71–83.
23. Cybulski C, Wokołorczyk D, Kluźniak W, et al. A personalised approach to prostate cancer screening based on genotyping of risk founder alleles. *Br J Cancer*. 2013;108:2601–2609.
24. Butoescu V, Ambroise J, Stainier A, Dekairelle AF, Gala JL, Tombal B. Does genotyping of risk-associated single nucleotide polymorphisms improve patient selection for prostate biopsy when combined with a prostate cancer risk calculator? *Prostate*. 2014;74:365–371.
25. Cremers RG, Galesloot TE, Aben KK, et al. Known susceptibility SNPs for sporadic prostate cancer show a similar association with "hereditary" prostate cancer. *Prostate*. 2015;75:474–483.
26. Grönberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol*. 2015;16:1667–1676.
27. Szulkin R, Whitington T, Eklund M, et al. Prediction of individual genetic risk to prostate cancer using a polygenic score. [published correction appears in Prostate. 2015 Dec;75:1972. Lim, Hui-Yi [corrected to Lin, Hui-Yi]]. *Prostate*. 2015;75:1467–1474.
28. Conran CA, Na R, Chen H, et al. Population-standardized genetic risk score: the SNP-based method of choice for inherited risk assessment of prostate cancer. *Asian J Androl*. 2016;18:520–524.
29. Gómez-Acebo I, Dierssen-Sotos T, Fernandez-Navarro P, et al. Risk model for prostate cancer Using environmental and genetic factors in the Spanish Multi-Case-Control (MCC) Study. *Sci Rep*. 2017;7:8994. doi:10.1038/s41598-017-09386-9.
30. Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. *J Clin Oncol*. 2017;35:2240–2250.
31. Chen S, Fann J, Sipeky C, et al. Risk Prediction of Prostate Cancer with Single Nucleotide Polymorphisms and Prostate Specific Antigen. *J Urol*. 2019;201:486–495.
32. Sipeky C, Talala KM, Tammela TLJ, et al. Prostate cancer risk prediction using a polygenic risk score. *Sci Rep*. 2020;10:17075. doi:10.1038/s41598-020-74172-z.
33. Black MH, Li S, LaDuca H, et al. Validation of a prostate cancer polygenic risk score. *Prostate*. 2020;80:1314–1321.
34. Zhang W, Dong Y, Sartor O, Zhang K. Comprehensive Analysis of Multiple Cohort Datasets Deciphers the Utility of Germline Single-Nucleotide Polymorphisms in Prostate Cancer Diagnosis. *Cancer Prev Res (Phila)*. 2021;14:741–752.
35. Wang L, Desai H, Verma SS, et al. Performance of polygenic risk scores for cancer prediction in a racially diverse academic biobank. *Genet Med*. 2021 S1098-3600(21)05367-3. doi:10.1016/j.gim.2021.10.015.
36. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155:529–536.
37. Huynh-Le MP, Karunamuni R, Fan CC, et al. Prostate cancer risk stratification improvement across multiple ancestries with new polygenic hazard score. *Prostate Cancer Prostatic Dis*. 2022. doi:10.1038/s41391-022-00497-7.
38. Seibert TM, Fan CC, Wang Y, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts. *BMJ*. 2018;360:j5757. doi:10.1136/bmj.j5757.
39. Benafif S, Ni Raghallaigh H, McGrowder E, et al. The BARCODE1 Pilot: a feasibility study of using germline single nucleotide polymorphisms to target prostate cancer screening. *BJU Int*. 2022;129:325–336.