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Improving the Specificity of Screening for Lethal Prostate Cancer Using Prostate-specific Antigen and a Panel of Kallikrein Markers: A Nested Case–Control Study

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Abstract

Background: A disadvantage of prostate-specific antigen (PSA) for the early detection of prostate cancer (PCa) is that many men must be screened, biopsied, and diagnosed to prevent one death.
Objective: To increase the specificity of screening for lethal PCa at an early stage.
Design, setting, and participants: We conducted a case–control study nested within a population-based cohort. PSA and three additional kallikreins were measured in cryopreserved blood from a population-based cohort in Västerbotten, Sweden. Of 40 379 men providing blood at ages 40, 50, and 60 yr from 1986 to 2009, 12 542 men were followed for >15 yr. From this cohort, the Swedish Cancer Registry identified 1423 incident PCa cases, 235 with distant metastasis.
Outcome measurements and statistical analysis: Risk of distant metastasis for different PSA levels and a prespecified statistical model based on the four kallikrein markers.
Results and limitations: Most metastatic cases occurred in men with PSA in the top quartile at age 50 yr (69%) or 60 yr (74%), whereas 20-yr risk of metastasis for men with PSA below median was low (≤0.6%). Among men with PSA >2 ng/ml, a prespecified model based on four kallikrein markers significantly enhanced the prediction of metastasis compared with PSA alone. About half of all men with PSA >2 ng/ml were defined as low risk by this model and had a ≤1% 15-yr risk of metastasis.
Conclusions: Screening at ages 50–60 yr should focus on men with PSA in the top quartile. A marker panel can aid biopsy decision making.
Patient summary: For men in their fifties, screening should focus on those in the top 10% to 25% of PSA values because the majority of subsequent cases of distant metastasis are found among these men. Testing of four kallikrein markers in men with an elevated PSA could aid biopsy decision making.

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1. Introduction

Recent evidence from randomized trials provides clear evidence that screening for prostate cancer (PCa) by testing serum levels of prostate-specific antigen (PSA) reduces cancer-specific mortality in men who would not otherwise be screened [1,2]. However, PSA is not specific to lethal PCa. As a result, many men need to be screened, biopsied, and diagnosed to prevent one death. One estimate is that 781 men need to be screened and 27 diagnosed per PCa death avoided at 13 yr [1].

One way to change the harm-to-benefit ratio would be to screen for cancers that are destined to become lethal. Metastatic PCa is associated with severe disease morbidity and a very high risk of PCa-specific death. We tested the hypothesis that PSA and a panel of PSA-related markers could predict the long-term risk of metastatic PCa in a large representative population-based longitudinal study of men providing cryopreserved blood at ages 40, 50, and 60 yr from 1986 to 2009.

2. Patients and methods

2.1. Study population

The Västerbotten Intervention Project (VIP) [3] is an ongoing population-based cohort study initiated in 1986 in which residents of Västerbotten County, Sweden, are invited to receive a health examination at ages 40, 50, and 60 yr with blood drawn for cryopreservation. By January 2009, VIP included data on 40 379 unique men with 50 557 blood draws, representing >57% of the total background population [4]. Initially the rate of PSA testing in this population was low, but it has increased over recent years: The proportion of PCa cases for which opportunistic screening was the cause for work-up leading to diagnosis increased from 9% in 2000 to 26% in 2005 and to 38% in 2011 [5]. However, these recent changes are likely to have little impact on metastasis rates in our current cohort due to the long lead time between diagnosis and metastasis.

2.2. Case identification and outcomes

In January 2009, the VIP cohort was linked to the Northern Sweden Regional Cancer Registry, part of the Swedish Cancer Registry, using the Swedish personal identity number. We identified 1423 incident PCa cases in the VIP cohort, 1377 of which had cryopreserved blood available for analysis. Clinical data were retrieved from the National Prostate Cancer Register. We reviewed hospital medical charts of men diagnosed with cancer to identify men who later had documented evidence of metastatic disease (ie, a positive bone scan) during the follow-up period. There were 126 patients with metastatic PCa diagnosed during follow-up who subsequently died from PCa, according to the Cause of Death Registry. Cause of death was assessed by medical chart review or, when charts were not available ($n = 4$), the Swedish Cause of Death Registry. An additional 12 men who died of PCa but who had not had metastases diagnosed prior to death were considered to have had metastatic disease at the date of death.

2.3. Control selection

Separate case–control matches were conducted for each end point: PCa diagnosis, PCa metastases, and PCa-specific death. There were separate analyses for men aged 40, 50, and 60 yr at baseline. For each relevant end point, we randomly selected three controls who were alive and event free at the date of the pertinent event for the index case, were within 3 mo of age of the index case, and had provided a blood sample within 3 mo of the blood draw for the index case. For the end point of PCa-specific death, all cases were matched successfully to three controls; for PCa metastases and PCa diagnosis, we expanded the window in 1-mo increments to 12 mo until three controls were identified.

All participants gave written informed consent at the time of recruitment, and the project was approved by the research ethics board at Umeå University (research authorization number 2009-1436-31).

2.4. Laboratory methods

We measured four kallikrein (KLK) markers—human kallikrein-related peptidase 2 (hK2) and total, free, and intact PSA—in cryopreserved blood samples from cases and controls. All laboratory analyses were conducted blind to outcome and case–control status. We measured total and free PSA with the dual-label DELFIA ProStatus assay (PerkinElmer, Turku, Finland) [6], calibrated against the World Health Organization (WHO) 96/670 (PSA-WHO) and WHO 68/668 (free PSA-WHO) standards, in previously unthawed cryopreserved heparin anticoagulated blood plasma. Intact PSA and hK2 were measured using F(ab′)2 fragments of the monoclonal capture antibodies to reduce the frequency of nonspecific assay interference [7].

2.5. Statistical methods

To estimate absolute risk, we used predictive mean matching to impute marker levels for men not selected as controls and for 16 men (1 man aged 50 yr and 15 men aged 60 yr) with metastasis who had missing samples. Statistical analyses were performed on the population level utilizing the measured and imputed values combined across 10 imputations using the Rubin rules. The four KLK markers were combined as previously described [8] into a statistical risk prediction model that gives

Table 1 – Participant characteristics in the Västerbotten Intervention Project*

	Age 40 yr† ($n = 17\,086$)	Age 50 yr† ($n = 17\,837$)	Age 60 yr† ($n = 15\,634$)
PSA, ng/ml, at ages 40, 50, and 60 yr	Median (25th, 75th percentile)		
Subsequent prostate cancer diagnosis	$n = 77$‡ 1.3 (0.9, 2.1)	$n = 399$‡ 2.0 (1.3, 3.3)	$n = 947$‡ 3.6 (2.0, 6.0)
Subsequent distant metastasis	$n = 10$‡ 1.1 (0.7, 3.1)	$n = 52$‡ 1.7 (1.2, 3.4)	$n = 173$‡ 4.5 (2.1, 9.8)
Controls with PSA measurement	$n = 228$ 0.7 (0.5, 0.9)	$n = 1157$ 0.8 (0.6, 1.2)	$n = 2598$ 1.1 (0.7, 2.0)
Controls with imputed PSA measurement	$n = 16\,781$ 0.7 (0.5, 0.9)	$n = 16\,281$ 0.8 (0.6, 1.2)	$n = 12\,089$ 1.1 (0.7, 2.0)
	No. of men		
Men at risk§			
10 yr	9172	9100	6725
15 yr	5115	4339	3088
20 yr	1117	645	422

PSA = prostate-specific antigen.
* A total of 12 men died from prostate cancer without documented metastasis. These were recorded as having metastasis on the date of death.
† Age at baseline showing the number of men providing blood samples.
‡ Number of men providing blood at ages 40, 50, and 60 yr later diagnosed with prostate cancer and with documented evidence of distant metastases.
§ Number of men providing blood at ages 40, 50, and 60 followed for 10, 15, and 20 yr.

the risk of any grade (or Gleason score ≥7) cancer at prostate biopsy. However, because the current study used anticoagulated blood plasma rather than serum, the model was adjusted using biopsy data from the UK Prostate Testing for Cancer and Treatment (ProtecT) study [9] that used blood plasma samples anticoagulated with ethylenediaminetetraacetic acid to predict Gleason score ≥7 (high-grade) cancer at 10-core prostate biopsy. The model was completed before it was applied to the VIP cohort [10], making the current study an external validation of a prespecified model. All analyses were conducted in Stata v.12 software (StataCorp, College Station, TX, USA).

3. Results

Table 1 shows the number of men in the VIP cohort who were aged 40, 50, and 60 yr at the time of the blood draw and PSA concentrations at those ages in men subsequently diagnosed with PCa and in men with documented evidence of distant metastases and their matched controls. It also shows the number of living men at risk of a PCa diagnosis or metastatic PCa at different durations of follow-up and the number of men with documented metastases. The VIP cohort included 12 542 men followed for >15 yr, 1423 men diagnosed with incident PCa, and 235 cases with documented evidence of distant PCa metastasis. Details on patient and tumor characteristics (including PSA level at time of diagnosis) are described in Supplementary Table 1. PSA concentrations at ages 40, 50, and 60 yr in controls were similar to previous population estimates in Sweden [11,12], Ireland [13], and the United States [14–16].

There were very few metastatic cases ($n = 10$) in men aged 40 yr at blood collection; further analyses are not presented in the primary text of this paper (Supplementary Table 2). For the older cohorts, as shown in Figure 1 and Table 2, there was a strong association between 15- to 20-yr risk of metastases and PSA, with a C-index of 0.816 (95% confidence interval [CI], 0.718–0.889) for PSA at age 50 and

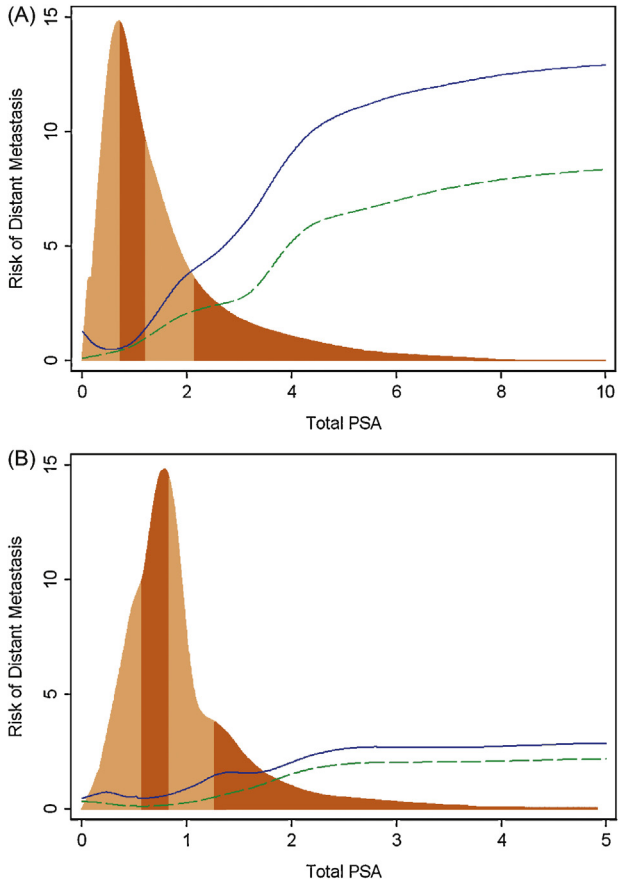

Fig. 1 – Risk of distant metastasis within 15 yr (dashed line) and 20 yr (solid line) by prostate-specific antigen (PSA). The four areas depicted in dark and light orange reflect the four quartiles of the population distribution of PSA levels. (A) Age 60 yr; (B) age 50 yr.
PSA = prostate-specific antigen.

Table 2 – Risk of distant prostate cancer metastases by 15 and 20 yr of follow-up

	PSA level, ng/ml	Absolute risk of metastases (95% CI)		Cumulative proportion of metastases,* % (95% CI)
		15-yr risk	20-yr risk	
Age 50 yr				
Top decile	>1.9	2.40 (1.47–3.70)	3.15 (1.94–4.82)	48 (34–61)
Top quartile	>1.3	1.48 (0.99–2.12)	2.14 (1.40–3.14)	69 (57–82)
Second quartile	0.8–1.3	0.25 (0.08–0.67)	0.89 (0.33–2.03)	85 (75–95)
Third quartile	0.6–0.8	0.13 (0.02–0.54)	0.56 (0.12–1.89)	92 (85–100)
Bottom quartile	<0.6	0.15 (0.03–0.47)	0.48 (0.07–1.98)	100
Below 63rd centile	<1.0	0.14 (0.05–0.31)	0.55 (0.23–1.17)	
Below median	<0.8	0.14 (0.05–0.35)	0.53 (0.18–1.34)	–
Overall		0.52 (0.37–0.72)	1.06 (0.72–1.51)	–
Age 60 yr				
Top decile	>3.8	9.33 (7.26–11.71)	14.29 (10.73–18.35)	56 (48–64)
Top quartile	>2.1	5.28 (4.25–6.46)	8.84 (6.97–10.99)	74 (67–81)
Second quartile	1.2–2.1	1.55 (0.95–2.41)	2.56 (1.53–4.02)	91 (86–95)
Third quartile	0.7–1.2	0.59 (0.27–1.18)	0.76 (0.34–1.52)	97 (95–100)
Bottom quartile	<0.7	0.26 (0.07–0.81)	0.48 (0.12–1.39)	100
Below median	<1.2	0.44 (0.23–0.79)	0.63 (0.32–1.14)	–
Below 41st centile	<1.0	0.43 (0.21–0.83)	0.56 (0.26–1.10)	
Overall		2.00 (1.66–2.39)	3.31 (2.71–4.00)	–

PSA = prostate-specific antigen.
* Cumulative proportions are given by cumulative quantile. For example, 85% of documented metastases occurred in men who had PSA in the top or second quartile at age 50 yr; 56% of metastases occurred in men in the top decile of PSA levels at age 60 yr.

0.847 (95% CI, 0.807–0.886) for PSA at age 60 (Supplementary Table 3). Most cases with metastasis were found among men whose PSA was above median for a decade or more before metastases were diagnosed (Supplementary Fig. 1; Supplementary Table 4). PSA measured at age 50 or 60 provided a wide separation of risk, with a 4- to 14-fold higher relative risk of metastases in men with PSA concentrations in the top quartile compared with those below the median (Table 2). As shown in Table 2, 69% of metastatic cases were documented in men with PSA in the top quartile at age 50 (>1.3 ng/ml); 74% of metastatic cases were documented in men with PSA in the top quartile at age 60 (>2.1 ng/ml). However, PSA levels below the median at ages 50–60 yr were associated with a very low risk of distant metastases. The 20-yr risk of metastasis for men with PSA ≤1.0 ng/ml at age 60 (close to the median) was <0.6% (Table 2). Despite the substantially elevated long-term risk of distant metastases associated with a PSA concentration in the top quartile or decile at age 50 or 60, the vast majority of these men remained metastasis free at 15–20 yr (Fig. 1; Supplementary Table 2 and 4).

We then examined whether a prespecified statistical model based on four KLK markers measured in the ProtecT study participants and developed to predict the risk of high-grade cancer at prostate biopsy [10] also could predict distant metastasis occurring 10–20 yr later (Supplementary Table 3). Although the model did not enhance discrimination of PSA in all men, it did so in men with PSA above the median at age 50 or 60. For instance, among men with PSA >2 ng/ml at age 50, discrimination was 0.751 for total PSA alone compared with 0.863 for the model (increase of 0.112; 95% CI, 0.020–0.219); for men with PSA >2 ng/ml at age 60, discrimination increased from 0.805 to 0.875 (0.070; 95% CI, 0.040–0.097).

Given these results, we conducted a decision analysis evaluating the hypothetical clinical outcomes had the KLK marker–based model data been used to aid decisions about biopsy in the VIP cohort. Biopsying all men with PSA ≥3.0 ng/ml, the approach used in the randomized trial supporting PSA screening [1,2] would have resulted in a biopsy performed on 15.6% of men aged 60 yr. This rate would have been reduced by 38% (Fig. 2A) if biopsy was recommended only to those with ≥7.5% risk of high-grade cancer according to the model (Table 3; Supplementary Table 5). Among men aged 60 yr with PSA ≥3 ng/ml and <7.5% risk according to the model, the 15-yr risk of distant metastases remained low (0.99%) compared with the population average (2%). For men with PSA ≥2 ng/ml at age 50 (top decile of PSA levels at age 50), using ≥5% risk according to the model as the criterion for biopsy would lead to only 41% of these men undergoing a biopsy (Fig. 2B). Among all men aged 50 yr with PSA ≥2 ng/ml, those with <5% risk according to the model had a very low 15-yr risk (≤0.5%) of distant metastasis (Table 3). Thus a substantial proportion of men with modestly increased PSA but low KLK risk scores identified by our screening strategy would be excluded from biopsy, and for these men, there is little risk of missing a lethal cancer even in the absence of frequent (e.g. biennial) follow-up.

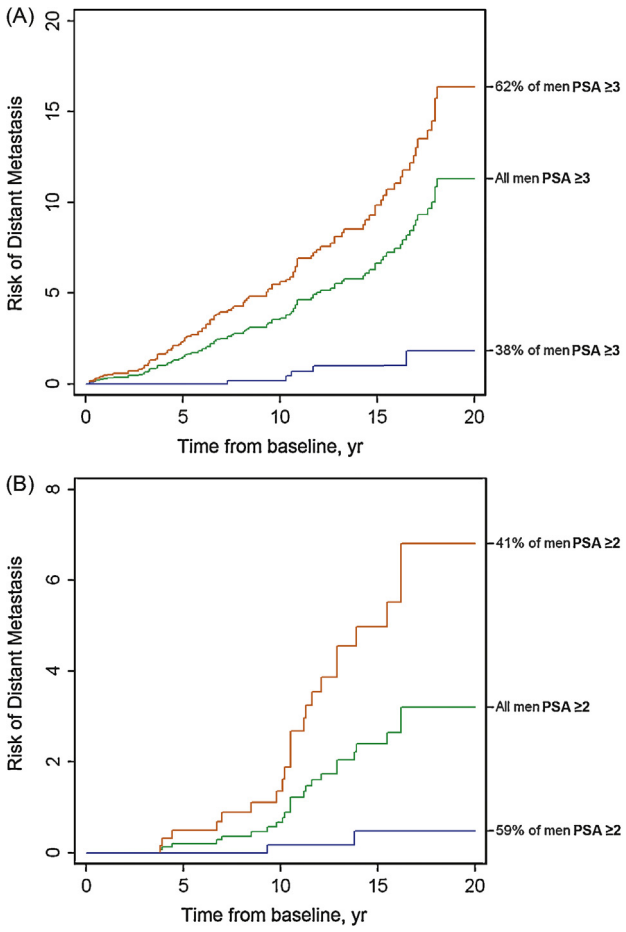

Fig. 2 – Risk of distant metastasis among men with elevated prostate-specific antigen (PSA) by four kallikrein (KLK) panel score. (A) Age 60 yr and PSA ≥3 ng/ml (*n* = 2432). Green line: overall risk of distant metastasis; orange line: risk of distant metastasis among men with four KLK panel score ≥7.5% (62% of the men); blue line: risk of distant metastasis among men with four KLK panel score <7.5% (38% of the men). (B) Age 50 yr and PSA ≥2 ng/ml (*n* = 1692). Green line: overall risk of distant metastasis; orange line: risk of distant metastasis among men with four KLK panel score ≥5% (41% of the men); blue line: risk of distant metastasis among men with four KLK panel score <5% (59% of the men).
PSA = prostate-specific antigen.

4. Discussion

In this large representative cohort from Sweden, with >12 500 men followed for >15 yr and initially low rates of opportunistic PSA testing, PSA measured in cryopreserved blood collected at age 50 or 60 predicted metastasis at 15- to 20-yr follow-up. In the subset of men with modestly elevated PSA, a prespecified model based on a panel of four KLK markers increased the predictive discrimination of metastasis.

Risk stratification contributed by PSA was far greater than that reported for other risk factors such as race or family history [17]. Among men with modestly elevated PSA at age 50 or 60, the four KLK panel yielded C-indexes from 0.82 to 0.88 for the prediction of documented distant metastasis. This can be compared with discrimination close

Table 3 – Risk of distant metastasis by prostate-specific antigen and kallikrein risk*

PSA group	*n* (%)	10 yr (95% CI)	15 yr (95% CI)	20 yr (95% CI)	Metastases by 10 yr per 10 000 men	Metastases by 20 yr per 10 000 men
Age 50						
PSA ≥0 ng/ml	17 837	0.09 (0.05–0.17)	0.52 (0.37–0.72)	1.06 (0.72–1.51)	9	106
PSA ≥2 ng/ml	1692	0.67 (0.30–1.36)	2.41 (1.46–3.73)	3.20 (1.96–4.93)	6	30
KLK risk ≥5%	696 (41)	1.37 (0.56–2.88)	4.97 (2.91–7.83)	6.80 (3.99–10.61)	5	27
<5%	996 (59)	0.18 (0.01–1.24)	0.49 (0.07–2.06)	0.49 (0.07–2.06)	1	3
KLK risk ≥7.5%	318 (19)	2.40 (0.88–5.31)	8.25 (4.41–13.62)	10.68 (5.74–17.38)	4	19
<7.5%	1374 (81)	0.26 (0.04–1.03)	0.90 (0.34–2.04)	1.25 (0.47–2.79)	2	11
KLK risk ≥10%	189 (11)	4.01 (1.41–8.83)	10.67 (5.10–18.58)	10.67 (5.10–18.58)	4	11
<10%	1502 (89)	0.23 (0.04–0.93)	1.26 (0.58–2.45)	2.17 (1.06–3.98)	2	19
PSA ≥3 ng/ml	549	1.51 (0.56–3.36)	4.66 (2.45–7.92)	6.13 (3.25–10.26)	5	19
Age 60						
PSA ≥0 ng/ml	15 634	0.88 (0.70–1.08)	2.00 (1.66–2.39)	3.31 (2.71–4.00)	88	331
PSA ≥2 ng/ml	4318	2.42 (1.89–3.06)	5.04 (4.06–6.17)	8.47 (6.69–10.50)	67	234
KLK risk ≥5%	3104 (72)	3.27 (2.54–4.13)	6.77 (5.44–8.29)	11.04 (8.71–13.69)	65	219
<5%	1214 (28)	0.19 (0.01–1.28)	0.38 (0.06–1.50)	1.42 (0.19–5.52)	2	15
KLK risk ≥7.5%	2005 (46)	4.81 (3.72–6.09)	9.05 (7.21–11.16)	14.17 (11.02–17.72)	62	182
<7.5%	2313 (54)	0.25 (0.06–0.76)	1.31 (0.64–2.44)	3.00 (1.48–5.40)	5	52
KLK risk ≥10%	1337 (31)	6.65 (5.09–8.47)	11.99 (9.45–14.86)	18.88 (14.51–23.69)	57	161
<10%	2982 (69)	0.42 (0.18–0.87)	1.70 (0.99–2.73)	3.22 (1.89–5.12)	10	73
PSA ≥3 ng/ml	2432	3.63 (2.77–4.65)	6.65 (5.22–8.29)	11.30 (8.65–14.35)	56	176
KLK risk ≥5%	1954 (80)	4.49 (3.43–5.74)	8.08 (6.34–10.08)	13.73 (10.50–17.38)	56	172
<5%	478 (20)	0 (NA)	0.48 (0.02–3.36)	0.48 (0.02–3.36)	0	4
KLK risk ≥7.5%	1510 (62)	5.62 (4.29–7.20)	9.85 (7.69–12.32)	16.36 (12.44–20.74)	54	158
<7.5%	922 (38)	0.18 (0.01–1.30)	0.99 (0.28–2.64)	1.82 (0.47–4.99)	2	18
KLK risk ≥10%	1180 (49)	7.01 (5.34–8.99)	12.35 (9.62–15.43)	19.88 (15.10–25.15)	53	150
<10%	1252 (51)	0.23 (0.04–0.94)	0.82 (0.27–2.01)	1.95 (0.64–4.66)	3	26

CI = confidence interval; KLK = kallikrein; PSA = prostate-specific antigen.
* A previously developed model to predict risk of Gleason score ≥7 (high-grade) prostate cancer at biopsy based on a panel of four KLK markers measured in the blood.

to 0.60 for the Gail model that is used clinically to determine eligibility for breast cancer chemoprevention [18].

Several long-term studies including a prospective observational study reported by Parkes et al [19] and others reviewed by Loeb et al [16] have found PSA to be highly prognostic of the long-term risk of aggressive PCa in unscreened men. The Malmö Preventive Project (MPP) [11,12] that involved blood samples taken from 1974 to 1986 with follow-up for metastasis and death through 2006 is most comparable with the current study. Although overall estimates of PCa risk are very similar between the two studies, the C-index of PSA for metastasis was somewhat lower in the current study: 0.86 at 25 yr in MPP versus 0.85 within <20 yr in VIP. This may be related to the advent of opportunistic PSA testing in Sweden. Some men with elevated PSA at age 60 destined to develop metastases would have their cancer detected early by PSA testing and be cured by early treatment.

Our results also replicated prior findings that the KLK markers measured in blood enhance the discrimination of malignant from benign PSA elevations [8,20]. Enormous efforts have been invested searching for biomarkers to be used with PSA to improve screening for PCa [21–25]. Although some markers are predictive of biopsy outcome, this is the first time markers have been shown to improve long-term prediction of distant metastasis, in this case with large increases in discrimination. These findings support the use of the KLK panel as a reflex test for biopsy in midlife among men with a modestly elevated PSA. For instance, compared with biopsying all men with PSA ≥3 ng/ml, biopsying men with PSA ≥2 ng/ml and ≥10% risk from the panel would reduce biopsy rates by 45% but detect a similar number of men who would develop distant metastases within 10 yr (56 vs 57 per 10 000 men). Men with a modest PSA elevation but a low risk of high-grade cancer according to the panel could be exempted from biopsy and reassured that they would be unlikely to develop metastatic disease, even if PSA and the other KLK markers were not monitored every year.

Our findings strongly support a risk-stratified approach to screening and biopsy. In men aged 50 yr, the 15-yr risk of metastasis among those in the top decile for PSA was 3.15%, sixfold higher than men with PSA below the median. The concentration of high-risk disease in this age group, with 48% of metastatic cases occurring in the men with PSA levels in the highest 10%, suggests that screening should focus on those men. In contrast, we were unable to identify a subgroup of men aged 40 yr at a substantially increased risk of distant metastasis within 15 yr, making it difficult to justify screening in this age group. The identification of a small subset of men with elevated PSA at ages 50–60 yr with a substantially increased risk of developing metastatic disease many years later has important implications for the development of novel preventive strategies. Use of the KLK markers as a reflex test may further refine stratification of risk.

The very low long-term risk for PCa [26,27] and metastases [11] in men with PSA <1 ng/ml was observed

in earlier studies. Our findings are consistent with prior research demonstrating that men with a low PSA at age 60 have no mortality reduction from PSA screening but are at considerable risk of overdiagnosis [28]. This supports the calls to limit screening in such men.

5. Conclusions

We found that blood levels of PSA at ages 50 and 60 yr are prognostic of the long-term risk of metastatic PCa and that a panel of KLK markers is strongly predictive of distant metastasis documented many years later in men with a modestly elevated PSA. Our study has the following clinical implications. First, widespread PSA testing at age 40 cannot be justified. Second, screening can stop in men with PSA below the median (<1 ng/ml) at age ≥60 yr. Third, for men in their fifties, screening could focus mainly on those in the top decile of PSA (>1.9 ng/ml) because close to half of the subsequent cases of distant metastasis are found in this group; men with lower PSAs should still be screened but less intensively. Finally, four KLK markers measured in the blood can be used as a reflex test to aid biopsy decisions.

Author contributions: Hans Lilja 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: Stattin, Vickers, Lilja.
Acquisition of data: Stattin, Lilja, R. Johansson, Granfors, M. Johansson, Hallmans.
Analysis and interpretation of data: Stattin, Vickers, Sjoberg, R. Johansson, Granfors, M. Johansson, Hallmans, Lilja.
Drafting of the manuscript: Stattin, Lilja, Vickers.
Critical revision of the manuscript for important intellectual content: Stattin, Lilja, Vickers.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.01.009.

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