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Baseline Prostate-specific Antigen Level in Midlife and Aggressive Prostate Cancer in Black Men

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Abstract

Background: Prostate-specific antigen (PSA) measurement in midlife predicts long-term prostate cancer (PCa) mortality among white men.
Objective: To determine whether baseline PSA level during midlife predicts risk of aggressive PCa in black men.
Design, setting, and participants: Nested case-control study among black men in the Southern Community Cohort Study recruited between 2002 and 2009. A prospective cohort in the southeastern USA with recruitment from community health centers. A total of 197 incident PCa patients aged 40–64 yr at study entry and 569 controls matched on age, date of blood draw, and site of enrollment. Total PSA was measured in blood collected and stored at enrollment.
Outcome measurements and statistical analysis: Total and aggressive PCa (91 aggressive: Gleason ≥7, American Joint Committee on Cancer stage III/IV, or PCa-specific death). Exact conditional logistic regression estimated odds ratios (ORs) with 95% confidence intervals (CIs) for PCa by category of baseline PSA.
Results and limitations: Median PSA among controls was 0.72, 0.80, 0.94, and 1.03 ng/ml for age groups 40–49, 50–54, 55–59, and 60–64 yr, respectively; 90th percentile levels were 1.68, 1.85, 2.73, and 3.33 ng/ml. Furthermore, 95% of total and 97% of aggressive cases had baseline PSA above the age-specific median. Median follow-up was 9 yr. The OR for total PCa comparing PSA >90th percentile versus ≤median was 83.6 (95% CI, 21.2–539) for 40–54 yr and 71.7 (95% CI, 23.3–288) for 55–64 yr. For aggressive cancer,

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ORs were 174 (95% CI, 32.3–infinity) for 40–54 yr and 51.8 (95% CI, 11.0–519) for 55–64 yr. A composite endpoint of aggressive PCa based on stage, grade, and mortality was used and is a limitation.
Conclusions: PSA levels in midlife strongly predicted total and aggressive PCa among black men. PSA levels among controls were similar to those among white controls in prior studies.
Patient summary: Prostate-specific antigen (PSA) level during midlife strongly predicted future development of aggressive prostate cancer among black men. Targeted screening based on a midlife PSA might identify men at high risk while minimizing screening in those men at low risk.

1. Introduction

The United States Preventive Services Task Force (USPSTF) recently updated their evaluation of prostate-specific antigen (PSA) screening for prostate cancer (PCa) to a "C" grade, recommending that physicians selectively provide PSA testing to individual patients based on professional judgment and patient preferences [1]. This is based on evidence that screening reduces PCa mortality but at the cost of significant over-diagnosis and over-treatment. This C recommendation applies to the general US population, including black men, who suffer a higher burden of disease [2,3]. However, the USPSTF noted an absence of direct evidence on the benefits and harms of screening in this high-risk population and recommended that research on screening in African-American men should be a national priority.

Risk-stratified screening targeting men at higher risk of aggressive PCa could capture much of the benefit of population-wide screening while reducing over-diagnosis. One approach to targeted screening is to use a baseline PSA measured during midlife to estimate risk and determine the frequency of further screening, with more frequent screening among men with high baseline PSA and minimal to no further testing for men with the lowest levels [4,5]. This strategy is based on the natural history of the disease; autopsy studies show that PCa begins early in adulthood, with significant rates of cancer in men in their 30s and is even more pronounced in black men [6,7]. Thus, PSA levels measured in midlife may reflect early stages of the disease process while being less prone to elevation due to benign prostatic hyperplasia (BPH) than levels later in life [8].

Multiple studies of this baseline PSA strategy in the US [2,9–13] and Sweden [14–17], have shown that baseline PSA levels at age 40–60 yr strongly predict PCa incidence and mortality over several decades among primarily white men. To date, there have been only two studies of baseline PSA levels and subsequent aggressive PCa risk among black men [9,11].

In this context, we undertook a nested case-control study among black men in the Southern Community Cohort Study (SCCS) to determine whether baseline PSA levels in midlife predicted future risk of PCa, with a focus on aggressive disease, as this is the most clinically relevant and less likely to be over-diagnosed.

2. Materials and methods

2.1. Study population

The National Cancer Institute-funded SCCS was established in 2001 to address and identify the underlying causes of cancer health disparities. This prospective cohort of 86 000 men and women from the southeastern US has the highest representation of African-Americans (n = 22 905 men) among existing cohorts and has a large biorepository [18]. We performed a nested case-control study of incident PCa including 766 men selected from among 10 504 black men aged 40–64 yr at study entry during 2002–2009 who gave blood at enrollment, were free of diagnosed cancer at enrollment, and provided informed consent. Recruitment took place at community health centers across 12 southern states. This project was approved by the SCCS Data and Biospecimen Use Committee and the Brigham and Women's Hospital's Institutional Review Board.

2.2. Identification of PCas and deaths

Incident PCa among cohort members was identified through linkage with state cancer registries. Although linkage and reporting lags are common, the registries provide nearly complete (>90%) and unbiased ascertainment of cancers diagnosed among the participants after their entry into the SCCS [18]. We identified 197 incident PCa *cases* through 2015, 91 of whom had aggressive disease (Gleason $\geq$7 [n = 75], American Joint Committee on Cancer (AJCC) stage III or IV [n = 26], or PCa-specific death [n = 16]; stage was available for 83% of cases, and grade was available for 70% of cases). We identified deaths attributed to PCa as those with underlying cause of death coded as ICD-9-CM 185 or ICD-10 C61. For each case, up to three controls who were alive without a PCa diagnosis at the case's diagnosis date were selected by incidence density sampling, matching on age ($\pm$1 yr), study site, and date of blood draw ($\pm$1 yr), resulting in 197 PCa cases and 569 controls for this analysis. For the analysis of aggressive cancer, we included only controls who were alive and free of aggressive PCa at the date of the case's "aggressive-defining" event (advanced stage or high-grade at diagnosis or PCa death). Five of the 91 aggressive cases were defined as aggressive based only on death from PCa, and we excluded three controls who were not alive at time of their matched case's death.

2.3. Total PSA assay

Blood samples were analyzed in Dr. Lilja's laboratory at Lund University, Malmö, Sweden. Plasma aliquots from cases and controls were grouped in blinded case-control sets and handled together throughout processing and analysis along with blinded quality control samples. Total PSA measurements were performed on the AutoDelfia 1235 automatic immunoassay system using the dual-label DELFIA Prostatus total/free PSA-Assay (Perkin-Elmer, Turku, Finland) as described previously

[19]. Intra- and inter-batch coefficients of variation were 4.5% and 6.5%, respectively. Concentrations of total PSA in plasma stored at–80 °C for 20 yr are comparable to concentrations in samples measured soon after blood draw [20].

2.4. Statistical analysis

Exact conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between categories of baseline PSA and risk of total and aggressive PCa, overall and within two age groups: 40–54 and 55–64 yr. Baseline PSA values were categorized into quantiles within narrower age groups (40–49, 50–54, 55–59, and 60–64 yr) according to the distribution of levels among the controls, as age is a major determinant of PSA levels. For the analysis of aggressive PCa among men aged 40–54 yr, there were no cases in the reference group (≤median); therefore, the median unbiased estimate was used [21].

In secondary analyses, we excluded men with PSA >4 ng/ml (81 cases, 24 controls) to test the predictive ability of baseline PSA among men with PSA in a normal range for whom baseline PSA could be used to determine an on-going risk-stratified screening strategy. We also conducted analyses excluding cases diagnosed within the first 2 yr (excluding 46 total, 41 aggressive) and 5 yr (excluding an additional 64 total, 47 aggressive) of follow-up to better assess the ability of baseline PSA to predict disease over a longer period. Finally, we conducted a sensitivity analysis among cases that were fatal or AJCC stage III/IV at diagnosis (n = 33), as these advanced cases are most likely to be clinically apparent and less likely to be diagnosed based only on PSA screening. For these sensitivity analyses, as matching was broken due to exclusions, we controlled for matching factors.

Self-reported information was recorded at enrollment on race/ethnicity, height, weight, marital status, education, diabetes, smoking, family history of PCa, and ever having a PSA test, or digital rectal exam prior to study entry. We present only models adjusted for matching factors, as results were similar when adjusted for covariates. Data on PSA testing after study entry was available from a subset of men who completed one or two follow-up questionnaires an average of 4.5 and 7.5 yr after baseline.

Two-sided p values <0.05 indicated statistical significance. Analyses were performed using SAS version 9.4 (SAS Institute, Inc.; Cary, NC) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria, 2015).

3. Results

Descriptive statistics of the study population are shown in Table 1. Median age at blood draw was 56 yr. Median time from blood draw to diagnosis was 4.4 yr among all cases and 5.0 yr among aggressive cases, with a maximum time of 10.25 yr (Table 1). Median PSA levels among controls ranged from 0.72 ng/ml for age 40–49 yr to 1.03 ng/ml for age 60–64 years; full distributions by age group, which were used to create the categories discussed below, are shown in Table 3.

Risk of PCa rose monotonically with rising PSA regardless of age. Compared to men with PSA at or below the age-specific median, men with levels above the median had significantly increased risk of PCa; ORs were 25.2 (95% CI, 8.01–127) for men aged 40–54 yr and 17.5 (95% CI, 7.10–55.9) for men aged 55–64 yr. ORs for men with a baseline PSA >90th percentile (compared to ≤median) were: 83.6 (95% CI, 21.2–539) for men aged 40–54 and 71.7 (95% CI, 23.2–288) for 55–64 yr (Table 2).

Compared to men with PSA at or below the age-specific median, men with levels above the median had significantly increased risk of aggressive PCa across age groups. Comparing PSA levels >median versus ≤median, ORs for aggressive PCa were 49.6 (95% CI, 10.8–infinity) for men aged 40–54 yr and 18.7 (95% CI, 4.71–162) for men aged 55–64 yr. ORs comparing men with PSA >90th percentile versus ≤median were 174 (95% CI, 32.2–infinity) for age 40–54 yr and 51.8 (95% CI, 11.0–519) for age 55–64 yr (Table 2). Men between the 75th and 90th percentile were also at significantly increased risk of aggressive disease (Supplementary Table 1).

Baseline PSA was still highly associated with risk of total and aggressive disease when excluding men with PSA >4 ng/ml (Table 2). The elevated risks persisted after excluding cases diagnosed within 2 or 5 yr of blood draw, though results were attenuated. Finally, the elevated risks persisted when aggressive cases were limited to those that were fatal or AJCC stage III/IV at diagnosis, with an OR for >90th percentile versus ≤median of 39.5 (95% CI, 7.37–infinity) for ages 40–54 yr and 28.3 (95% CI, 5.73–infinity) for age 55–64 yr.

Table 3 shows the proportion of cases captured in different PSA categories by age group. All 36 aggressive PCa cases in men aged 40–54 yr occurred among those with baseline PSA above the age-specific median. Among men aged 55–64, 52/55 aggressive cases (95%) were in men with baseline PSA above the age-specific median.

4. Discussion

In this prospective study among US black men, we found that a single baseline PSA level measured during midlife strongly predicted subsequent diagnosis of total and aggressive PCa up to 12 yr after blood draw. Risk was significantly higher for men with PSA levels above the age-specific median than for those with PSA levels below the age-specific median. Men above the 90th percentile had the greatest risk relative to those below the median. As expected, PSA was somewhat less predictive of PCa among the older age group of 55–64 yr, likely because BPH becomes more common in older men and influences PSA levels apart from PCa [8].

Of note, increased risk was seen with PSA levels of 1.1–1.7 ng/ml at ages 40–54 yr, well within the “normal” range, and low enough not to trigger follow-up in usual clinical practice. These findings do not imply that prostate biopsy or definitive treatment is immediately required in younger men with higher PSA levels at baseline, as this could lead to over-diagnosis, but that they undergo more intensive PSA screening to enable earlier identification of cancer and potential cure while still possible. This “smarter screening” approach may allow identification of men at high risk while reducing population-level harms through less intensive screening of very low-risk men [22].

The new USPSTF recommendation applies to men aged 55–69 yr but acknowledges that men at higher risk, including African-American men and men with a family history, may wish to start screening earlier [1]. Similarly, guidelines from other organizations recommend screening begin at age 50 yr, while men at increased risk due to family

Table 1 – Characteristics of prostate cancer cases and controls aged 40–64 yr, Southern Community Cohort Study

	Controls (n = 569)	Cases (n = 197)	Aggressive cases[a] (n = 91)
Follow-up time, yr, median (IQR)	9.0 (7.0–11.0)	9.0 (7.0–11.0)	9.0 (7.0–10.0)
Blood markers, median (IQR)			
Total PSA (ng/ml)	0.83 (0.51–1.40)	3.50 (2.08–6.48)	3.68 (2.25–9.83)
Age at blood draw, n (%)			
40–49 yr	110 (19)	36 (18)	15 (16)
50–54 yr	143 (25)	45 (23)	21 (23)
55–59 yr	172 (30)	59 (30)	27 (30
60–64 yr	144 (25)	57 (29)	28 (31)
Ever had DRE by baseline (%)	63	67	73
Ever had PSA test by baseline (%)	56	58	48
Marital status, n (%)			
Married	175 (31)	77 (39)	29 (32)
Separated/divorced	243 (43)	79 (40)	47 (52)
Widowed	31 (5)	11 (6)	5 (5)
Single, never married	120 (21)	30 (15)	10 (11)
Education, n (%)			
<9 yr	71 (12)	20 (10)	8 (9)
9–11 yr	154 (27)	53 (27)	28 (31)
High school/GED	189 (33)	71 (36)	33 (36)
Vocational school/some college	116 (20)	31 (16)	11 (12)
College/graduate school	39 (7)	22 (11%)	11 (12)
BMI at baseline, n (%)			
<25 kg/m^2	198 (35)	63 (32)	31 (34)
25–29 kg/m^2	203 (36)	69 (35)	27 (30)
≥30 kg/m^2	168 (30)	65 (33)	33 (36)
Smoking status at baseline, n (%)			
Never	128 (22)	38 (19)	17 (19)
Past	137 (24)	62 (31)	22 (24)
Current	304 (53)	97 (49)	52 (57)
Pack-years among ever smokers, mean	22.8	24.2	23.3
Case characteristics			
Median age at diagnosis, yr (IQR)		60.4 (55.5–64.3)	60.5 (55.9–65.0)
Median time to diagnosis, yr (IQR)		4.4 (2.2–6.1)	5.0 (2.5–6.3)
Diagnosed within 1 yr of blood draw, n (%)		17 (9)	5 (5)
Diagnosed within 2 yr of blood draw, n (%)		46 (23)	18 (20)
Diagnosed within 5 yr of blood draw, n (%)		110 (55)	47 (52)
Fatal cases		16 (8)	16 (16)
Aggressive cases [a], n (%)		91 (46)	91 (100)
AJCC stage at diagnosis, n (%)			
I		11 (6)	0 (0)
II		127 (64)	56 (62)
III		14 (7)	14 (15)
IV		12 (6)	12 (13)
Unknown		33 (17)	9 (10)
Gleason grade at diagnosis, n (%)			
≤6		63 (32)	2 (2)
7: 3 + 4		41 (21)	41 (45)
7: 4 + 3		15 (8)	15 (16)
8–10		19 (10)	19 (21)
Unknown		59 (30)	14 (15)

AJCC = American Joint Committee on Cancer; BMI = body mass index; DRE = digital rectal exam; IQR = interquartile range; PSA = prostate-specific antigen.
[a] Aggressive prostate cancer: Gleason grade ≥7, or AJCC stage III or IV, or prostate cancer death.

history or race may initiate screening at 40–50 yr [23,24]. However, midlife PSA predicts subsequent aggressive PCa better than either family history or race [25], suggesting that using midlife PSA level to determine ongoing screening needs may be superior to these traditional risk factors.

Only two studies of baseline PSA have included enough black men to compare results from white and black men. One small nested case-control study [9] in California found similar associations in white and black men between PSA levels at age 50 yr and risk of advanced stage PCa over 7 yr. Another nested case-control study [11] in a different California population found that PSA at a median age of 34 yr was associated with increased risk of total and aggressive PCa over several decades, though loss to follow-up was high and outcome ascertainment somewhat incomplete [11].

Our results are in line with those studies as well as with studies of the longer-term predictive value of baseline PSA among primarily white men in the USA [2,9–11,13] and Sweden [15,16]. We [2] and others have found substantially increased risk of PCa metastasis or death over 20–30 yr of

Table 2 – Odds ratios[a] and 95% confidence intervals of the association between baseline total prostate-specific antigen in midlife and risk of total (*n* = 197) and aggressive (*n* = 91) prostate cancer among African-American men in the Southern Community Cohort study

	Total prostate cancer Age-specific total PSA percentiles[b]				Aggressive prostate cancer[c] Age-specific total PSA percentiles[b]			
	≤50th percentile	>50th percentile	>75th percentile	>90th percentile	≤50th percentile	>50th percentile	>75th percentile	>90th percentile
Full study population, 40–64 yr								
Cases/controls	9/289	188/280	174/141	140/59	3/133	88/129	83/64	65/24
OR (95% CI)	1.00 (ref)	18.8 (9.50–42.3)	32.1 (15.6–75.9)	71.5 (31.0–190)	1.00 (ref)	24.9 (8.04–125)	37.0 (11.7–189)	78.8 (21.7–454)
40–54 yr								
Cases/controls	3/129	78/124	73/62	62/26	0/61	36/54	35/25	27/8
OR (95% CI)	1.00 (ref)	25.2 (8.01–127)	46.4 (13.2–267)	83.6 (21.2–539)	1.00 (ref)	49.6 (10.8–inf)[d]	87.4 (18.0–inf)[d]	174 (32.2–inf)[d]
55–64 yr								
Cases/controls	6/160	110/156	101/79	78/33	3/72	52/75	48/39	38/16
OR (95% CI)	1.00 (ref)	17.5 (7.10–55.9)	28.9 (11.2–96.4)	71.7 (23.3–288)	1.00 (ref)	18.7 (4.71–162)	25.3 (6.32–221)	51.8 (11.0–519)
Excluding men with total PSA > 4 ng/ml[2], age 40–64 yr								
Cases/controls	9/166	107/159	96/81	66/29	3/71	47/69	43/34	27/8
OR (95% CI)	1.00 (ref)	11.8 (5.59–28.6)	18.4 (8.49–46.1)	33.5 (13.8–94.7)	1.00 (ref)	12.7 (3.93–65.5)	18.5 (5.68–96.3)	39.8 (9.74–260)
Excluding cases diagnosed within 2 yr of blood draw, age 40–64 yr								
Cases/controls	9/226	142/213	129/108	98/48	3/104	70/107	65/52	47/22
OR (95% CI)	1.00 (ref)	14.5 (7.27–33.0)	24.8 (11.8–59.3)	46.9 (20.2–125)	1.00 (ref)	18.8 (5.99–95.5)	28.9 (8.97–149)	53.7 (14.5–314)
Excluding cases diagnosed within 5 yr of blood draw, age 40–64 yr								
Cases/controls	6/125	81/127	71/68	46/26	2/64	42/63	38/33	22/12
OR (95% CI)	1.00 (ref)	11.7 (4.96–33.7)	18.2 (7.42–54.3)	36.2 (12.6–128)	1.00 (ref)	18.5 (4.56–163)	25.0 (6.14–220)	40.6 (8.32–411)

CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen.
[a] Estimated using exact conditional logistic regression due to sparse data in some strata. Matching factors were age and community health center of enrollment.
[b] Based on 5-yr age group-specific quantiles; see Table 3 for values. Cutoffs for sensitivity analysis excluding PSA >4 ng/ml are based on age-group specific distribution among controls after excluding PSA >4 ng/ml; median, 75th, and 90th percentile cut points by age group in this analysis are as follows: For 40–49 yr: 0.71, 1.07, 1.62 mg/ml. For 50–54 yr: 0.80, 1.07, 1.74 ng/ml. For 55–59 yr: 0.85, 1.40, and 2.18 ng/ml. For 60–65 yr: 1.00, 1.48, and 2.77 ng/ml. Cutoffs for analysis excluding cases diagnosed in first 2 yr are based on distributions as shown in Table 3.
[c] Aggressive prostate cancer: Gleason grade 7 and above, or AJCC Stage III or IV, or prostate cancer death.
[d] Median unbiased estimate.

Table 3 – Proportion of total and aggressive prostate cancers captured by percentiles of total PSA levels in controls by age group

	PSA level (ng/ml)	Total prostate cancer, % (*n* = 197)	Aggressive cancer[a], % (*n* = 91)
40–49 yr			
Top 10th percentile	>1.68	31 (86)	15 (100)
Top quartile	>1.15	32 (89)	15 (100)
Above median	>0.72	34 (94)	15 (100)
Below median	≤0.72	2 (6)	0 (0)
Bottom quartile	≤0.44	0 (0)	0 (0)
Bottom 10th percentile	≤0.32	0 (0)	0 (0)
50–54 yr			
Top 10th percentile	>1.85	31 (69)	12 (57)
Top quartile	>1.08	41 (91)	20 (95)
Above median	>0.80	44 (98)	21 (100)
Below median	≤0.80	1 (2)	0 (0)
Bottom quartile	≤0.46	0 (0)	0 (0)
Bottom 10th percentile	≤0.33	0 (0)	0 (0)
55–59 yr			
Top 10th percentile	>2.73	39 (66)	20 (74)
Top quartile	>1.66	51 (86)	23 (85)
Above median	>0.94	55 (93)	25 (93)
Below median	≤0.94	4 (7)	2 (7)
Bottom quartile	≤0.52	2 (3)	1 (4)
Bottom 10th percentile	≤0.36	1 (2)	0 (0)
60–64 yr			
Top 10th percentile	>3.33	39 (68)	18 (64)
Top quartile	>1.89	50 (88)	25 (89)
Above median	>1.03	55 (96)	27 (96)
Below median	≤1.03	2 (4)	1 (4)
Bottom quartile	≤0.64	2 (4)	1 (4)
Bottom 10th percentile	≤0.39	1 (2)	1 (4)

PSA = prostate-specific antigen.
[a] Aggressive prostate cancer: Gleason grade 7 and above, or AJCC Stage III or IV, or prostate cancer death.

follow-up for men with higher PSA at age 35–55 yr. Also in line with our results, these studies found that men with PSA below the median for their age had a very low long-term risk of aggressive PCa.

Table 4 compares baseline PSA levels and the proportion of cases captured by different PSA categories between our study and results from the Physicians' Health Study (PHS) [2] and the Malmo Preventive Project [15]. Our study differs from these two studies with regards to not only race but also other key factors, including length of follow-up (one decade vs 2+ decades), outcome definition (aggressive vs metastatic/fatal disease), time period (pre-PSA vs post-PSA screening eras), and socioeconomic position/access to health care. To facilitate comparison, we have included unpublished results in Table 4 for "aggressive" PCa in PHS using the same definition and follow-up period as in the present analysis. Within PHS, the difference between the proportion of aggressive cases captured over 10 yr and that of lethal cases captured over 30 yr is not large; the proportions remain slightly lower than those in SCCS. This suggests that the higher sensitivity of baseline PSA observed in SCCS is more likely due to differences in race, time period, and characteristics of the study population rather than differences in the outcome definition and length of follow-up. Based on this comparison, it appears that baseline PSA captures aggressive PCa at least as well in black men as in white men.

In addition, it is noteworthy that baseline PSA levels among controls in our study were similar to those among white controls from other prospective nested case-control studies of baseline PSA levels in midlife (Tables 4 and 5) [2,15,16]. Only one prior study [11] reported results for black controls while also finding similar PSA distributions among black and white controls.

The similarity in distributions of baseline PSA levels between black and white controls in nested case-control studies is in contrast to that in many cross-sectional studies, including an earlier study in SCCS participants [26], which found higher PSA levels in black men [27–33], particularly among older age groups. These studies measured PSA in men without clinical evidence of PCa at time of blood draw but did not assess eventual case/control status over time. Thus, they include men with undiagnosed, prevalent PCa. National cancer statistics [34] and autopsy studies [6] show that black men have higher rates of disease at every age; therefore, cross-sectional studies would be expected to find higher PSA levels among black men due to a higher prevalence of latent disease. Nested case-control studies of PSA are less likely to include men with prevalent disease, as there is follow-up time after baseline during which prevalent disease might be diagnosed. The observations of similar midlife PSA between black and white men in this and other nested case-control studies [11,12,15,16] suggest that a risk-stratified screening strategy of PSA measured in midlife might use similar cut points for black and white men.

While this is the largest prospective study exploring prediction of PCa by baseline PSA in a population of black men, our study is subject to limitations. Importantly, there exists an issue of "verification bias" due to presence of opportunistic PSA screening during the study period. However, results of PSA measurements made for this

Table 4 – Comparison between studies of baseline prostate-specific antigen distribution and proportion of prostate cancer cases captured by percentile groups

	Southern Community Cohort Study (100% black men; max. 13-yr follow-up)		Physicians' Health Study [2] (96% white men; max. 30-yr follow-up)			Malmo Preventative Project [15] (>95% white men; max. 32-yr follow-up)	
Age-specific PSA categories	PSA level (ng/ml)	Aggressive[a] prostate cancer (%)	PSA level (ng/ml)	Lethal[b] prostate cancer (%)	Aggressive[c] prostate cancer, 10-yr follow-up (%)	PSA level (ng/ml)	Lethal[b] prostate cancer (%)
Age 40–49 yr							
Top 10th percentile	>1.68	100	>1.68	55	62	>1.6	44
Top quartile	>1.15	100%	>1.04	82	85	>1.1	54
Above median	>0.72	100	>0.68	82	92	>0.68	72
Age 50–54 yr							
Top 10th percentile	>1.85	57	>1.96	65	67	>2.4	44
Top quartile	>1.08	95	>1.4	65	67	>1.4	59
Above median	>0.8	100	>0.88	71	81	>0.85	84
Age 55–59 yr							
Top 10th percentile	>2.73	74	>2.88	51	60		
Top quartile	>1.66	85	>1.64	70	75		
Above median	>0.94	93	>0.96	86	89		
Age 60–64 yr							
Top 10th percentile	>3.33	64				>3.43	61
Top quartile	>1.89	89				>1.9	80
Above median	>1.03	96				>1.1	91

PSA = prostate specific antigen.

[a] Aggressive prostate cancer: Gleason grade 7 and above, or AJCC Stage III or IV, or prostate cancer death.

[b] Lethal prostate cancer: metastatic cancer at diagnosis or during follow-up, or prostate cancer death.

[c] For the Physicians' Health Study, results for aggressive cancer are previously unpublished and presented here for comparison with Southern Community Cohort Study results. These results are based on 10 yr of follow-up and aggressive prostate cancer as defined in note 1.

Table 5 – Distribution of total PSA (ng/ml) by age group and race among controls from case-control studies of prostate cancer[a]

Age group	Race	*n*	Study population	Total PSA, ng/ml				Reference
				25th percentile	50th percentile	75th percentile	90th percentile	
40–49 yr								
40–49	Black	110	SCCS	0.44	0.72	1.15	1.68	Current study
40–55	Black	69	CHDS[b]	0.24	0.41	0.72	–	Whittemore et al., 2005 [11]
40	White	228	VIP	0.50	0.70	0.90	–	Stattin et al., 2015 [16]
40–55	White	78	CHDS[b]	0.27	0.48	0.87	–	Whittemore et al., 2005 [11]
40–49	White (94%)	104	PHS	0.52	0.68	1.04	1.68	Preston et al., 2016 [2]
45–49	White	514	Malmo	0.41	0.60	0.94	–	Vickers et al., 2013 [15]
50–55 yr								
50–54	Black	143	SCCS	0.46	0.80	1.08	1.85	Current study
50	White	1157	VIP	0.60	0.80	1.20	–	Stattin et al., 2015 [16]
50–54	White (94%)	202	PHS	0.59	0.88	1.40	1.96	Preston et al., 2016 [2]
51–55	White	3970	Malmo	0.52	0.84	1.36	–	Vickers et al., 2013 [15]
55–59 yr								
55–59	Black	172	SCCS	0.52	0.94	1.65	2.73	Current study
55–59	White (94%)	405	PHS	0.60	0.96	1.64	2.88	Preston et al., 2016 [2]

CHDS = Child Health and Development Study; PHS = Physicians' Health Study; PSA = prostate-specific antigen; SCCS = Southern Community Cohort Study; VIP = Västerbotten Intervention Project.

[a] PSA levels by race among controls from all nested case-control studies of baseline PSA that reported PSA levels by age group.

[b] PSA values for both races were low in this study, possibly due to differences in laboratory assay or storage of blood samples, which were collected in the early 1960s.

research were not known by participants. In addition, among the 48% of men who completed follow-up questionnaires approximately 4.5 yr after cohort entry and 36% who completed a second follow-up at 7.5 yr, there was no difference among controls in the prevalence of PSA testing between those with baseline PSA above or below the median.

Sensitivity analyses support limited verification bias as we note the increased risk of PCa for men with baseline PSA well below 4.0 ng/ml, which is the cutoff that typically triggers follow-up in clinical practice. Indeed, associations remained very strong when we excluded men with baseline PSA >4 ng/ml. In addition, we observed a strong association with advanced disease which is less affected by "overdiagnosis".

With a median follow-up of 9 yr and maximum time between blood draw and PCa diagnosis of 12 yr, we were unable to test the longer-term ability of a single baseline PSA test to predict risk of aggressive PCa. The high ORs observed would likely be attenuated with additional follow-up as cancer is diagnosed in controls and PSA becomes less predictive over time [35]. In addition, we could not distinguish stage T3a and T3b cancers due to the level of detail available in cancer registry data for most of the men. Thus, our definition of "aggressive" disease likely includes some men with T3a disease, which is less aggressive than stage T3b. Finally, we note that many of the reported OR CIs are wide, with infinite upper limits in certain cases when there were no cases in the reference group. However, since the exact logistic regression procedures used here are known to be conservative [36], the fact that all lower limits are bounded well away from 1.00 alleviates concern of false-positive associations.

5. Conclusion

PSA levels in midlife strongly predict subsequent development of aggressive PCa in a cohort of black men subject to opportunistic PSA screening. PSA levels from 1 to 3 ng/ml were indicative of large increases in risk, with few PCa cases occurring among men with levels <1 ng/ml. The totality of evidence from this study and previous work provides strong support for use of midlife PSA level to determine a personalized screening strategy.

Author contributions: Mark A. Preston and Kathryn M. Wilson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Blot, Signorello, Steinwandel, Lilja.
Analysis and interpretation of data: Preston, Wilson, Gerke, Blot, Markt.
Drafting of the manuscript: Preston, Wilson, Gerke, Markt, Trinh, Carlsson.
Critical revision of the manuscript for important intellectual content: Kibel, Vickers, Signorello, Mucci, Blot.
Statistical analysis: Wilson, Gerke, Carlsson, Vickers, Sjoberg.
Obtaining funding: Preston, Mucci, Lilja.
Administrative, technical, or material support: Kibel, Lilja, Mucci.
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for a statistical method to detect prostate cancer. The marker assay patents and the patent application for the statistical model has been licensed and commercialized as the 4 K score by OPKO Diagnostics. Drs. Vickers and Lilja receive royalties from sales of this test. Additionally, Dr. Lilja owns stock and Dr. Vickers owns stock options in OPKO.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.08.032.

References

[1] US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2018;319:1901–13.
[2] 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.
[3] Chornokur G, Dalton K, Borysova ME, Kumar NB. Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer. Prostate 2011;71:985–97.
[4] Loeb S, Carter HB, Catalona WJ, Moul JW, Schroder FH. Baseline prostate-specific antigen testing at a young age. Eur Urol 2012;61:1–7.
[5] Ross KS, Carter HB, Pearson JD, Guess HA. Comparative efficiency of prostate-specific antigen screening strategies for prostate cancer detection. JAMA 2000;284:1399–405.
[6] Jahn JL, Giovannucci E, Stampfer MJ. The high prevalence of undiagnosed prostate cancer at autopsy: Implications for epidemiology and treatment of prostate cancer in the prostate-specific antigen-era. Int J Can 2015;137:2795–802.
[7] Zlotta AR, Egawa S, Pushkar D, et al. Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst 2013;105:1050–8.
[8] Nadler RB, Humphrey PA, Smith DS, Catalona WJ, Ratliff TL. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. J Urol 1995;154:407–13.
[9] Whittemore AS, Lele C, Friedman GD, Stamey T, Vogelman JH, Orentreich N. Prostate-specific antigen as predictor of prostate cancer in black men and white men. J Natl Cancer Inst 1995;87:354–60.
[10] Fang J, Metter EJ, Landis P, Chan DW, Morrell CH, Carter HB. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. Urology 2001;58:411–6.
[11] Whittemore AS, Cirillo PM, Feldman D, Cohn BA. Prostate specific antigen levels in young adulthood predict prostate cancer risk: results from a cohort of Black and White Americans. J Urol 2005;174:872–6, discussion 6.
[12] Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology 2006;67:316–20.
[13] Kuller LH, Thomas A, Grandits G, Neaton JD. Elevated prostate-specific antigen levels up to 25 years prior to death from prostate cancer. Cancer Epidemiol Biomarkers Prev 2004;13:373–7.
[14] Lilja H, Cronin AM, Dahlin A, et al. Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. Cancer 2011;117:1210–9.
[15] Vickers AJ, Ulmert D, Sjoberg DD, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. BMJ 2013;346:f2023.
[16] Stattin P, Vickers AJ, Sjoberg DD, et al. Improving the specificity of screening for lethal prostate cancer using prostate-specific antigen and a panel of kallikrein markers: a nested case-control study. Eur Urol 2015;68:207–13.
[17] Vickers AJ, Cronin AM, Bjork T, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. BMJ 2010;341:c4521.
[18] Signorello LB, Hargreaves MK, Blot WJ. The Southern Community Cohort Study: investigating health disparities. J Health Care Poor Underserved 2010;21:26–37.
[19] Vickers AJ, Gupta A, Savage CJ, et al. A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening. Cancer Epidemiol Biomarkers Prev 2011;20:255–61.
[20] Ulmert D, Becker C, Nilsson JA, et al. Reproducibility and accuracy of measurements of free and total prostate-specific antigen in serum vs plasma after long-term storage at -20 degrees C. Clin Chem 2006;52:235–9.
[21] Hirji K, Tsiatis A, Mehta C. Median unbiased estimation for binary data. Am Stat 1989;43:7–11.
[22] 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.
[23] American Cancer Society Recommendations for Prostate Cancer Early Detection. 2016. https://www.cancer.org/cancer/prostate-cancer/early-detection/acs-recommendations.html.
[24] American Urological Association. Early Detection of Prostate Cancer. 2015. http://www.auanet.org/guidelines/early-detection-of-prostate-cancer-(2013-reviewed-and-validity-confirmed-2015).
[25] Vertosick EA, Poon BY, Vickers AJ. Relative value of race, family history and prostate-specific antigen as indications for early initiation of prostate cancer screening. J Urol 2014;192:724–9.
[26] Fowke JH, Signorello LB, Chang SS, et al. Effects of obesity and height on prostate-specific antigen (PSA) and percentage of free PSA levels among African-American and Caucasian men. Cancer 2006;107:2361–7.
[27] Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW. Age-specific reference ranges for prostate-specific antigen in black men. N Engl J Med 1996;335:304–10.
[28] Weinrich MC, Jacobsen SJ, Weinrich SP, et al. Reference ranges for serum prostate-specific antigen in black and white men without cancer. Urology 1998;52:967–73.

[29] Abdalla I, Ray P, Ray V, Vaida F, Vijayakumar S. Comparison of serum prostate-specific antigen levels and PSA density in African-American, white, and Hispanic men without prostate cancer. Urology 1998;51:300–5.
[30] Preston DM, Levin LI, Jacobson DJ, et al. Prostate-specific antigen levels in young white and black men 20 to 45 years old. Urology 2000;56:812–6.
[31] Cooney KA, Strawderman MS, Wojno KJ, et al. Age-specific distribution of serum prostate-specific antigen in a community-based study of African-American men. Urology 2001;57:91–6.
[32] Martin B, Cheli C, Pollard S, et al. Similar age-specific PSA, complexed PSA, and percent cPSA levels among African-American and white men of southern Louisiana. Prostate-specific antigen. Urology 2003;61:375–9.
[33] Lacher DA, Thompson TD, Hughes JP, Saraiya M. Total, free, and percent free prostate-specific antigen levels among U.S. men, 2001–04. Adv Data 2006;1–12.
[34] SEER Cancer Statistics Review 1975–2013, National Cancer Institute. Bethesda, MD: National Cancer Institute; 2016.
[35] Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA 1995;273:289–94.
[36] Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. BMJ 2016;352:i1981.