PSA screening: to do or not?

Ravindran KANESVARAN
Senior Consultant Medical Oncologist, National Cancer Centre Singapore
Program Director, Medical Oncology Senior Residency
Medical Director, NCCS @Sengkang Hospital
Disclosures

• Speaker Bureau: Pfizer, J&J, Sanofi, Novartis, MSD

• Advisory Board/ Consultant: GSK, Novartis, Bayer, J&J, Mundipharma, Astellas, MSD, BMS, Eisai

• Research support: Sanofi, J&J, Astellas
Impact of PSA screening on PC incidence

- PSA test invented and patented in 1984
- Urologists began routinely PSA testing men in the USA in the mid 1980s and early 1990s

- Impact on PC incidence
  - The age-adjusted incidence rate of PC among men aged ≥ 65 years rose 82% from 1986 to 1991, with the largest annual increases occurring in 1990 (20%) and 1991 (19%)

The value of PSA screening

- large RCTS
  - ERSPC
  - PLCO
  - CAP

- Smaller screening studies
  - Goteborg
  - Stockholm
  - Noorkoping
ERSPC

• PSA screening on PCa mortality
• 7 EU countries, n=182,000 men
• PSA testing every 4 years
• Age 50-74 years
• Latest update – 13 years F/U

• Screening variation
  • Sweden screen 2 years, Belgium 7 years
  • On average, men screened 2.3 times

*Lancet.* 2014 December 6; 384(9959): 2027–2035
Men included
All ages
182,160

Men randomised
Core age group
(aged 55-69)
162,388

145 died before randomisation date
(62 intervention arm - 83 control arm)

Intervention arm
N = 72,891

Prostate cancer cases
Years 1-11 6797
Years 1-13 7408 (10.2%)

Distribution of risk groups*:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
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<td>570</td>
<td>7.7</td>
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<tr>
<td>Low</td>
<td>4441</td>
<td>59.9</td>
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<tr>
<td>Intermediate</td>
<td>1625</td>
<td>21.9</td>
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<tr>
<td>High</td>
<td>518</td>
<td>7.0</td>
</tr>
<tr>
<td>M1 and/or PSA &gt; 100</td>
<td>254</td>
<td>3.4</td>
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</table>

Deaths all causes
15369

Prostate cancer deaths
Years 1-11 265
Years 1-13 355 (0.49%)

Control arm
N = 89,352

Prostate cancer cases
Years 1-11 5262
Years 1-13 6107 (6.8%)

Distribution of risk groups*:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Missing</td>
<td>600</td>
<td>9.8</td>
</tr>
<tr>
<td>Low</td>
<td>2543</td>
<td>41.6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1711</td>
<td>28.0</td>
</tr>
<tr>
<td>High</td>
<td>667</td>
<td>10.9</td>
</tr>
<tr>
<td>M1 and/or PSA &gt; 100</td>
<td>586</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Deaths all causes
19108

Prostate cancer deaths
Years 1-11 415
Years 1-13 545 (0.61%)

* Low risk = T1,T2 with Gleason score (GS) = 6; Intermediate risk = T1,T2 with GS 7 and T3 with GS <=7; High risk = T1,T2,T3 with GS 8-10 and T4 with any GS; M1 or PSA > 100 may occur any T stage or GS; "Missing" = missing T stage or GS, not M1 or PSA>100
ERSPC Trial

Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson–Aalen method was used to calculate the cumulative hazard of death from prostate cancer.

NNN Engl J Med 360;1320-8, 2009

Reduction in mPca

- Reduction in metastatic Pca
  - Imaging diagnosis or PSA >100

- HR 0.70 (0.60-0.82, p<0.001)

- 30% reduction in risk of metastasis
Figure 3

PC Mortality rate in each arm by 4 year period
# Prostate Cancer Mortality

## ERSPC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths from any cause</td>
<td>0.99 (0.97–1.02)</td>
<td>0.50</td>
</tr>
<tr>
<td>All deaths from prostate cancer</td>
<td>0.80 (0.67–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding the Netherlands</td>
<td>0.81 (0.67–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Excluding Finland</td>
<td>0.74 (0.58–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding Sweden</td>
<td>0.84 (0.70–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Excluding Belgium</td>
<td>0.79 (0.66–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding Spain</td>
<td>0.79 (0.67–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding Italy</td>
<td>0.79 (0.66–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding Switzerland</td>
<td>0.80 (0.68–0.96)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Rate ratios, which were calculated with the use of Poisson regression, compare the rate of death from prostate cancer in the screening group with the rate in the control group. The calculations were restricted to men in the core age group (55 to 69 years).

† P values have not been corrected for multiple testing.

NNN Engl J Med 360;1320-8, 2009
Summary

• Screening reduces PCa mortality / risk of metastasis

• Benefit increase with time of F/U

• Optimal screening frequency not clear
PLCO

- PCa mortality by PSA screening
- N=76,685 men, 55-74 years
- PSA year, DRE every 2 years
- PSA >4, abnormal DRE -> trigger ‘usual care’

- Opportunistic screen if requested by patient
Figure 3. Cumulative deaths from prostate cancer in the intervention and control arms from year 1 to year 13. C = control arm; I = intervention arm; PY = person-years.
Table 1. Comparison of Randomized Prostate-Cancer Screening Trials.*

<table>
<thead>
<tr>
<th>Data</th>
<th>PLCO</th>
<th>ERSPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (yr)</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>PSA screening interval</td>
<td>Annually for 6 yr</td>
<td>Every 2 to 4 yr</td>
</tr>
<tr>
<td>Nonattendance (%)</td>
<td>15.0</td>
<td>17.4</td>
</tr>
<tr>
<td>Contamination (%) †</td>
<td>85</td>
<td>24</td>
</tr>
<tr>
<td>Difference in rate of PSA testing between study groups (%) ‡</td>
<td>0</td>
<td>58.6</td>
</tr>
<tr>
<td>Prerandomization PSA testing (%)</td>
<td>44</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rate ratio for death from prostate cancer in men undergoing randomization to screening vs. usual care (95% CI)</td>
<td>1.09 (0.87–1.36)</td>
<td>0.79 (0.65–0.98)</td>
</tr>
</tbody>
</table>

* Data are from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial or the European Randomized Study of Screening for Prostate Cancer (ERSPC) unless noted otherwise. CI denotes confidence interval, and PSA prostate-specific antigen.

† Data on contamination are from Pinsky et al.⁵ for the PLCO screening trial and from Kerkhof et al.⁶ for the ERSPC.

‡ The difference in the rate of PSA testing between study groups refers to the difference in the rate of testing between those who underwent randomization to usual care and those who underwent randomization to screening.
# ERSPC & PLCO PSA screening trials: summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Characteristics</th>
<th>Weaknesses</th>
<th>Result</th>
</tr>
</thead>
</table>
| **ERSPC**<sup>1</sup> | - RCT (N = 182,160)  
- PSA at 4-year intervals  
- PSA cut-off: ≥ 3 ng/mL (mainly) | - Heterogeneity of Protocols  
- Treatment bias  
- Findings significant only in core group (55–69-year-old men) | - 21% reduction in PC mortality in screening group |
| **Prostate, Lung, Colorectal, and Ovarian Cancer screening trial (PLCO)**<sup>2</sup> | - RCT (N = 76,693)  
- PSA/DRE annually  
- PSA cut-off: > 4 ng/mL | - Highly pre-screened population  
- Contamination of control arm | - No difference in PC mortality between groups |
Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality
The CAP Randomized Clinical Trial

Richard M. Martin, PhD; Jenny L. Donovan, PhD; Emma L. Turner, PhD; Chris Metcalfe, PhD; Grace J. Young, MSc; Eleanor I. Walsh, MSc; J. Athene Lane, PhD; Sian Noble, PhD; Steven E. Oliver, PhD; Simon Evans, MD; Jonathan A. C. Sterne, PhD; Peter Holding, MSc; Yoav Ben-Shlomo, PhD; Peter Brindle, MD; Naomi J. Williams, PhD; Elizabeth M. Hill, MSc; Siaw Yein Ng, PhD; Jessica Toole, MSc; Marta K. Tazewell, MSc; Laura J. Hughes, BA; Charlotte F. Davies, PhD; Joanna C. Thorn, PhD; Elizabeth Down, MSc; George Davey Smith, DSc; David E. Neal, MD; Freddie C. Hamdy, MD; for the CAP Trial Group

**IMPORTANCE** Prostate cancer screening remains controversial because potential mortality or quality-of-life benefits may be outweighed by harms from overdetection and overtreatment.

**OBJECTIVE** To evaluate the effect of a single prostate-specific antigen (PSA) screening intervention and standardized diagnostic pathway on prostate cancer-specific mortality.

**DESIGN, SETTING, AND PARTICIPANTS** The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) included 419,582 men aged 50 to 69 years and was conducted at 573 primary care practices across the United Kingdom. Randomization and recruitment of the practices occurred between 2001 and 2009; patient follow-up ended on March 31, 2016.
Pca Mortality

Figure 2. Cumulative Incidence of Prostate Cancer Detection and Mortality in the Single Prostate-Specific Antigen Testing Intervention Group vs Standard Practice (Control)

Martin et al JAMA 2018
Results

Key Points

**Question** What is the effect of an invitation to a single prostate-specific antigen (PSA) screening on prostate cancer detection and median 10-year prostate cancer mortality?

**Findings** In this randomized clinical trial comparing men aged 50 to 69 years undergoing a single PSA screening (n = 189,386) vs controls not undergoing a PSA screening (n = 219,439), the proportion of men diagnosed with prostate cancer was higher in the intervention group (4.3%) than in the control group (3.6%); however, there was no significant difference in prostate cancer mortality (0.30 per 1000 person-years for the intervention group vs 0.31 for the control group) after a median follow-up of 10 years.

**Meaning** The single PSA screening intervention detected more prostate cancer cases but had no significant effect on prostate cancer mortality after a median follow-up of 10 years.

Martin et al JAMA 2018
Goteborg

- PSA screening on PCa mortality
- Randomised, population-based prostate screening

- N=20,000, age 56-64
- Median f/u 14 years
- PSA testing every 2 years
- PSA threshold 3.0 (ERSPC level)

- Above threshold -> DRE, sextant TRUS biopsy

- Diagnosis of cancer tracked via West-Swedish Regional Cancer Registry

*Lancet Oncol*. 2010 August; 11(8): 725–732
Figure 1.
CONSORT diagram of the study
Goteborg

• Incidence PCa – 12.7% vs 8.2%
• (HR 1.64, 95% CI 1.5-1.8, p<0.0001)

To prevent one prostate cancer death:
• NNS – 231
• NND – 10
(2018 update)
Hugosson Scand J Urol 2018
Figure 3.
Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates
Public health policy (1)

- 2012 US Task Force
- Grade D recommendation
- Recommend **against** routine PSA testing
- All ages
Public health policy (2)

- **AUA**
  - consider screening 55-69 years
  - 40-55 years – discussion, personalised
  - 2 yearly PSA

- **ACS**
  - Consider screen >50 years for average age
  - >40 years for African American or family history
  - Baseline PSA determines frequency

- **EAU**
  - Consider screen at 40s, then decide frequency
Singapore guidelines for population screening: no screening for prostate cancer

- Population screening not recommended
- High-risk men aged > 50 years
  - First-degree relative diagnosed with PC aged < 65 years
- Combined PSA and DRE better
Baseline PSA Midlife

- 40-59 years old US physicians
- N= 22,071
- Physician’s Health Study
- Aspirin vs B-carotene trial

- 234 PCa, 711 age-matched controls
Risk of lethal PCa

• Median PSA (controls)
  • 40-49 years (0.68 ng/ml)
  • 50-54 years (0.88)
  • 55-59 years (0.98)

• Risk of lethal PCa if PSA >90th percentile per age group
  • OR 8.7 (1.0 to 78.2) - 40 to 49 years
  • OR 12.6 (1.4 to 110.4) 50 to 54 years
  • OR 6.9 (2.5 to 19.1) 55 to 59 years

Journal of Clinical Oncology 2016 34:23, 2705-2711
A population-based stratified approach...

- PSA screening general population
  - Should not offer routinely
  - coupled with physical examination
  - Higher risk individuals
  - 50 years onwards (with discussion on pros and cons)
  - baseline PSA
  - 2 to 4 yearly depending on baseline PSA
  - those with less than 10 years life expectancy
To your next patient...

• A discussion of pros and cons is important
  • Benefits
    • PCa mortality
    • Metastatic disease
  • Cons
    • Over diagnosis
    • PSA cripple
Primary PC therapies can have a major impact on quality of life

<table>
<thead>
<tr>
<th>Radical prostatectomy</th>
<th>Radiotherapy</th>
<th>Watchful waiting</th>
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</thead>
<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>Local bowel and bladder symptoms</td>
<td>Progression</td>
</tr>
<tr>
<td>Incontinence</td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Erectile dysfunction</td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

Take Home Messages

• PSA screening reduces PCa mortality/ M1 disease

• Screening strategy
  • Personalised, no ideal one as of now
  • Use baseline PSA at middle age to decide, 40-50 years??
  • Family history, race

• Screening relevance
  • Contextual to patient
  • Pros and Cons
  • Stratification of risk