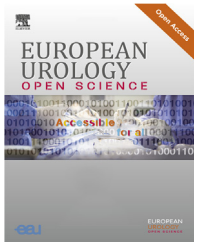
EUROPEAN UROLOGY OPEN SCIENCE 50 (2023) 27–30

available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Brief Correspondence

Addition of a Genetic Risk Score for Identification of Men with a Low Prostate-specific Antigen Level in Midlife at Risk of Developing Lethal Prostate Cancer

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Article info

Article history:
Accepted January 19, 2023

Associate Editor:
Guillaume Ploussard

Keywords:
Lethal prostate cancer
Prostate-specific antigen
Polygenic risk score

Abstract

Men with a low prostate-specific antigen (PSA) level (<1 ng/ml) in midlife may extend the rescreening interval (if aged 40–59 yr) or forgo future PSA screening (if aged >60 yr) owing to their low risk of aggressive prostate cancer (PCa). However, there is a subset of men who develop lethal PCa despite low baseline PSA. We investigated how a PCa polygenic risk score (PRS) in addition to baseline PSA impacts the prediction of lethal PCa among 483 men aged 40–70 yr from the Physicians' Health Study followed over a median of 33 yr. We examined the association of the PRS with the risk of lethal PCa (lethal cases vs controls) using logistic regression adjusted for baseline PSA. The PCa PRS was associated with risk of lethal PCa (odds ratio per 1 standard deviation in PRS [OR] 1.79, 95% confidence interval [CI] 1.28–2.49). The association between the PRS and lethal PCa was stronger for those with PSA <1 ng/ml (OR 2.23, 95% CI 1.19–4.21) than for men with PSA ≥1 ng/ml (OR 1.61, 95% CI 1.07–2.42). Our PCa PRS improved the identification of men with PSA <1 ng/ml at greater risk of future lethal PCa who should consider ongoing PSA testing.

Patient summary: A subset of men develop fatal prostate cancer despite having low prostate-specific antigen (PSA) levels in middle age. A risk score based on multiple genes can help in predicting men who may be at risk of developing lethal prostate cancer and who should be advised to have regular PSA measurements.

Prostate-specific antigen (PSA) screening effectively reduces prostate cancer (PCa)-specific mortality [1] but also results in overdiagnosis of indolent cancers [2]. Baseline PSA in midlife has been identified as a strong predictor of total and lethal PCa for both Black and White men, and could be used to risk-stratify future screening [3,4]. One study found that repeated PSA screening was associated with lower cancer-specific mortality for men with baseline PSA

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https://doi.org/10.1016/j.euros.2023.01.012

≥2 ng/ml at age 60 yr [5]. Another suggested that baseline PSA is highly specific and that men with PSA <1 ng/ml in midlife could discontinue screening because of the very low risk of developing lethal PCa (0.2% risk by age 85 yr) [6]. Studies have found that men aged 55–59 yr with PSA above the median (~1 ng/ml) accounted for ~90% of lethal or aggressive PCa cases [3,4]. However, there is still a proportion of men with PSA <1 ng/ml who develop lethal or aggressive PCa during their lifetime [3–6]. In addition to PSA, PCa genetic risk variants have the potential to inform risk-stratified screening. A polygenic risk score (PRS) combining 269 PCa-associated genetic variants accounted for 33.6–43.2% of PCa familial relative risk [7]. We investigated how this PRS might improve prediction of lethal PCa in addition to baseline PSA levels.

The Physicians' Health Study began in 1982 as a randomized, double-blind trial among 22 071 male US physicians. Cases were histologically confirmed between 1982 and 2012. Lethal PCa was defined as metastatic disease at diagnosis or during follow-up, or fatal PCa. Controls were never diagnosed with PCa during follow-up (Supplementary material). The study was approved by the institutional review boards of the Brigham and Women's Hospital and those of participating registries as required.

Baseline PSA was measured in two different nested studies [8,9]. As elevated PSA may indicate the presence of cancer, we excluded participants with PSA >25 ng/ml. As baseline PSA in midlife was the primary interest, we excluded men aged >70 yr at baseline. Germline genetic variants were assessed as part of the PRACTICAL Consortium OncoArray and a weighted PRS was created [7]. There were 483 participants with both PSA and genetic data available.

We performed unconditional logistic regression to determine the association between the PRS (in terms of its standard deviation) and the risk of PCa and lethal outcomes, adjusting for age and PSA at baseline. We also stratified by baseline PSA (<1 vs ≥1 ng/ml) and categorized men according to their baseline PSA and PRS. We compared lethal PCa cases to nonlethal PCa cases and controls. Multivariable models including an interaction term for the PRS and the dichotomous PSA variable were run to generate *p* values for the interaction. The area under the receiver operating characteristic curve (AUC) for models with and without the PRS was compared to assess model performance. All *p* values are two-sided, and analyses were performed with SAS v9.4 (SAS Institute, Cary, NC, USA).

The baseline characteristics of the participants are reported in Table 1. Of the 97 lethal and 274 nonlethal PCa cases, 22 and 72, respectively, had baseline PSA <1 ng/ml. Men with low baseline PSA had a longer time from baseline to diagnosis in comparison to men with higher

Table 1 – Characteristics of lethal and nonlethal PCa cases and control subjects in the Physicians' Health Study

	Lethal PCa cases		Nonlethal PCa cases		Control group	
	Overall	PSA <1 ng/ml	Overall	PSA <1 ng/ml	Overall	PSA <1 ng/ml
	(*n* = 97)	(*n* = 22)	(*n* = 274)	(*n* = 72)	(*n* = 112)	(*n* = 47)
Median age at blood draw, yr (range)	59.7 (41–70)	57.5 (41–68)	56.1 (40–70)	53.5 (40–66)	60.1 (43–70)	57.9 (43–68)
Median time from BD to Dx, yr, (IQR)	9.2 (6.3)	12.3 (4.4)	10.1 (5.3)	14.2 (5.8)		
Median time from BD to EFU, yr (IQR)	20.0 (11.4)	21.4 (13.1)	33.2 (4.8)	33.3 (2.5)	32.9 (11.6)	32.9 (13.1)
Median age at Dx, yr (IQR)	69.3 (9.1)	68.5 (8.9)	67.5 (9.0)	66.6 (9.8)		
Median PSA at baseline, ng/ml (IQR)	2.37 (4.98)	0.74 (0.20)	1.66 (2.13)	0.68 (0.29)	1.10 (1.34)	0.56 (0.27)
Median PSA at Dx, ng/ml (IQR)	15.6 (29.2)	7.2 (31.5)	7.2 (6.9)	5.8 (4.0)		
Data missing, *n* (%)	44 (45.4)	7 (31.8)	24 (8.8)	3 (4.2)		
Dx before 1989, *n* (%)	32 (33.0)	1 (4.6)	35 (12.8)	3 (4.2)		
Clinical stage, *n* (%)						
T1/T2	58 (59.8)	14 (63.6)	254 (92.7)	69 (95.8)		
T3	6 (6.2)	0 (0)	13 (4.7)	0 (0)		
T4/N1/M1	19 (19.6)	7 (31.8)	3 (1.1)	1 (1.4)		
Data missing	14 (14.4)	1 (4.6)	4 (1.5)	2 (2.8)		
Biopsy Gleason score, *n* (%)						
≤6	31 (32.0)	5 (22.7)	186 (67.9)	50 (69.4)		
7	25 (25.8)	7 (31.8)	54 (19.7)	13 (18.1)		
8–10	20 (20.6)	8 (36.4)	17 (6.2)	6 (8.3)		
Data missing	21 (21.7)	2 (9.1)	17 (6.2)	3 (4.2)		
RP Gleason score, *n* (%)						
≤6	3 (3.1)	1 (4.6)	90 (32.9)	23 (31.9)		
7	9 (9.3)	2 (9.1)	73 (26.6)	20 (27.8)		
8–10	10 (10.3)	2 (9.1)	15 (5.5)	6 (8.3)		
No RP or data missing	75 (77.3)	17 (77.3)	96 (35.0)	23 (31.9)		
Primary treatment, *n* (%)						
No treatment	4 (4.1)	1 (4.6)	20 (7.3)	2 (2.8)		
RP	26 (26.8)	5 (22.7)	184 (67.2)	49 (68.1)		
Radiation	26 (26.8)	5 (22.7)	59 (21.5)	19 (26.4)		
Hormones/orchiectomy	17 (17.5)	5 (22.7)	5 (1.8)	1 (1.4)		
Other	0 (0)	0 (0)	4 (1.5)	1 (1.4)		
Data missing	24 (24.7)	6 (27.3)	2 (0.7)	0 (0)		
PRS distribution by quartile, *n* (%)						
Quartile 1 (score 21.55–23.01)	9 (9.3)	3 (13.6)	18 (6.6)	6 (8.3)	28 (25.0)	15 (31.9)
Quartile 2 (score 23.02–23.68)	19 (19.6)	5 (22.7)	43 (15.7)	4 (5.6)	28 (25.0)	10 (21.3)
Quartile 3 (score 23.69–24.24)	22 (22.7)	4 (18.2)	60 (21.9)	24 (33.3)	27 (24.1)	13 (27.7)
Quartile 4 (score 24.25–25.96)	47 (48.5)	10 (45.5)	153 (55.8)	38 (52.8)	29 (25.9)	19 (19.2)

BD = blood draw; Dx = diagnosis; EFU = end of follow-up; IQR = interquartile range; PSA = prostate-specific antigen; PRS = polygenic risk score; RP = radical prostatectomy.

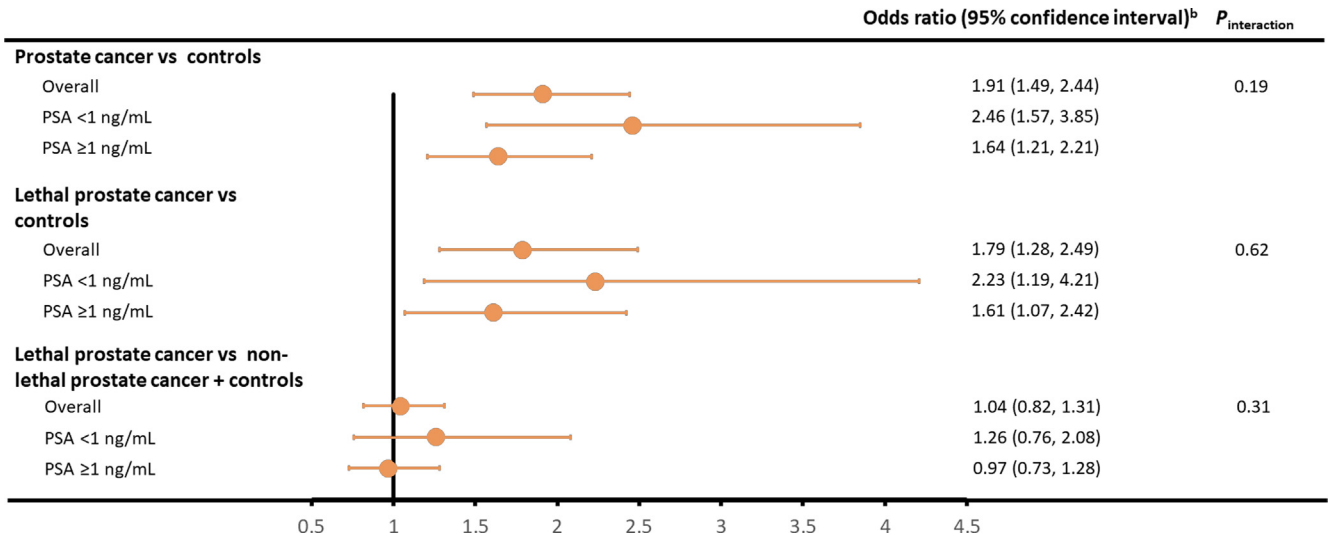

Fig. 1 – Association of the prostate cancer polygenic risk score with overall and lethal prostate cancer, Physicians' Health Study 1982–2015[a]. [a] All models adjusted for baseline age and baseline prostate-specific antigen (PSA). [b] Per 1 standard deviation increment in the polygenic risk score.

baseline PSA. The median PSA at diagnosis for men with low baseline PSA who had a lethal outcome was 7.2 ng/ml.

The PRS was significantly associated with overall PCa risk (odds ratio [OR] 1.91, 95% confidence interval [CI] 1.49–2.44) and the risk of lethal PCa (OR 1.79, 95% CI 1.28–2.49; Fig. 1 and Supplementary Table 1). The association between the PRS and lethal PCa was stronger for men with PSA <1 ng/ml (OR 2.23, 95% CI 1.19–4.21) than for men with PSA ≥1 ng/ml (OR 1.61, 95% CI 1.07–2.42) at baseline. For men with baseline PSA <1 ng/ml, PRS above the median was associated with a suggestive higher odds of lethal PCa (OR 1.92, 95% CI 0.67–5.52; Supplementary Table 2) relative to PRS below the median. We also examined the association between the PRS and lethal PCa versus nonlethal PCa and controls: the OR was 1.26 (95% CI 0.76–2.08) for PSA <1 ng/ml and 0.97 (95% CI 0.73–1.28) for PSA ≥1 ng/ml (Fig. 1 and Supplementary Table 1). Addition of the PRS to age at blood collection and baseline PSA improved the AUC for prediction of lethal PCa for men with baseline PSA <1 ng/ml (from 0.69 to 0.74; Supplementary Fig. 1).

We observed that the PCa PRS was associated with higher risk of lethal PCa among men aged 40–69 yr with low baseline PSA. Although men with high baseline PSA account for the majority of lethal PCa cases [3,4] and the advice for men with low baseline PSA at age 60 is that they can consider discontinuing screening [6], a proportion of men with low baseline PSA later die of PCa. In the Malmö Preventive Project, 9% of lethal cases occurred in the group of men aged 60–64 yr with baseline PSA <1.1 ng/ml [5]. In a USA-based study with 20% non-White participants, 11% of men with clinically significant PCa (aged 55–60 yr) had baseline PSA <1 ng/ml (Supplementary Table 3) [6]. Interestingly, men with low baseline PSA in our study had a PSA level at diagnosis that was well within the range typically detectable on PSA screening, suggesting that if all men with baseline PSA <1 ng/ml discontinued screening, some of them would miss the opportunity for PCa detection earlier in the disease course.

Consistent with prior studies, we observed that the PRS was associated with total PCa risk and lethal PCa risk [7,10]. The association between PRS and lethal PCa was stronger for men with low baseline PSA in comparison to those with high PSA. The PRS was even associated with a suggestive higher risk of lethal PCa versus nonlethal PCa and controls in the group with low baseline PSA, although this was not statistically significant. Moreover, addition of the PRS to baseline PSA improved the prediction of lethal PCa: the change in AUC was 0.05, which is comparable to a previously reported AUC change [10]. In this study, 63.7% of lethal PCa cases with PSA <1 ng/ml had a PRS above the median. These men are likely to benefit from continued PSA screening.

The current study has long-term follow-up and PSA levels were measured in prospectively collected samples, allowing analysis of how the PCa PRS is related to the risk of lethal outcomes by baseline PSA level. A limitation of the study is that the participants were predominantly White; however, given that a similar proportion (~10%) of men with lethal PCa have low baseline PSA across multiple studies [3–6] and that the PRS was generated from multiethnic populations, our findings could probably be generalized to other populations. The number of participants with both PSA and genetic data available was limited, and there was lack of information on PSA screening protocols regarding screening interval, age at cessation, and biopsy and treatment indications. The significant association between the PRS and lethal PCa outcomes should be validated in additional populations with larger sample sizes.

There is a proportion of men with lethal PCa who have baseline PSA <1 ng/ml. A PCa PRS may improve identification of men with low baseline PSA who should consider continued PSA screening.

Author contributions: Mark A. Preston 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: Preston, Penney.
Acquisition of data: Penney.
Analysis and interpretation of data: Ma, Penney, Preston.
Drafting of the manuscript: Ma, Penney, Preston.
Critical revision of the manuscript for important intellectual content: Carlsson, Lilja, Kibel, Graff, Plym, Giovannucci, Mucci, Preston, Penney.
Statistical analysis: Ma, Penney.
Obtaining funding: Preston, Carlsson, Lilja.
Administrative, technical, or material support: Plym.
Supervision: Preston, Penney.
Other: None.

Financial disclosures: Mark A. Preston certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** This study was funded by the Department of Defense (W81XWH-19-1-0708, M.A.P.) and the National Institutes of Health/National Cancer Institute (P30-CA008748, S.V.C and H.L.; K22-CA234400, S.V.C.). Physicians' Health Study PSA data generation was supported by the Department of Defense (W81XWH-18-1-0158). The sponsor played a role in manuscript preparation. K.L.P., M.A.P., and R.E.G. are Prostate Cancer Foundation young investigators. The content is solely the responsibility of the authors and does not necessarily represent the official views of the sponsors.

Data sharing statement: The data sets analyzed in the current study are not publicly available because of restricted access, but further information about the data sets is available from the corresponding authors on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.01.012.

References

[1] Frånlund M, Månsson M, Godtman RA, et al. Results from 22 years of follow-up in the Göteborg randomized population-based prostate cancer screening trial. J Urol 2022;208:292–300.
[2] Martin RM, Donovan JL, Turner EL, et al. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. JAMA 2018;319:883–95.
[3] Preston MA, Batista JL, Wilson KM, et al. Baseline prostate-specific antigen levels in midlife predict lethal prostate cancer. J Clin Oncol 2016;34:2705–11.
[4] Preston MA, Gerke T, Carlsson SV, et al. Baseline prostate-specific antigen level in midlife and aggressive prostate cancer in Black men. Eur Urol 2019;75:399–407.
[5] Carlsson S, Assel M, Sjoberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. BMJ 2014;348:g2296.
[6] Kovac E, Carlsson SV, Lilja H, et al. Association of baseline prostate-specific antigen level with long-term diagnosis of clinically significant prostate cancer among patients aged 55 to 60 years: a secondary analysis of a cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. JAMA Netw Open 2020;3:e1919284.
[7] 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.
[8] Gann PH, Ma J, Catalona WJ, et al. Strategies combining total and percent free prostate specific antigen for detecting prostate cancer: a prospective evaluation. J Urol 2002;167:2427–34.
[9] Ma C, Wang Y, Wilson KM, et al. Circulating insulin-like growth factor 1-related biomarkers and risk of lethal prostate cancer. JNCI Cancer Spectr 2021;6:pkab091.
[10] Klein RJ, Vertosick E, Sjoberg D, et al. Prostate cancer polygenic risk score and prediction of lethal prostate cancer. NPJ Precis Oncol 2022;6:25.

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