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Platinum Priority – Prostate Cancer

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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.