Erasmus MC
University Medical Center Rotterdam

**Screening, early diagnosis, and treatment including Active Surveillance for prostate cancer:**

***where is Europe heading for?***

**Europa Uomo meeting Stockholm 2009**

Chris H.Bangma
Rotterdam, The Netherlands

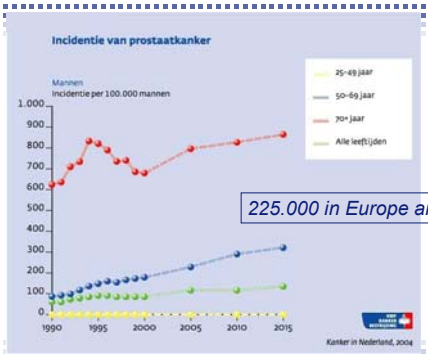
## To be covered

- Problem orientation
- Population effects of screening (ERSPC)
- Population versus individual screening
- Active Surveillance
- Marker research ongoing
- Discussion on the positioning research

## Problem orientation

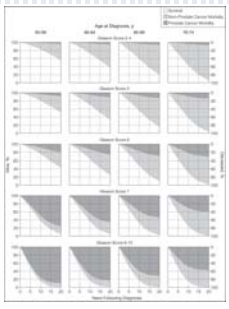
- Increased Pca awareness enhances large volume of diagnostic procedures
- ERSPC reports on cancer mortality difference by screening
- Low specificity of PSA, level-dependent
- Increasing number of indolent cancers diagnosed, at lower age
- Prognostic factors lacking
  - For initial therapy
  - During active surveillance
  -

## Increasing Pca incidence with age




*225.000 in Europe annually*

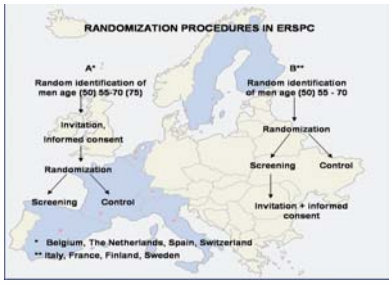
## Natural course Pca *(Albertsen 2005)*



- N=767
- Clinical stage ≤ T2
- Palliative treatment
- Dark grey = PCa †
- Light grey = nonPCa †
- White = survival

*19,7 % of men with Gleason ≤ 6 die of Pca*

ERSPC
European Randomized Study of Screening for Prostate Cancer




**205.000 participants in Europe**

Acknowledgements

**The European Randomized Study of Screening for Prostate Cancer (ERPSC): Endpoints**

- Prostate cancer mortality
- Prostate cancer morbidity
- Quality of life
- Quality of life adjusted life years (QUALY's)
- First mortality analysis: November 2008

**At which initial PSA is rescreen (not) needed?**

- PLCO: *Crawford et al, J Urol. 2006 Apr;175(4):1286-90*
- ERSPC: *Roobol et al, Prostate. 2006 May 1;66(6):604-12*
- Biopsy indication PSA>4.0 PLCO, PSA>3.0 ERSPC

| | N First-second-third round | Follow-up years | Number Pca when initial PSA 0-1 | Number Pca when initial PSA 1-2 | Pca when initial PSA 2-3 |
|---|---|---|---|---|---|
| PLCO | 30.495 | Annual to 5 | 8 (0.2 %) (1.5 % conv) | 15 (0.5%) (7.4 % conv) | 20 (0.6 %) (33 % conv) |
| ERSPC | 1703-1362-1311 | 0-4-8 | 0 | 3 (0.23 %) | 5 (0.29 %) |

*No rescreen in 5 years needed when PSA < 1 (36 % of population aged 55-74)*

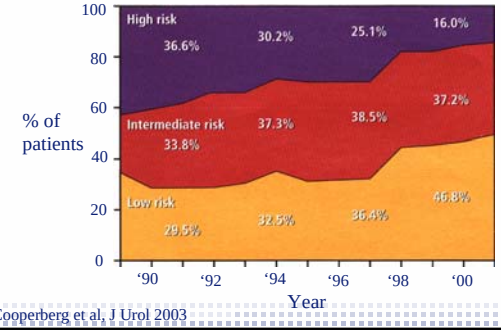
Schröder FH, Roobol MJ, Andriole GL, Fleshner N J Urol. 2009 Jan;181(1):69-74

- *A prostate specific antigen of 1.5 ng/ml or greater in men older than 50 years represents an indicator for greater than average future risk of prostate cancer.*

**Accomplishments ERSPC**

- Beneficial stage and grade shift confirmed
- 43 % of detected cancers are indolent (small, well differentiated tumours) *(Postma 2007)*
- 53 % of cancers diagnosed will not become symptomatic *(Draisma 2005)*
- Rescreen interval can be lengthened according to PSA level *(Roobol, Crawford, 2006),* ***POSTER 284 EAU***
- In men older than 50, PSA of 1.5 ng/ml or more indicates more than average future risk *(Schröder, Roobol, Andriole, Fleshner, J Urol 2009)*
- Value of population based screening still unproven….till today!

The diagnosis of low risk prostate cancer is increasing




Cooperberg et al, J Urol 2003

## How to screen the general population?

*Problems currently:*

1. *PSA is little specific >> False positive Bx indications*
2. *No prognostic factors for agressivity >> overdetection and overtreatment*
3. *Invasive therapies >> side effects*

- Option I: maximize detection
- Option II: select for “those who need cure and can be cured”. Is that possible?

## Option I: maximize detection

- Low or no PSA threshold
- 12 or more biopsies
- Low age limit
- Short interval

Results in

- Pca incidence between current results (21,9 % PTCP trial) and autopsy/cystoprostatectomy incidence (30-60 %: Montironi 2005, Haas 2008)
- Estimated ratio between Pca diagnosis and Pca death is 25 : 1 when all men PSA > 2.5 are biopsied….(Welch 2006, Schröder 2007)
- Overdiagnosis is inherent to screening – how much is acceptable?

## Option II: minimize detection

- Use higher PSA cut-off
- Biopsy less aggressively

Results in

- Missing cancers which might be cured later…

- Is it safe to do so?

**PCPT (option 1 = Bx everybody) versus ERSPC (option 2 = PSA cut-off): what is the difference for men with PSA<3?**

- **PCPT**: Men with PSA <3.0 ng/ml are screened yearly and all biopsied during or after 7 years
- **ERSPC**: Men with PSA <3.0 ng/ml were screened with a 4 year interval and biopsied for PSA progression to >3.0 ng/ml

- *12 year follow-up in ERSPC Rotterdam (3 rounds)*
- *On ‘PTCP’ strategy 3472 cancers would have been found in 15.773 biopsied men*
- *700 ERSPC cancers were found in little over 2500 biopsies: 80/700 interval cancers*
- *6 Pca deaths (0.032 %)*

## Screening will NOT prevent all PCa deaths

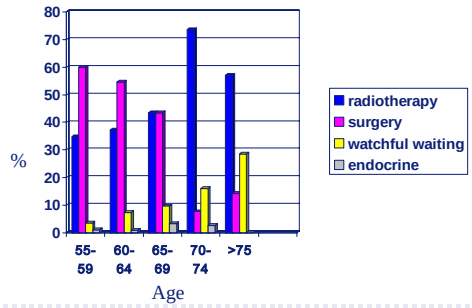
- Cut-off of 3.0 ng/ml: few of the missed cancers are diagnosed clinically within 12 years (80 of 3.472, 2%)
- A shorter interval does not improve detection of aggressive PC *(Roobol, Hugosson, JNCI 2008)*
- Improvement of detection in the PSA range 2-3 is desirable
- It is not necessary to detect all biopsy detectable PC in the low PSA ranges *(Schroder, Bangma, Eur Urol 2008)*

## Effect of using PSA > 2.5 ng/ml as biopsy indication in the USA

- Welch et al (2005): 2.74 million men, age 50-69 in the US have PSA > 2.5 ng/ml
- PCPT (Thompson et al 2003): PPV of PSA 2.1-4.0 ng/ml = 24.7%
- Biopsying all these men with PSA >= 2.5 will diagnose 676,780 PC, 457,890 more than expected in 2006, 15.1 times more than the 30,350 PC deaths in 2006

## Treatment of 1014 cancers detected

initial screening Rotterdam

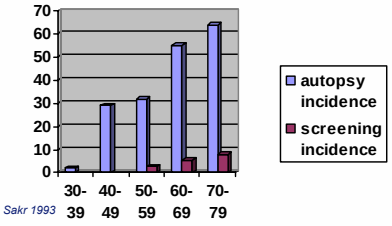



## Population based screening: who is deciding?

- Epidemiologist:
  - Minimase screening population: age cut-offs
  - reduce rescreening: increase screening interval based on PSA
  - Design screening protocol
- Urologist:
  - prevent overtreatment: initiate active surveillance
  - optimise diagnostics (markers and imaging)
  - Optimise treatment options
- Government:
  - Study the benefit in QOLY
  - Calculate costs

## Still more cancers may be diagnosed: There is more cancer than we can detect currently

- Autopsy data (Gosselaer 2005)
- Cystoprostatectomy data *(Damiano R, Eur Urol 2007)*




*Sakr 1993*

## When is a tumor indolent ?

- In retrospect:
  - clinical: not relevant, minimal
  - histologic: Epstein criteria after radical prostatectomy conform features of autopsy / radical cystoprostatectomy series
    - *Gleason < 7*
    - *< 0.5 ml*
- Prospective:
  - Histologic: focal
  - 'clinical' : Epstein criteria in biopsy combined with clinical criteria
    - *No Gleason pattern 4*
    - *≤ 2 biopsy cores with invasion*
    - *≤ 50 % invasion per core*
    - *PSA density ≤ 0,15 ng/ml/cm3*

## Score chart for the prediction of indolent prostate cancer (Steyerberg et al 2007)

| Variable | Values | Score | | Variable | Values | Score | Sum |
|---|---|---|---|---|---|---|---|
| Serum PSA (ng/mL) | 20 | 0 | | Biopsy Gleason | 3+3 | 0 | |
| | 13 | 2 | | Scores 1 and 2 | 2+3 | 1 | |
| | 9.0 | 4 | | | 2+2 | 4 | |
| | 6.0 | 6 | | | | | |
| | 5.0 | 7 | | mm cancerous | 20 | 0 | |
| | 4.0 | 8 | | tissue (total | 10 | 2 | |
| | 3.3 | 9 | | over biopsy cores) | 8 | 3 | |
| | 2.2 | 11 | | | 4 | 5 | |
| | 1.0 | 15 | | | 2 | 7 | |
| Ultrasound volume (cc) | 20 | 0 | | | 1 | 9 | |
| | 40 | 2 | | mm non-cancerous | 40 | 0 | |
| | 60 | 4 | | tissue (total over | 60 | 2 | |
| | 80 | 6 | | biopsy cores) | 80 | 4 | |
| | | | | Score (sum all scores) | | | 24 |

## Proportions of immediate versus delayed treatment for important (N=142) and indolent (N=136) PC using different score cut-offs (total N=278). ERSPC

| Treatment (Tx) | Important PC – treated N (%) | Indolent PC Tx delayed N (%) |
|---|---|---|
| No tx if probability indolent >30% (score >=15) | 50/142 (35) | 126/136 (93) |
| No tx if probability indolent > 60% (score > 20) | 120/142 (85) | 62/136 (46) |
| No tx if probability indolent > 70% (score > 21) | 133/142 (94) | 43/136 (32) |

## How to deal with this situation if individual screening is requested?

- Screening (early detection) by request cannot be refused
- Individual risk assessment is different from general population

- Refuse DRE + PSA in men with low risk?
- Avoid biopsy in low PSA ranges – what is "normal" PSA?
- Use available algorithms to decide
- Diagnose aggressively – avoid treatment in indolent cases?

## 'Easy' rules: refuse DRE and (follow-up) PSA

- Do not screen when life-expectancy ≤ average tumor lead time
  *(a 70 years old man has a life expectancy of 12.9 years)*
- Do not screen later in life if PSA < 0.6 ng/ml before the age of 50
- Do not re-screen within 5 years when your PSA was below 1.0 ng/ml

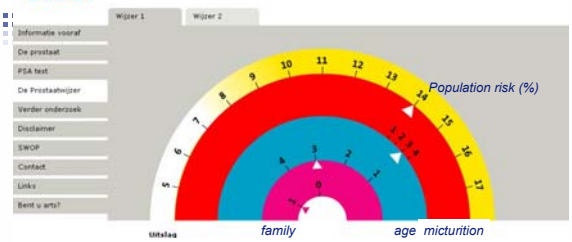
## Risk assessment
## Men want to know their risks

- Level 1: Man age 55 – 74: do I need to screen?
- Level 2: PSA known: shall I visit a urologist?
- Level 3: Levels 1+2, DRE, TRUS, and prostate volume known: do I need a biopsy? ***POSTER 287***
- Level 4: PSA less than 4: do I need a second screen?
- Level 5: first biopsy negative: do I need another biopsy?
- Level 6: Biopsy result known: do I need a therapy?

---

- Level 7: in case of cancer: what is my risk to get metastases?
- Level 8: *what is my risk of dying from Pca? (= outcome ERSPC)*

## Prostate risk calculator: www.uroweb.org




- Risk on Pca
- Risk on positive biopsy
- Risk on positive re-biopsy
- Risk on indolence

## So PSA is not sufficient?

- Current screening protocol ERSPC unacceptable for population based screening
- Increased specificity needed
- Multiple paramater risk assessment instead of PSA-only
- Marker development activity
  - Serum markers: P-mark, PRONEST
  - Genomic/histologic markers on biopsies
  - Imaging impovement to detect tumours of relevant size

## Promising biomarkers validated in P-Mark

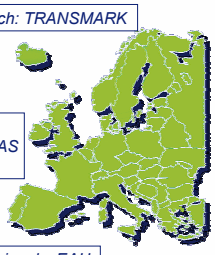
| Biomarker | Value |
|---|---|
| Multi-kallikreins (free PSA forms + human kallikrein 2) | diagnostic specificity PSA ↑ predicts long-term risk PCa |
| Osteoprotegerin (OPG) | predicts progressive PCa |
| PCA3 | diagnostic specificity PSA ↑ |

*P-Mark across marker validation study (outcome mid 2009)*
- Screening cohort from ERSPC study
- Analysis PCA3 (urine) and multi-kallikreins (blood)
- Comparison with PSA & correlation with aggressiveness

www.p-mark.org

## Europe as a scaffold to integrate research for prostate cancer patients

*Biomarker research: TRANSMARK*



*Patient organisations: Europa Uomo*

*Research programs: ERSPC , EORTC, PRIAS PROCABIO*

*Industry*

*Health care professionals: EAU*

## Biopsy scheme

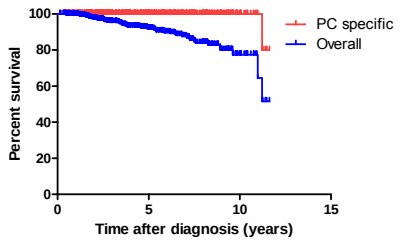
- Vashi-tabel: the chance to detect a tumor sized 1 ml in a 40 ml prostate with 8 biopsies is > 95 %
- Historical (Djavan): a sextant biopsy 'detects' 75 % of detectable cancers, a second series 94 % , a third series 97 %
- Increasing the number of biopsies from 6 to 12 hardly reduces the variation in grading

| Prostatic volume (cc) | Number of biopsy cores |
|---|---|
| 0-40 | 8 |
| 40-60 | 10 |
| >60 | 12 |

## Retrospective findings in screen-detected 'PRIAS-suitable' PCa (n = 616) (Sweden, Finland, Netherlands)

*(Van den Bergh et al, Eur Urol,2009)*

**PC specific and overall survival**




- (1 PC-death >11 years after diagnosis, patient abstained from active treatment despite rising PSA)

## Active surveillance misses some progression towards metastasis

| *Study, number of participants, mean follow-up time* | *Survival percentage over follow-up time* | *Metastases analysed* | *Percentage of pT3 in case of radical prostatectomy* | *Percentage of men with PSADT > 10 years* | *Conversion to invasive therapy* |
|---|---|---|---|---|---|
| Klotz 2006<br>N = 299<br>8 years | 99.3 % Pca specific | 2/299 % (N+) | 58 % (14/24) | 42 % | 35 % |
| Parker 2005<br>N = 80<br>3.5 years | 100 % Pca specific,<br>94 % overall | - | 50% (1/2) | 45 % | 20 % |
| Carter 2007<br>N = 405<br>2.8 years (range 0.4 – 12.5) | 98 % overall | 0.5 % (2) | 20 % (10/49) | - | 25 % after 2.2 years (PSADT no trigger) |
| Roemeling 2007<br>N = 278<br>3.4 years | 100 % Pca specific,<br>90 % overall | - | 1/13 (8%) | 44 % | 29 % after 2.5 years |
| Soloway 2008<br>N = 157<br>4 years | 100% Pca specific | 0 % | 0/2 (0%) | Mean 13.1 years in no treatment group,3.6 in treatment group | 8 % |

PRIAS: method for follow-up indolent Pca
**www.prias-project.org**

- PRIAS means Prostate cancer Research International: Active Surveillance
- web-based
- Password protected
- Information for patients and physicians in many European languanges
- Free of charge
- International observational study based on experience in watchful waiting and guided by experts to optimise active surveillance

- Inclusion criteria:
  - PSA-level at diagnosis ≤ 10 ng/mL
  - PSA density (PSA D) less than 0,2
  - Clinical stage T1C or T2
  - Adequate biopsy sampling (see 'biopsy protocol')
  - Gleason score 3+3=6
  - One or 2 biopsy cores invaded with prostate cancer
  - Participants must be willing to attend the follow-up visits

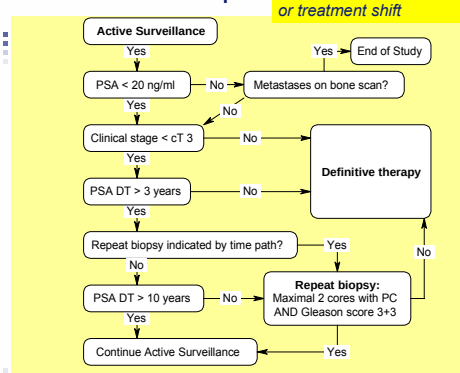
## Protocol PRIAS: Timetable

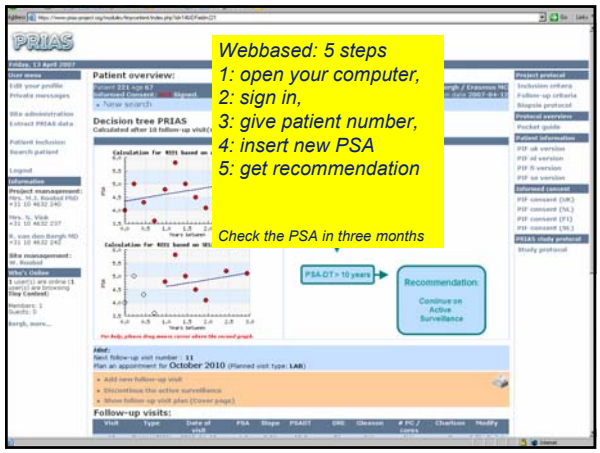
- Timetable:
  - PSA (1x / 3 months) (1x / 6 months after 2 years)
  - DRE (1x / 6 months) (1x / 12 months after 2 years)

| Year | 1 | | | | | 2 | | | 3 | | 4 | | 5 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Month | 0** | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 | 72 | 78 | 84 |
| PSA-test | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| DRE | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| Biopsy | ✓ | | | | ✓ | | | | | | | | ✓ | | | | | | ✓ |
| Evaluation | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |

## Flowchart for follow-up

*PSA kinetics can indicate a biopsy or treatment shift*




## Radical prostatectomy: also 5 steps…

1. Open the patient/ insert trocars
2. Mobilise the prostate (with/without lymfnodes)
3. Leave the nerves
4. Make anastomosis
5. Close the patient

- Check the PSA in three months



## prospects

- Risk dependent individual screening by Prostate Risk Indictor
- ?? Population based screening after adequate studies on QOL?
- Marker/imaging adjusted risk calculators
- Targeted therapy
- Biobanks for validation programs
- Technology driven marker discovery

*EU funded Marie Curie Programs:*
*TRANSMARK*
*PRONEST*

## Questions

- Where do we need new markers for?
- At time of diagnosis? To reduce false pos Biopsy indications?
  - To adjust / integrate in powerful instruments, like risk calculator?
- At time of biopsy? To indicate the number of biopsies?
- At time of treatment choice? Prognostic factors indicating targeted treatment?
  - To define indolent tumours?
- At time of ongoing treatment, esp. active surveillance?

**Now we have shoulders to stand on: what should we do?**

- Get Pca screening on the EU agenda of the new commissioners
- Make Prostate health a European demand equal over all countries
- Get marker research supported (ERSPC, PRIAS, PROCABIO)
- Organise axis of strength in centres of excellence
- Role for Europa Uomo