Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

Long-term Prostate-specific Antigen Velocity in Improved Classification of Prostate Cancer Risk and Mortality

David D. Ørsted a,b, Stig E. Bojesen a,b,c, Pia R. Kamstrup a, Børge G. Nordestgaard a,b,c,*

*Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Denmark; bFaculty of Health and Medical Sciences, University of Copenhagen, Denmark; cThe Copenhagen City Heart Study, Bispebjerg Hospital, Copenhagen University Hospital, Denmark

Article info

Article history:
Accepted January 24, 2013
Published online ahead of print on • • •

Keywords:
Long-term PSA velocity
Prostate cancer incidence and mortality
Risk classification

Abstract

Background: It remains unclear whether adding long-term prostate-specific antigen velocity (PSAV) to baseline PSA values improves classification of prostate cancer (PCa) risk and mortality in the general population.

Objective: To determine whether long-term PSAV improves classification of PCa risk and mortality in the general population.

Design, setting, and participants: We studied 503 men aged 30–80 yr, with and without PCa, who had repeated PSA measurements over 20 yr and up to 28 yr before PCa diagnosis. These were selected from among 7455 men in the Copenhagen City Heart Study, a prospective, general population study with follow-up from 1981 through 2010. Results were subsequently applied to all 1 351 441 men aged 40–80 yr living in Denmark from 1997 through 2006.

Outcome measurements and statistical analysis: PCa risk and mortality were assessed using Cox regression. Improvement in risk classification was assessed using the net reclassification index (NRI).

Results: Age-adjusted hazard ratios for PCa risk and mortality were 2.7–5.3 and 2.3–3.4, respectively, for long-term PSAV when added to models already including baseline PSA values. For PCa risk and mortality, adding long-term PSAV to models already including baseline PSA values and age yielded continuous NRIs of 98–99% and 56–106%, respectively. Used on a nationwide scale (eg, for men aged 60–64 yr), long-term PSAV > 0.35 versus < 0.35 ng/mL per year appropriately reclassified 128 of 10 000 men with PCa and 8095 of 10 000 men with no PCa. Correspondingly, inappropriately reclassified were 49 of 10 000 men with PCa and 1658 of 10 000 men with no PCa.

Conclusions: Long-term PSAV in addition to baseline PSA value improves classification of PCa risk and mortality. Applying long-term PSAV nationwide, the ratio of appropriately to inappropriately classified men would typically be 5:1.

* Corresponding author, Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark. Tel: +45 3868 3297; Fax: +45 3868 3311. E-mail address: Boerge.Nordestgaard@regionh.dk (B.G. Nordestgaard).

1. Introduction

Baseline prostate-specific antigen (PSA) values predicted long-term risk of prostate cancer (PCa) incidence and mortality in two large, population-based studies [1,2].

While elevation of PSA level also can be due to benign prostatic hyperplasia (BPH), prostatic inflammation, and increasing age [3], in general, PCa leads to more rapid increases in PSA levels compared to benign conditions [4,5]. Therefore, in addition to baseline PSA value, evaluation of PSA velocity (PSAV) is recommended in guidelines on risk prediction and diagnosis of PCa [6,7].

Most previous studies have focused on PSAV in the short-term period leading up to a diagnosis of PCa [8–14]; a few studies have examined long-term risk prediction, but they have reported contradictory results [15–20]. Also, most previous studies examined how often a test of short-term PSAV is positive or negative among those with or without PCa. As a result, no studies have documented that long-term PSAV improves classification of PCa risk and mortality when compared to the use of PSA alone [21]. In the present study, we did exactly that, and tried to answer the following question: Given the PSA history of a healthy man in the general population, what is the probability of PCa risk and mortality?

We performed a study of 503 men aged 30–80 yr, with and without PCa, and with repeated PSA measurements taken over 20 yr and up to 28 yr before PCa diagnosis, who were selected from among 7455 men in the Copenhagen City Heart Study. We first examined individual changes in PSA during 20 yr of follow-up spanning two to three PSA measurements. Second, we tested the hypothesis that long-term PSAV is associated with PCa risk and mortality in the general population, that is, above and beyond that predicted by a baseline PSA measurement. Third, we tested the hypothesis that adding long-term PSAV to baseline PSA level leads to improved classification of risk. Fourth, in decision curve analysis, we tested the hypothesis that adding long-term PSAV to baseline PSA level increases net benefit values. Finally, we applied these findings to all 1 351 441 men aged 40–80 yr living in Denmark from 1997 through 2006.

2. Materials and methods

2.1. Study population

Study participants were men in the Copenhagen City Heart Study 1981–1983, 1991–1994, and 2001–2003 examinations [22–25] who were selected randomly from the Danish Central Person Register to represent the general population. Individual participants were followed in the Danish health registries, blinded to PSA measurements. Details on these registries are described in the online supplemental material. Due to the unique civil registration number assigned to every person in Denmark, the completeness of the Danish national registries, we had complete information on PCa hospitalisation, death, and emigration for every participant (Supplemental Fig. 1). Thus, follow-up was 100% complete.

The study was approved by Herlev Hospital, Copenhagen University Hospital, and a Danish ethical committee (H-1002039/01). Participants gave written informed consent.

2.2. Biochemical analysis

Blood samples were drawn on the day of attendance in the Copenhagen City Heart Study 1981–1983, 1991–1994, and 2001–2003 examinations, and after centrifugation plasma was stored at −80 °C or −20 °C. In 2010–2011, samples were thawed and total PSA was measured immunochromically using the ADVIA Centaur XP Immunoassay (Siemens AG, Erlangen, Germany) (Supplement 1). The technician was blinded to PCa status.

2.3. Study design

First, we calculated the individual and overall, case and control, long-term PSAV in participants with repeated PSA measurements over 20 yr (1981–1983, 1991–1994, and 2001–2003 examinations); thus, two or three PSA measurements for each participant were included in calculating long-term PSAV. Second, we performed a study in which each man with a diagnosis of PCa after the 1991–1994 examination was matched by birth year and number of PSA measurements with up to four control subjects without PCa and without hospitalisation for BPH at similar length of follow-up as the patient, creating subsets of up to five men. Each control subject was only matched with one man with PCa, and therefore sometimes fewer than four control subjects were available. The second PSA value was the baseline value in the hazard/odds ratio (1991–1994 or 2001–2003) and reclassification calculations (1991–1994 only), and defined the start of follow-up. Participants were followed until the occurrence of the end point in question (PCa [n = 121] or PCa death [n = 54]), or censored at death (n = 140) or end of follow-up August 2010, whichever came first. Third, we calculated reclassification for PCa risk and mortality in extended models with long-term PSAV, baseline PSA level, and age, versus a classical model with baseline PSA level and age alone.

3. Results

Among 7455 men in the Copenhagen City Heart Study and randomly selected from the Danish general population, we identified 121 patients with PCa that developed after 1991–1994 and matched them with 382 control subjects based on birth year and two or three PSA measurements (1981–1983, 1991–1994, and/or 2001–2003 examinations) (Supplemental Fig. 1). Median age at baseline in 1991–1994 for patients and control subjects was 68 yr (interquartile range: 63–74) and 69 yr (64–75), respectively. Median time to diagnosis was 6 yr (range: 0–16). Baseline characteristics are shown in Supplemental Table 1.

3.1. Long-term prostate-specific antigen velocity

Absolute long-term PSAV (nanograms per millilitre per year) increased continuously as a function of time from >20 yr before diagnosis up until PCa diagnosis in patients compared with matched control subjects (p = 0.002) (Fig. 1A). Also, individual participant, absolute, long-term PSAVs were generally higher in patients versus control subjects (Fig. 2A).

Similarly, relative long-term PSAV (percent per year) increased continuously as a function of time from >20 yr before diagnosis until PCa diagnosis in patients compared with matched control subjects (p = 0.001) (Fig. 1B). Also, individual participant, relative long-term PSAVs were generally higher in patients versus control subjects (Fig. 2B).

3.2. Prostate cancer risk and mortality

In Cox regression analyses, increased long-term PSAV was associated with increased PCa risk and mortality in models already including age and baseline PSA level (Table 1).
Fig. 1 – Individual and overall prostate-specific antigen (PSA) levels for case and control subjects as a function of time to diagnosis for the case in each matched subset. (A) Equidistant scale: Overall values (lower panel) were fitted using local polynomial smoothing with 95% confidence intervals (CIs); (B) Logarithmic scale: Overall values (lower panel) were fitted using linear regression with 95% CIs. Based on 503 men (121 patients with prostate cancer; 382 matched control subjects) from the Copenhagen City Heart Study with PSA measured in samples from 1981–1983, 1991–1994, and 2001–2004. PCa = prostate cancer.

For PCa risk, the age-adjusted hazard ratio (HR) was 2.8 (95% confidence interval [CI], 2.2–3.6) for a doubling in baseline PSA level (Table 1). For absolute long-term PSAV >0.35 versus ≤0.35 ng/ml per year, the age-adjusted HR (95% CI) for PCa risk was 5.3 (2.2–13) in an extended model already including baseline PSA level. Similarly, for relative long-term PSAV >10% versus ≤10% per year, the corresponding HR was 2.7 (1.3–5.7).

For PCa mortality, the age-adjusted HR was 3.0 (95% CI, 2.1–4.4) for a doubling in baseline PSA (Table 1). For absolute long-term PSAV >0.35 versus ≤0.35 ng/ml per year, the age-adjusted HR (95% CI) for PCa mortality was 3.4 (1.0–10) in an extended model already including baseline PSA level. Similarly, for relative long-term PSAV >10% versus ≤10% per year, the corresponding HR was 2.5 (0.9–7.1).

In conditional logistic versus Cox regression analyses of PCa risk and mortality, risk estimates were generally higher in both classical and extended models, but overall results were similar (Table 1).  

3.3. Discrimination

For PCa risk, Harrell C index did not increase when long-term PSAV was added to the classical model already including baseline PSA levels (Table 1). For PCa mortality, the addition of long-term PSAV to the classical model yielded a slight but statistically insignificant increase in C index. The area under the curve (AUC) increased slightly for PCa risk and mortality when either long-term PSAV >0.35 versus ≤0.35 ng/ml per year and relative long-term PSAV

Please cite this article in press as: Ørsted DD, et al. Long-term Prostate-specific Antigen Velocity in Improved Classification of Prostate Cancer Risk and Mortality. Eur Urol (2013), http://dx.doi.org/10.1016/j.eururo.2013.01.028
### Table 1 – Relative risk and discrimination of prostate cancer incidence and mortality

<table>
<thead>
<tr>
<th></th>
<th>Events/participants</th>
<th>Relative risk</th>
<th>Discrimination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cox regression</td>
<td>Logistic regression</td>
</tr>
<tr>
<td><strong>PCa incidence</strong></td>
<td>121/503</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA doubling</td>
<td></td>
<td>2.8 (2.2–3.6)</td>
<td>3.3 (2.5–4.4)</td>
</tr>
<tr>
<td>Extended model 1</td>
<td></td>
<td>2.0 (1.6–2.7)</td>
<td>2.1 (1.5–2.8)</td>
</tr>
<tr>
<td>PSA doubling</td>
<td></td>
<td>5.3 (2.2–13)</td>
<td>16 (4.9–50)</td>
</tr>
<tr>
<td>PSA velocity, &gt;0.35 vs ≤0.35 ng/ml/yr</td>
<td>2.4 (1.9–3.1)</td>
<td>2.7 (2.0–3.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Extended model 2</td>
<td></td>
<td>2.7 (1.3–5.7)</td>
<td>3.0 (1.4–6.2)</td>
</tr>
<tr>
<td><strong>PCa mortality</strong></td>
<td>69/503</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical model</td>
<td></td>
<td>3.0 (2.1–4.4)</td>
<td>4.9 (2.9–8.1)</td>
</tr>
<tr>
<td>PSA doubling</td>
<td></td>
<td>2.3 (1.6–3.4)</td>
<td>2.8 (1.6–4.8)</td>
</tr>
<tr>
<td>Extended model 1</td>
<td></td>
<td>3.4 (1.1–10)</td>
<td>20 (2.3–179)</td>
</tr>
<tr>
<td>PSA velocity, &gt;0.35 vs ≤0.35 ng/ml/yr</td>
<td>2.7 (1.9–3.9)</td>
<td>4.2 (2.5–7.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>PSA doubling</td>
<td></td>
<td>2.5 (0.9–7.1)</td>
<td>2.2 (0.7–6.8)</td>
</tr>
</tbody>
</table>

AUC = area under the curve; CI = confidence interval; HR = hazard ratio; OR = odds ratio; PCa = prostate cancer; PSA = prostate-specific antigen.

>10% versus ≤10% per year was added to the classical model already including baseline PSA levels; however, this was not statistically significant.

### 3.4. Reclassification of prostate cancer risk and mortality

Addition of long-term PSAV to the classical model with baseline PSA level and age improved event and nonevent reclassification of both PCa risk and mortality (Fig. 3, Supplemental Table 2). The distributions of individual predicted risk of PCa incidence and mortality for all participants, using extended models with and classical models without long-term PSAV, are shown in Supplemental Figure 2. Applying a cut-off for 10-yr risk of 10% for PCa and 5% for PCa mortality also improved reclassification for PCa risk and mortality (Table 2).

For PCa risk, adding long-term PSAV >0.35 versus ≤0.35 ng/ml per year to the classical model yielded a combined NRI of 98% (95% CI, 76–121; \( p = 3 \times 10^{-14} \)) (Fig. 3A, Supplemental Table 2). This extended model appropriately reclassified 52% and inappropriately reclassified 20% of PCa events (28% were not reclassified), resulting in a PCa NRI of 32% (95% CI, 13–52; \( p = 2 \times 10^{-3} \)) compared to the classical model. For nonevents, 83% were appropriately reclassified and 17% inappropriately reclassified, yielding a no PCa NRI of 66% (95% CI, 55–77; \( p = 1 \times 10^{-18} \)). Similarly, relative long-term PSAV >10% versus ≤10% per year resulted in a combined NRI of 99% (95% CI, 77–119; \( p = 2 \times 10^{-14} \)) (Fig. 3B, Supplemental Table 2). This model appropriately reclassified 62% and inappropriately reclassified 11% of PCa events (17% were not reclassified), yielding a PCa NRI of 51% (95% CI, 34–68; \( p = 2 \times 10^{-6} \)). For nonevents, 74% were appropriately reclassified and 26% inappropriately reclassified, yielding a no PCa NRI of 48% (95% CI, 35–61; \( p = 2 \times 10^{-10} \)).

For PCa mortality, the addition of long-term PSAV >0.35 versus ≤0.35 ng/ml per year yielded a combined

![Fig. 2 – Distribution of individual (A) absolute and (B) relative long-term prostate-specific antigen (PSA) velocities for patients and control subjects. The dotted lines represent the cut-offs for long-term PSA velocity of 0.35 ng/ml per year and 10% per year, respectively. Based on 503 men (121 patients with prostate cancer; 382 matched control subjects) in the Copenhagen City Heart Study with PSA measured in samples from 1981–1983, 1991–1994, and 2001–2004. PCa = prostate cancer.](image-url)
Reclassification of risk of prostate cancer (PCa) risk and mortality with (A) absolute and (B) relative long-term prostate-specific antigen (PSA) velocity. Long-term PSA velocity was added to classical models of age and baseline PSA levels. Based on 359 men (77 patients with PCa; 52 PCa deaths; 282 matched control subjects) in the 1991–1994 Copenhagen City Heart Study to ensure ≥10 yr of follow-up. NRI = net reclassification index. CI = confidence interval.

NRI of 56% (95% CI, 23–90; \( p = 1 \times 10^{-3} \)) (Fig. 3A, Supplemental Table 2). Reclassification was appropriate for 60% and inappropriate for 35% of PCa mortality events (5% were not reclassified), resulting in a PCa mortality NRI of 24% (95% CI, −6–55; \( p = 0.13 \)). For nonevents, 66% were appropriately reclassified and 34% inappropriately reclassified, yielding a no-PCa mortality NRI of 32% (95% CI, 18–46; \( p = 1 \times 10^{-3} \)). Similarly, relative long-term PSAV >10% versus ≤10% per year resulted in a combined NRI of 106% (total possible NRI was 200% [Supplement 1]) (95% CI, 78–134; \( p = 2 \times 10^{-9} \)) (Fig. 3B, Supplemental Table 2). Reclassification was appropriate for 78% and...
Table 2 – Reclassification of risk of prostate cancer (PCa) incidence and mortality using a cut-point for 10-yr risk of 10% for PCa and 5% for PCa mortality

<table>
<thead>
<tr>
<th>PCa incidence</th>
<th>Cox regression</th>
<th>p value</th>
<th>Logistic regression</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA velocity, &gt;0.35 vs &lt;0.35 ng/ml/yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer NRI, % (95% CI)</td>
<td>-8.6 (−16 to −0.9)</td>
<td>0.03</td>
<td>-1.1 (−7.4 to 5.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Combined NRI, % (95% CI)</td>
<td>7.5 (−1.2 to 16)</td>
<td>0.10</td>
<td>4.5 (−2.7 to 11.7)</td>
<td>0.22</td>
</tr>
<tr>
<td>PSA velocity, &gt;10 yr vs ≤10 yr/yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer NRI, % (95% CI)</td>
<td>-3.2 (−7.9 to 1.5)</td>
<td>0.18</td>
<td>3.2 (−0.4 to 6.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Combined NRI, % (95% CI)</td>
<td>6.1 (2.4–9.9)</td>
<td>2 × 10⁻³</td>
<td>2.6 (−0.8 to 6.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>PCa mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA velocity, &gt;0.35 vs &lt;0.35 ng/ml/yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer mortality NRI, % (95% CI)</td>
<td>0 (−7.3 to 7.3)</td>
<td>1.00</td>
<td>−3.7 (−8.8 to 1.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>Combined NRI, % (95% CI)</td>
<td>13 (9.7–16)</td>
<td>3 × 10⁻¹</td>
<td>11 (8.0–15)</td>
<td>4 × 10⁻¹⁰</td>
</tr>
<tr>
<td>PSA velocity, &gt;10 yr vs ≤10 yr/yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer mortality NRI, % (95% CI)</td>
<td>2.2 (−5.1 to −9.4)</td>
<td>0.32</td>
<td>1.9 (−5.5 to 1.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Combined NRI, % (95% CI)</td>
<td>5.3 (1.7–8.8)</td>
<td>9 × 10⁻³</td>
<td>5.8 (2.3–9.3)</td>
<td>1 × 10⁻¹³</td>
</tr>
</tbody>
</table>

PCa = prostate cancer; PSA = prostate-specific antigen; NRI = net reclassification index; CI = confidence interval.
Shown are NRI values with 95% CI for PCa incidence and mortality calculated with both Cox regression and logistic regression analyses. For prostate cancer NRI, a positive value means that the percent of men with PCa move from a 10-year i.

4. Discussion

Novel findings of this study include that increased long-term PSAV in addition to baseline PSA levels were associated with a 2- to 5-fold increased risk for PCa and PCa mortality, and yielded net reclassification indices of 56–106% for PCa risk and mortality. Applying long-term PSAV nationwide, the ratio of appropriately to inappropriately reclassified men would typically be 5:1.

The use of long-term PSAV for long-term prediction of PCa has been considered in an attempt to improve prediction and diagnosis of PCa and to reduce the large number of unnecessary biopsies as a result of PSA testing [15]. Nonetheless, the optimal use of PSAV remains widely debated [26]. Several studies have examined the association between PSAV and PCa incidence, but few studies have included analyses of predictive accuracy [20], and none have documented improved classification using NRI. The only previous, population-based study of an unscreened cohort showed no increase in predictive accuracy [17], measured by Harrell C index, when PSAV was included in a model with baseline PSA level and age. However, obtaining increases in Harrell C index for a new model is very difficult when a strong risk factor is already included in the old model [27]. Also, a recent study tested measures of reclassification and did not find improved reclassification when PSAV over 13 yr was added to baseline PSA values [18]. However, that study used PSA values measured for 261 screening, which may have led to surveillance bias, that is, PSA values were used by physicians and may have influenced treatment decisions and possibly led to overdiagnosis. This is not the case in the present study. Thus, the different findings on the value of PSAV might be due to differences in the investigated populations (ie, screened vs unscreened).
Fig. 4 – Decision curve analysis for prostate cancer risk based on (A) logistic regression analyses and (B) Cox regression analyses. The dotted line indicates the benefit of performing a prostate biopsy in all men; the thick black line indicates net benefit of not performing any biopsies.

Fig. 5 – Nationwide reclassification of risk for prostate cancer in men aged 40–80 yr in 5-yr age groups with (A) absolute and (B) relative long-term prostate-specific antigen (PSA) velocity (number reclassified per 10 000 men during 10 yr in 5-yr age categories). Long-term PSA velocity was added to classical models of age and baseline PSA levels as shown in Figure 3. Based on 1 351 441 men aged 40–80 yr from the entire male Danish population followed from 1997 through 2006.

Please cite this article in press as: Ørsted DD, et al. Long-term Prostate-specific Antigen Velocity in Improved Classification of Prostate Cancer Risk and Mortality. Eur Urol (2013), http://dx.doi.org/10.1016/j.eururo.2013.01.028
The strengths of our study should be considered. The study population is representative of the male general population, follow-up was from 1981 through 2010 and was 100% complete, and the study population is well characterised. Yet another important strength is that PSA measurements are still not recommended for general population screening purposes in Denmark [28], and the informal screening rate has remained low, ranging from 0.4% in 1997 to 2.4% in 2006 for men >20 yr of age (ie, this corresponds to 2–12 men tested per year in our cohort) [29]. Importantly, PSA testing was not introduced into general clinical practice in Denmark before 1995, which precludes informal screening of the participants in the study during the first 14 yr of follow-up. Thus, the PCa cases in the present study are unlikely to be chance findings due to widespread PSA screening, but rather were diagnosed after patients presented with symptoms. Therefore, this study might reflect the value of PSAV during the natural history of the development of PCa and lethal PCa. Further, it is likely that our results would also be valid for men from a highly prescreened population who have had repeated measurements of PSA, given that they have not been examined further with transrectal ultrasound and biopsy. Additionally, because PSA concentrations were measured for up to 6–30 yr after blood sampling and thus not reported to participants or their doctors, these measurements have not influenced ascertainment of PCa during follow-up. Finally, we were able to apply measures of reclassification on a nationwide scale on all men aged 40–80 yr.

The clinical implications of our findings should be considered. Our results suggest that long-term PSAV may better inform the decision to proceed to biopsy for a man with a recent high PSA. In particular, our results imply that long-term PSAV may be useful for identifying men with a low probability of PCa, and as a consequence, may lead to fewer unnecessary biopsies. This has also been reported in a previous study by Loeb et al. [30], and is in contrast to most other studies that have investigated the use of PSAV for finding men with high risk for PCa or PCa mortality [8,9,19,20,31–33]. Importantly, if PSA is measured repeatedly rather than every 10 yr, as in our study, more reliable PSAV added to baseline PSA values possibly may fulfil these clinical purposes even better than demonstrated here.

When PSA level should first be measured in an asymptomatic man, and what the interval between PSA measurements should be are two other important questions. Previous studies have shown that measuring PSA for the first time at age 45–50 yr allows prediction of risk of PCa incidence and mortality [1,34]. A subsequent screening interval may then be based on the result of the first PSA measurement. The present study cannot be used to determine the optimal length of such a screening interval, but merely shows that long-term PSAV based on repeated PSA measurements may improve prediction above and beyond that of a single baseline PSA measurement.

A final important point is whether a possible PCa is curable at the point when PSAV indicates intervention. In the present study, the majority of the participants with PSAV <0.35 ng/ml per year and/or >10% per year had PSA levels <10 ng/ml (data not shown), that is, levels generally not indicating high-risk PCa and, thus, levels at which men are likely to benefit from treatment [35].

A limitation of our study is that our study population mainly included white participants of Danish descent. On the other hand, we are not aware of any data to suggest that results like those in our study should not be valid for men of all races. Another limitation is that we had only two or three PSA values for each participant, compared to more frequent measurements that allow recognising outlying values better. Outlying values due to short-term variation of PSA would tend to bias our estimates toward the null hypothesis; despite this, we were able to show an incremental value of adding PSAV to baseline PSA levels. Yet another possible limitation is that some men were diagnosed with PCa or died after their first examination, which could potentially have excluded men with the most aggressive cancers. However, this is an inherent possibility of any prospective study with repeated examinations. Another potential limitation is the lack of predefined risk categories for PCa risk and mortality. As a result, we used a continuous measure of reclassification, which means that even small changes in individual predicted risk may lead to improved or worsened reclassification. However, when we applied a cut-point for 10-yr risk of 10% for PCa and 5% for PCa mortality, NRIs for PSAV added to baseline PSA values still improved, particularly for nonevents. Finally, a potential limitation is possible misclassification of PCa and PCa death in health registries. However, such misclassification is probably nondifferential to the PSA measurements, since they were carried out later. This would likely bias results toward the null hypothesis, and therefore is unlikely to explain our results.

5. Conclusions

In conclusion, increased long-term PSAV in addition to baseline PSA levels were associated with a 2- to 20-fold increased risk for PCa or PCa mortality, and yielded continuous NRIs of 56–106% for PCa risk and mortality. Applying long-term PSAV nationwide, the ratio of appropriately to inappropriately classified men would typically be 5:1.

Author contributions: Børge G. Nordestgaard 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: Ørsted, Bojesen, Nordestgaard.

Acquisition of data: Ørsted, Nordestgaard.

Analysis and interpretation of data: Ørsted, Bojesen, Kamstrup, Nordestgaard.

Drafting of the manuscript: Ørsted.

Critical revision of the manuscript for important intellectual content: Ørsted, Bojesen, Kamstrup, Nordestgaard.

Obtaining funding: Nordestgaard.

Administrative, technical, or material support: Nordestgaard.

Supervision: Nordestgaard.

Other (specify): None.
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.2013.01.028.

References


Please cite this article in press as: Ørsted DD, et al. Long-term Prostate-specific Antigen Velocity in Improved Classification of Prostate Cancer Risk and Mortality. Eur Urol (2013), http://dx.doi.org/10.1016/j.eururo.2013.01.028