Second Round Results of the Finnish Population-Based Prostate Cancer Screening Trial

Tuukka Mäkinen, Teuvo L. J. Tammela, Ulf-Håkan Stenman, Liisa Määtäinen, Jussi Aro, Harri Juusela, Paula Martikainen, Matti Hakama, and Anssi Auvinen

1Department of Surgery, Seinäjoki Central Hospital, Seinäjoki; 2Department of Urology, Tampere University Hospital and Medical School, University of Tampere, Tampere; Departments of 3Clinical Chemistry and 4Urology, Helsinki University Central Hospital, Helsinki; 5Finnish Cancer Registry, Helsinki; 6Department of Surgery, Jorvi Hospital, Helsinki University Central Hospital, Espoo; 7Department of Pathology, Tampere University Hospital, Tampere; and 8Tampere School of Public Health, University of Tampere, Tampere, Finland

Abstract

Purpose: Large randomized trials provide the only valid means of quantifying the benefits and drawbacks of prostate-specific antigen (PSA) screening, but the follow-up of ongoing studies is still too short to allow evaluation of mortality. We report here the intermediate indicators of screening efficacy from the second round of the Finnish trial.

Experimental Design: The Finnish trial, with ~80,000 men in the target population, is the largest component in the European Randomized Study of Screening for Prostate Cancer. The first round was completed in 1996–1999. Each year 8,000 men 55–67 years of age were randomly assigned to the screening arm, and the rest formed the control arm. Men randomized to the screening arm in 1996 were reinvited 4 years later, in 2000, and PSA was determined.

Results: Of the eligible 6415 men, 4407 (69%) eventually participated in the second round of screening. Of the first-round participants, up to 84% (3833 of 4556) attended rescreening. A total of 461 screenees (10.5%) had PSA levels ≥4 µg/liter. Altogether, 97 cancers were found, yielding an overall detection rate of 2.2% (97 of 4407). Seventy-nine cases were found among the 3833 second-time screenees (detection rate 2.1%) and 18 in those 574 men (3.1%) who had not participated previously. A PSA of ≥4 µg/liter, but negative biopsy in the first screening round was associated with an up to 9-fold risk of cancer in rescreening relative to those with lower PSA levels at baseline. Ninety-one (94%) of all of the detected cancers were clinically localized.

Conclusions: As surrogate measures of an effective screening program, both compliance as well as the overall and advanced prostate cancer detection rates remained acceptable. Men defined as screen-positive but with a negative confirmation of cancer at prevalence screen formed a high-risk group at rescreening.

Introduction

Prostate cancer is the second leading cause of male cancer death in most industrialized countries (1). In the United States and also in some European populations prostate cancer mortality peaked in the late 1990s (2). The subsequent decrease has been assumed to be largely attributable to widespread prostate-specific antigen (PSA) testing. Nonetheless, temporal and geographical differences provide inconclusive evidence to establish the benefits of PSA screening. The best means to obtain valid evidence on PSA screening is through large, randomized screening trials. Such trials are currently under way in both the United States (Prostate, Lung, Colorectal and Ovary Cancer trial, Quebec trial) and Europe (the European Randomized Study of Screening for Prostate Cancer), but conclusive mortality analyses are not expected until 2008–2010 (3–5). The common feature in all of these trials is the use of serum PSA, with however variable cutoff criteria, as a principal test for screening (6). The trials also diverge in recruitment strategy (volunteer versus population-based programs) and frequency of screening (from annual screening up to an interval of 4 years). These differences may have a considerable influence on both program performance, including process indicators, and final outcome, i.e., prostate cancer mortality. The Finnish trial represents a large, population-based study applying a conservative screening policy with a 4-year screening interval. So far, little is known regarding the program performance of PSA screening in a population of screened men at subsequent screens (5, 7–9). We here report intermediate screening efficacy indicators such as coverage of target population as well as the rate of prostate cancer detection and tumor characteristics at repeat screening in the second round of the Finnish trial, and compare these indicators with those of the first round.

Materials and Methods

Subjects. The Finnish prostate cancer screening trial, initiated in 1996 with a sample size of 80,000 men, forms the largest component in the European Randomized Study of Screening for Prostate Cancer. Study subjects residing in two metropolitan areas (Tampere and Helsinki) were identified from the Population Register of Finland, and those with a previous diagnosis of prostate cancer were excluded before randomization. Annually a random
sample of 8000 men aged 55, 59, 63, or 67 years was allocated to the screening arm until 1999, and the remainder formed the control arm without intervention. A detailed description of the design has been published elsewhere (10). The present study covers the cohort of 8000 men randomly assigned to the screening arm in 1996 and invited for rescreening after an interval of 4 years, i.e., in 2000 (Fig. 1). Men diagnosed with prostate cancer during the first round of screening, men deceased, moved outside the study area, or forbidding the use of their addresses were excluded. Eventually, a total of 6415 men were invited for rescreening at the ages of 59, 63, 67, or 71 years during the first year of the second screening round in 2000. The main outcome measure of the trial is mortality from prostate cancer.

**Laboratory Methods.** A blood sample was drawn after written informed consent to determine the serum concentration of total PSA by both Hybritech Tandem-E and Wallac Delfia assays. Determination of the percentage of free PSA was performed with the Wallac ProStatus free/total PSA assay. All of the serum analyses were carried out at the Department of Clinical Chemistry, Helsinki University Central Hospital.

**Screening Algorithm.** The total concentration of serum PSA was used as screening criterion. All of the men with PSA ≥4 μg/liter were referred for diagnostic examination including a digital rectal examination, transrectal ultrasound, and sextant biopsies of the prostate supplemented by a directed biopsy if a focal finding was seen in either digital rectal examination or transrectal ultrasound. The percentage of free PSA was used as a supplemental screening criterion at PSA levels between 3.0 and 3.9 μg/liter, and only those with percentage of free PSA <16% were referred for diagnostic work.

**Diagnostics.** All of the prostate cancer cases were histologically confirmed. Tumor characteristics at biopsy were graded according to the Gleason score system (11). The WHO system was used in 3 cases due to insufficient biopsy material. Clinical staging was conducted according to the Tumor-Node-Metastasis classification using primarily digital rectal examination, transrectal ultrasound, and bone scan to evaluate possible extracapsular extension and distant metastases of prostate cancer (12). Bone scanning was not conducted in 42 cases with PSA levels <20 μg/liter, this indicating a low risk of bone metastases (13).

**Data Analyses.** Pearson’s χ² test was used to calculate the statistical significance of the difference in compliance with rescreening according to baseline PSA with a cutoff of 4 μg/liter. The detection rates by total PSA, age at diagnosis, Gleason score, and clinical stage of detected tumors were given with 95% confidence intervals (CIs). The positive predictive value of PSA for the second round of screening was defined here as the proportion of cancers found in men tested as screen positives (i.e., including also 31 men who did not undergo a biopsy). In addition, the positive predictive values were calculated for men rescreened (i.e., attending the second time of screening) in relation to the baseline PSA levels. The positive predictive values were all given with 95% CIs. The risk of prostate cancer by PSA values in the first screening round was given in terms of the ratio of detection rates with 95% CIs using men with baseline PSA levels ≥3.0 μg/liter as reference. Statistical analyses were performed on the CIA version 1.1 (Martin J. Gardner and British Medical Journal) and the S-PLUS version 4.0 (MathSoft Inc., Cambridge, MA).
Table 1  Numbers of men and detected prostate cancers by serum PSA\(^a\) concentration at the second round of the Finnish prostate cancer screening trial

<table>
<thead>
<tr>
<th>PSA, (\mu g/liter)</th>
<th>No. of men (%)</th>
<th>No. of men biopsied</th>
<th>No. of cancers</th>
<th>Positive predictive value, (%) (95% CI)</th>
<th>Detection rate, (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2.9</td>
<td>3,632 (82)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3.0–3.9</td>
<td>314 (7)</td>
<td>71</td>
<td>13</td>
<td>18(^c) (10–29)</td>
<td>0.3 (0.1–0.5)</td>
</tr>
<tr>
<td>4.0–9.9</td>
<td>413 (9)</td>
<td>386</td>
<td>66</td>
<td>18(^c) (15–22)</td>
<td>1.5 (1.1–1.9)</td>
</tr>
<tr>
<td>(\geq 10)</td>
<td>48 (1)</td>
<td>45</td>
<td>18</td>
<td>38(^c) (24–53)</td>
<td>0.4 (0.2–0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>4,407 (100)</td>
<td>502</td>
<td>97</td>
<td>—</td>
<td>2.2 (1.8–2.6)</td>
</tr>
</tbody>
</table>

\(^a\) PSA, prostate-specific antigen; CI, confidence interval.

\(^b\) The positive predictive value of the percentage of free PSA \(\leq 16\%\) in 72 men at PSA levels of 3.0–3.9 \(\mu g/liter\).

\(^c\) The positive predictive value at the lower end of the PSA range.

\(^d\) Not applicable.

Ethics. The ethical committee of each participating hospital approved the trial protocol. Permission to obtain medical records was obtained from the Ministry of Social Affairs and Health and for use of cancer registry data from the STAKES Research and Development Center for Welfare and Health.

Results

Overall, 69% (4407 of 6415) of eligible men participated in screening during the first year (i.e., in 2000) of the second round of the Finnish trial. Of the eligible 4556 men, who participated in the first round (in 1996), 84% (3833) attended rescreening. Of the 1859 first-round nonattendees, 31% (574) participated in the subsequent screening round. Compliance was higher among men with a baseline PSA \(< 4 \mu g/liter\) (85%; 3650 of 4272) as compared with those tested as positive on the basis of a PSA of 4 \(\mu g/liter\) (64%; 183 of 284) in the initial round \((P < 0.001)\).

Of the 4407 second round participants, 461 (10.5%) were defined as screen positive based on a serum PSA concentration of \(\geq 4 \mu g/liter\) and referred for prostate biopsies (Table 1). In addition, 314 (7.1%) screeners had a PSA between 3.0 and 3.9 \(\mu g/liter\), and 72 of these were referred for biopsies based on a percentage of free PSA \(\leq 16\%\). Forty-seven (1.1%) screeners had PSA levels of \(\geq 10 \mu g/liter\). A total of 31 men (5.8%; 31 of 533) either refused or did not undergo a prostate biopsy due to medical contraindications.

Altogether, 97 cancers were found, corresponding to an overall detection rate of 2.2% (95% CI, 1.8–2.6%; 97 of 4407; Table 1). Seventy-nine cases were seen in men attending both screening rounds, this corresponding to a detection rate of 2.1% (95% CI, 1.6–2.6%; 79 of 3833) among rescreened men (Table 2). The rate of prostate cancer detection was somewhat higher among the 574 men screened for the first time, with 18 diagnosed cases giving a detection rate of 3.1% (95% CI, 1.9–4.9%; 18 of 574). The rate of cancer detection increased with age from 1.0% (95% CI, 0.6–1.4%) among men aged 59 years to 1.5% (1.0–2.2%), 1.8% (1.1–2.7%), and 2.4% (1.6–3.4%) in the age groups of 63, 67, and 71 years, respectively (Fig. 2).

Of all of the detected cases, 13 were seen with PSA levels \(< 4 \mu g/liter\), 66 within the range of 4.0–9.9 \(\mu g/liter\), and 18 at \(\geq 10 \mu g/liter\), corresponding to detection rates of 0.3% (95% CI, 0.1–0.5%; 13 of 4407), 1.5% (1.1–1.9%; 66 of 4407), and 0.4% (0.2–0.6%; 18 of 4407), respectively. The positive predictive value of the PSA threshold of 4 \(\mu g/liter\) was 18% (95% CI, 15–22%; 84 of 461) and 38% (24–53%; 18 of 48) for the 10 \(\mu g/liter\) threshold.

At PSA levels of 3.0–3.9 \(\mu g/liter\), the percentage of free PSA with a cutoff of 16% gave a positive predictive value of 18% (95% CI, 10–29%; 13 of 72). In the 3833 second-time screeners, the positive predictive value was somewhat lower for both the PSA threshold of 4 \(\mu g/liter\) and 10 \(\mu g/liter\) yielding to the values of 17% (14–21%; 67 of 389) and 32% (17–51%; 10 of 31), respectively. The corresponding values for the first-time attenders were 24% (14–35%; 17 of 72) and 47% (23–72%; 8 of 17).

The initial PSA level at prevalence screening predicted a risk of prostate cancer in rescreening 4 years later. The risk was 6-fold in men with the baseline PSA levels between 3.0 and 3.9 \(\mu g/liter\) compared with those at PSA levels <3 \(\mu g/liter\) (Table 3). The risk increased up to 9-fold in men testing screen positive on the basis of a PSA of 4.0–9.9 \(\mu g/liter\) in the first round of screening. Only 1 cancer was seen among those 13 men with a baseline PSA of \(\geq 10 \mu g/liter\). The positive predictive value for the PSA threshold of 4 \(\mu g/liter\) at baseline was 11% (6–15%; 20 of 183) and 8% (2–36%; 1 of 13) for the threshold of 10 \(\mu g/liter\) in the second-time participants of screening.

The detection rate of Gleason score 2–6 prostate cancer

Table 2  Numbers of men and detected PCs\(^a\) by clinical stage and Gleason score in the first (1996) and second round (2000) of screening in the Finnish trial

<table>
<thead>
<tr>
<th>Stage</th>
<th>Round 1</th>
<th>Re-screen</th>
<th>Delayed 1st screen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of men invited</td>
<td>No. of men screened (%)</td>
<td>7,281</td>
</tr>
<tr>
<td></td>
<td>No. of PCs</td>
<td>105</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>T(_1), N(_0), M(_0)</td>
<td>42 (40)</td>
<td>43 (54)</td>
</tr>
<tr>
<td></td>
<td>T(_2), N(_0), M(_0)</td>
<td>49 (47)</td>
<td>31 (39)</td>
</tr>
<tr>
<td></td>
<td>T(_1), N(_0), M(_1)</td>
<td>14 (13)</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>T(_2), N(_0), M(_1)</td>
<td>7 (7)</td>
<td>3 (4)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3 (3)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Detection rate, %</td>
<td>2.1</td>
<td>2.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

\(^a\) PC, prostate cancer.

\(^b\) The first-round nonparticipants reinvited in 2000.
Discussion

Compliance with screening remained at an acceptable level (69%) in the second round of the Finnish population-based trial. Of the first-round participants, up to 84% attended rescreening. The overall rates of prostate cancer detection were practically the same in the first and second round of screening, but the reduction in age-specific detection rates was obvious at the second round (Fig. 2; Ref. 10). A substantial decrease was seen particularly in the rate of advanced cases, from 0.3% to 0.1%. Because tumor characteristics represent an intermediate indicator of screening efficacy, the few advanced cancers at rescreening constitutes encouraging, yet inconclusive, evidence for eventual mortality reduction attributable to PSA screening. In particular, early cases represent those with a potential to benefit from screening through early diagnosis and treatment, but are confounded by overdiagnosis. Advanced cases indicate failure of screening to reach these aims, and, hence, a reduction in them is a better surrogate for mortality as a definitive end point.

Tumor stage as a surrogate measure of screening efficacy is, however, closely associated with length bias, indicating a higher likelihood of detecting slow growing as against aggressive tumors in multiple screens. Slow-growing tumors are strongly overrepresented at the first (prevalence) screen, and, hence, these initially detected cases comprise the most biased sample of screen-detected cancers. Most prevalent, slow-growing tumors (length bias) are likely to be eliminated with the introduction of screening followed by a steady state in incident cases in successive screening cycles. Tumor characteristics at later (incidence) screens are, thus, more informative in assessing the efficacy of screening than those derived from prevalence screens (14). The efficacy of screening should after all be evaluated in terms of an outcome in screen-detected cases relative to what would have occurred if there had been no screening (which is not directly observable), and is estimable only after several years of follow-up in terms of mortality reduction in those screened compared with those in the control arm.

The American Cancer Society and American Urological Association have recommended annual PSA screening for men aged 50 years or older despite the lack of evidence for either optimal screening interval or eventual mortality reduction (15, 16). Several trials, including ours, use substantially longer screening intervals (6). Short intervals increase drawbacks, such as overdiagnosis and costs of screening without necessarily improving efficacy in terms of advanced cancers prevented, whereas too long an interval is likely to miss potentially lethal tumors at curable stages. Both observational and simulation studies have recently suggested the alternative of biannual instead of annual screening with a minimal risk of nonlocalized cancer (17, 18). Nonrandomized studies and modeling are, however, prone to several biases. The recent findings from the

Table 3  Numbers of men and detected PCs in the second round in relation with total PSA found at prevalence screen, the Finnish prostate cancer screening trial

<table>
<thead>
<tr>
<th>PSA (μg/liter)</th>
<th>1st screen</th>
<th>2nd screen</th>
<th>2nd screen</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of men</td>
<td>No. of men with PSA ≥3</td>
<td>No. of PC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>3,459</td>
<td>368</td>
<td>45</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3.0–3.9</td>
<td>191</td>
<td>145</td>
<td>14</td>
<td>5.6</td>
<td>3.2–10.1</td>
</tr>
<tr>
<td>4.0–9.9</td>
<td>170</td>
<td>144</td>
<td>19</td>
<td>8.6</td>
<td>5.1–14.4</td>
</tr>
<tr>
<td>≥10</td>
<td>13</td>
<td>11</td>
<td>1</td>
<td>5.9</td>
<td>0.2–47.8</td>
</tr>
<tr>
<td>Unscreened</td>
<td>574</td>
<td>105</td>
<td>18</td>
<td>2.4</td>
<td>1.4–4.1</td>
</tr>
</tbody>
</table>

a PC, prostate cancer; PSA, prostate-specific antigen; CI, confidence interval.

b The ratio of detection rates.
Table 4  
Clinical stage and Gleason score of prostate cancer by serum PSA concentration among the 4407 men screened at the second round of the Finnish prostate cancer screening trial

<table>
<thead>
<tr>
<th>Stage</th>
<th>3.0–3.9</th>
<th>4.0–9.9</th>
<th>≥10</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of PC</td>
<td>(DR, %)</td>
<td>No. of PC</td>
<td>(DR, %)</td>
</tr>
<tr>
<td>T1aN0M0</td>
<td>7</td>
<td>(0.2)</td>
<td>36</td>
<td>(0.8)</td>
</tr>
<tr>
<td>T2aN0M0</td>
<td>6</td>
<td>(0.1)</td>
<td>26</td>
<td>(0.6)</td>
</tr>
<tr>
<td>T1-4N0M1</td>
<td>4</td>
<td>(0.1)</td>
<td>2</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>10</td>
<td>(0.2)</td>
<td>49</td>
<td>(1.1)</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>(0.0)</td>
<td>15</td>
<td>(0.3)</td>
</tr>
<tr>
<td>8–10</td>
<td></td>
<td></td>
<td>4</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2b</td>
<td>(0.0)</td>
<td>2b</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>(0.3)</td>
<td>66</td>
<td>(1.5)</td>
</tr>
</tbody>
</table>

a PSA, prostate-specific antigen; PC, prostate cancer; DR, detection rate.
b Gleason score was unavailable for a total of 4 patients due to small sample size at biopsy. Three of these tumors were graded as well differentiated according to the WHO system. In one case grading was not possible.

Swedish section of the European Randomized Study of Screening for Prostate Cancer are also in favor of longer screening intervals (9). Only a few of both interval and advanced cancers were seen during the follow-up of biannual PSA screening in Sweden. In our randomized trial, 5 of 6 clinically advanced cases were negative in the initial screening. Nevertheless, a clear reduction was seen in the rate of advanced cancer in the second round of screening, but lack of data on interval cancers limits the applicability of our findings.

The findings of the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer are consistent with those in the Finnish trial showing only a modest reduction in the overall rate of prostate cancer detection in multiple screens with a 4-year interval even after correction for age (7). It is generally assumed that cancer detection rates will drop in subsequent screens as compared with the initial prevalence screen. Failure to achieve this may indicate too long a screening interval. The second round findings in both the present and the Dutch trial were, however, indicative of a favorable effect on tumor stage in repeat screening (7). The comparable cancer detection rates at prevalence and incidence screens may also be attributable to overdiagnosis, but this cannot be evaluated without information on interval cancers and incidence rates in the control population. The recent report from the Dutch trial, however, shows the rate of interval cancers to be modest (19). In our trial, the cumulative incidence of 4.6% in the two screens is thus far substantially lower than the lifetime risk of 7% in men aged 55–74 years in Finland, with relatively low rate of opportunistic screening (data from the Finnish Cancer Registry).

The Finnish trial is population-based, and, hence, our findings are readily applicable to a PSA-based screening program as a national health policy. The effectiveness of such programs is dependent upon the coverage of the target population. In our trial, the overall attendance rate in the second round of screening remained the same as in the first (i.e., at 69%), and it was close to rates obtained in multiple screens based on recruitment of volunteers (7, 8). However, 16% of the first-round screeners dropped out at rescreening, which is consistent with volunteer-based trials showing incomplete attendance after initial screening. Plausible explanations for this are both the possibility that men with a negative initial screen are opting out, as well as the increasing use of PSA testing (opportunistic screening) outside the trial. This issue may compromise the effectiveness of any organized screening, and it also complicates evaluation of the ongoing trials.

The overall detection rate of Gleason score 7–10 cancers was comparable (~0.5%) in the first and second screening rounds of the Finnish trial, although a shift toward cases with a Gleason score of 7 was observed at rescreening (20). On the other hand, the rate of Gleason score 2–6 tumors decreased slightly. Tumor grade is highly relevant for screening, as survival of patients with a well-differentiated tumor have proved similar to age-matched controls, whereas those with a more aggressive disease have substantially reduced life expectancy without potentially curative intervention (21). Hence, our screening strategy revealed a smaller number of potentially insignificant tumors at rescreening but maintained the diagnosis of aggressive ones (more likely to benefit from screening). This is in contrast with the results of the Dutch trial, where no change was seen in well-differentiated tumors, but a clear reduction in more aggressive cancers with a Gleason score of 7 or higher (7). A plausible explanation for this is the lower PSA cutoff of 3 µg/liter used as biopsy criterion in Holland. In that study more than a third of all of the cases were in fact found at PSA levels < 4 µg/liter. However, a shift in learning curve associated with the adoption of Gleason score system in the initial phase of the Finnish trial may attenuate the comparability of tumor grades.

The positive predictive value of PSA was lower in the second round of the Finnish trial compared with that at the initial screen (in the previously unscreened population). This corresponds to an increase in biopsy to cancer ratio from 3.9 to 5.5 per detected cancer for the PSA cutoff of 4 µg/liter (10). A similar change has been observed in two other trials (5, 7). The reduction in positive predictive value is presumably attributable to the elimination of large, slowly growing prostate cancers from the prevalence pool at the first screen, whereas the prevalence of benign prostatic hyperplasia causing elevated PSA...
levels will increase with age. In other words, positive predictive value is determined not only by the test itself, but also by the prevalence of the target condition in the source population. This is an important finding affecting interpretation of PSA measurements in both screening and clinical settings.

Few reports have assessed the association between baseline PSA levels and later risk of prostate cancer in screening (7, 9, 22). In our trial, the first-round PSA level predicted the risk of prostate cancer at repeat screening 4 years later. The risk was particularly high in men with a PSA of ≥4 μg/liter, but without cancer diagnoses at baseline. Studies with shorter screening intervals have also suggested an elevated risk of cancer at follow-up screens in men with initially increased PSA levels already within a year from entry in screening (9, 23). Both these and our findings are contrary to the Dutch study, indicating that baseline PSA levels do not predict a risk of prostate cancer at later screens (7). Concern must prevail that a negative biopsy may give false assurance of a low future risk of cancer in screen-positive men, which may affect compliance with repeated screening. In the present study, such men formed a high-risk group at rescreening, indicating precisely the opposite. In fact, more than a fifth of cancers found in the second round of screening were seen in this group. In the Swedish trial based on biannual screening, more than half of the cancers detected at the second round were seen in men with elevated baseline PSA levels. This is conceivably a result of missing smaller tumors at biopsy in the first round. However, most screen-positive men were referred for rebiopsies in the initial phase of our study to maximize sensitivity at biopsy. It is, hence, unlikely that the increased risk in men screen-positive in the first round is solely due to limited sensitivity of prostate biopsy. The fact that only 1 cancer seen in men with a baseline PSA >10 μg/liter limits conclusions, but is also consistent with a lower risk of missing large tumors at biopsy as well as with increased clinical surveillance after a markedly elevated PSA at screening. Nevertheless, an abnormal finding (PSA) at prevalence screen represented a significant risk factor for prostate cancer in repeat screening in the Finnish trial. It remains to be shown whether this finding can be confirmed at subsequent screens, and whether this information is applicable to the current screening practices (such as the follow-up of screen-positive men with negative biopsies as well as the frequency of screening).

In conclusion, the second round of screening in the Finnish population-based trial showed an acceptable level of compliance after a 4-year interval as well as a lower detection rate especially of advanced cancers compared with the initial (prevalence) screen. These are necessary conditions for an effective screening program, but comprise nonetheless inconclusive evidence for eventual mortality reduction attributable to PSA screening. Moreover, recognition of high-risk groups on the basis of the screening history may facilitate improvement of the performance of screening programs in future.

References
Clinical Cancer Research

Second Round Results of the Finnish Population-Based Prostate Cancer Screening Trial


**Updated version**
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/10/7/2231

**Cited articles**
This article cites 21 articles, 3 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/10/7/2231.full.html#ref-list-1

**Citing articles**
This article has been cited by 4 HighWire-hosted articles. Access the articles at:
/content/10/7/2231.full.html#related-urls

**E-mail alerts**
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.