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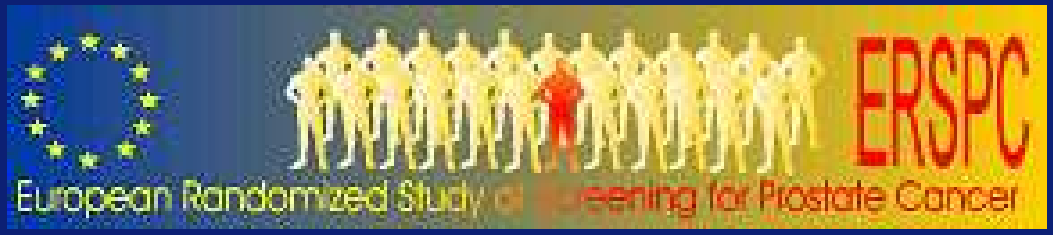



# Prostate cancer screening- pro and contra, lessons from the ERSPC study

## Are we ready for a population-based screening program?

Dr. Pim J.van Leeuwen

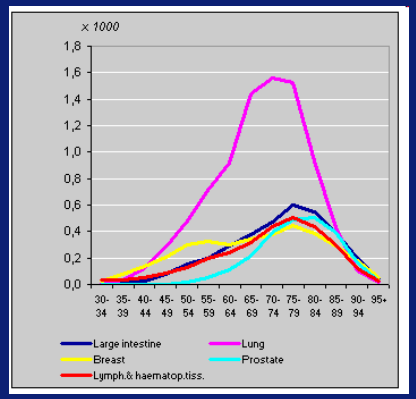
Erasmus MC, Rotterdam, The Netherlands

# On behalf of

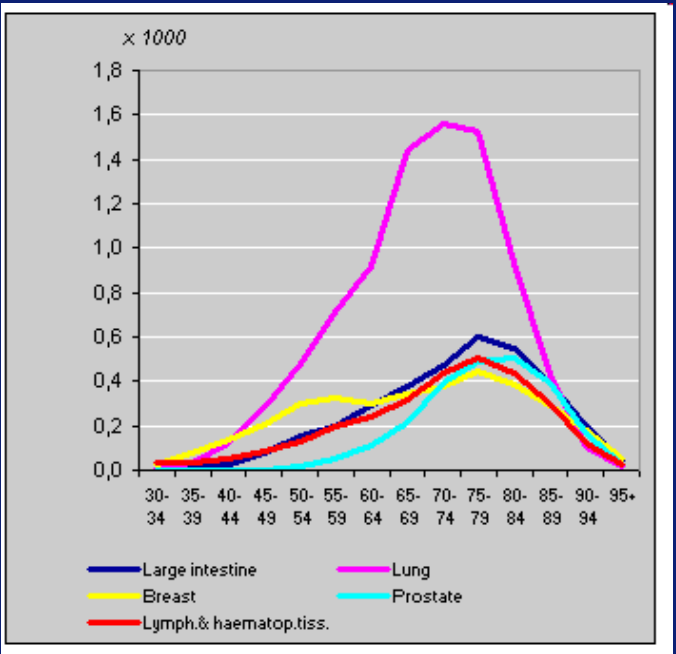
## The ERSPC study group

# Overview

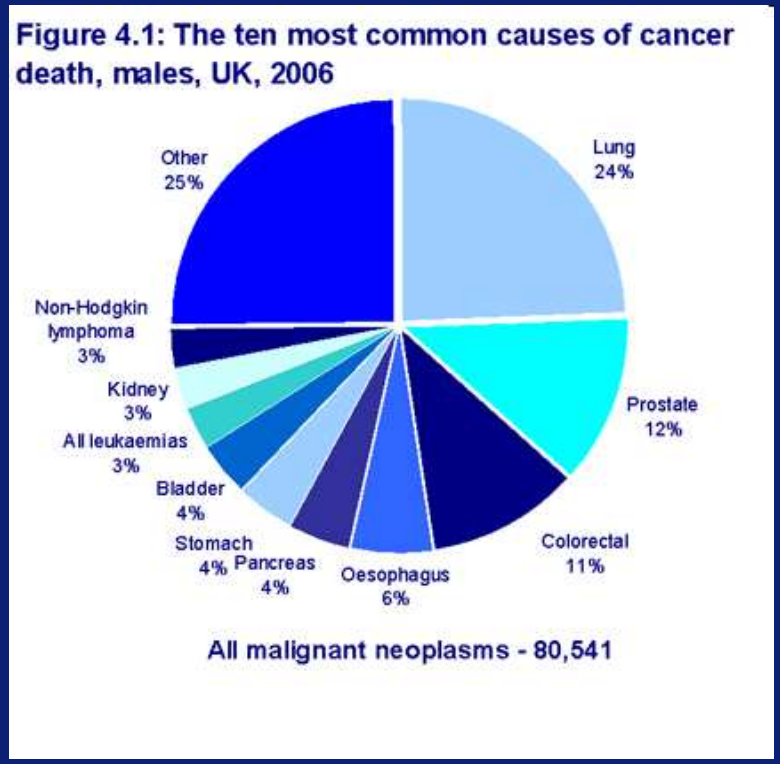
1. Facts of prostate cancer
2. Background cancer screening
3. Prostate cancer screening, The ERSPC study
4. An individualized approach
5. Active Surveillance



# The facts of prostate cancer



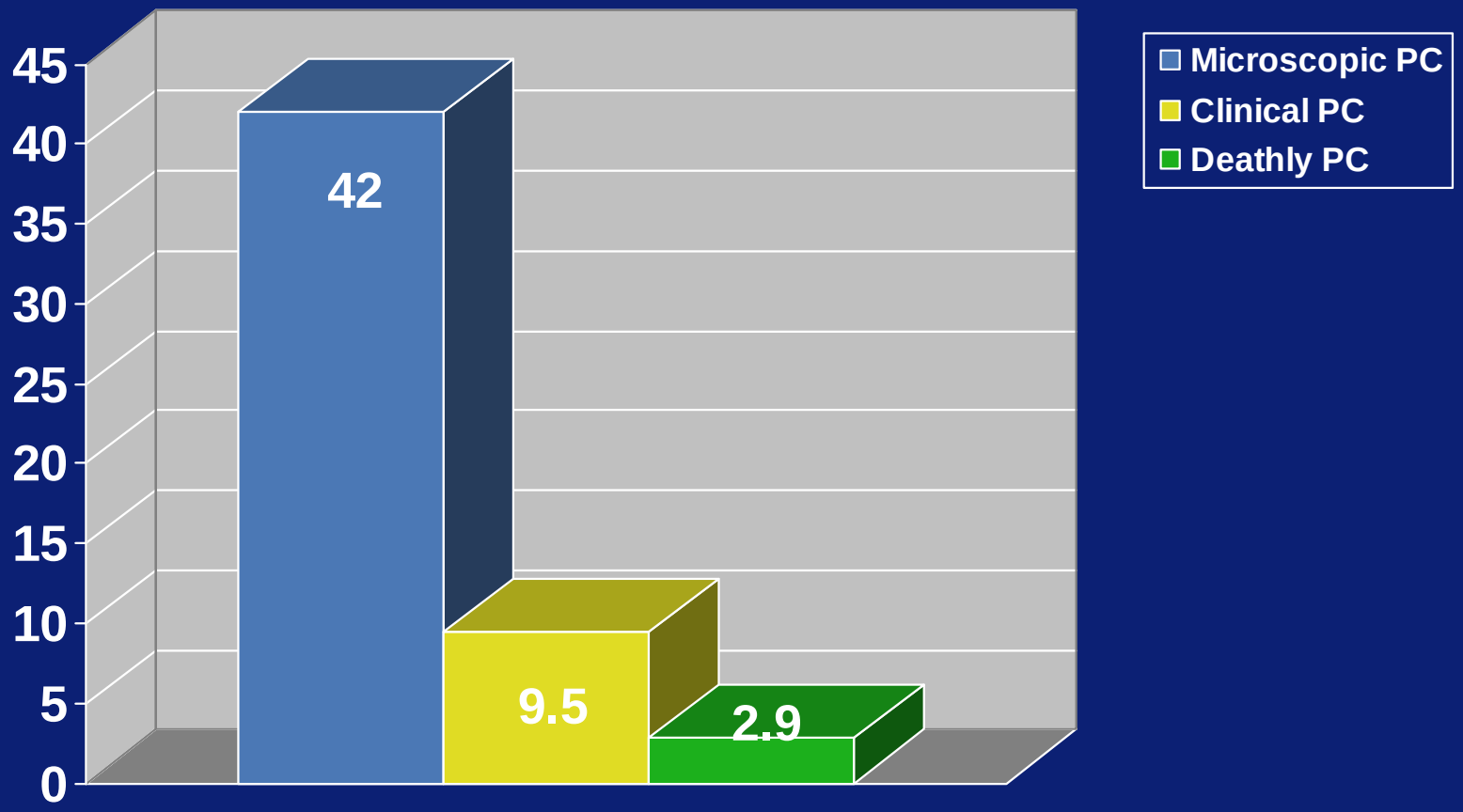

**Cancer death by type of cancer and age, The Netherlands, 2000**
www.CBS.nl




**Cancer mortality increases strongly from 50 years of age onwards, peaking at ages 75-79 years.**

**Prostate cancer is an important health problem.**

# The facts of prostate cancer




**Is PC always a life threatening disease?**

# The facts of prostate cancer

**Conclusions:**

1.Prostate cancer is a major health problem

2.Death from prostate cancer and/or metastatic prostate cancer should be avoided

3.The majority of detectable prostate cancer cases do not give any complaints or will lead to death

Early detection of especially those prostate cancer cases that cause symptoms and/or are life threatening is desirable

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# Definitions

**What is screening?**

Evaluation of a healthy population in order to identify individuals who have a disease, but do not yet have symptoms.

**What is the concept of screening?**

To identify a disease at a stage in its natural history where treatment can be applied in order to prevent death or suffering.

# Favourable effects

Reduction in unfavorable outcome of disease (e.g. cancer deaths, developmental disturbance)

Less treatment for advanced stages

Less intensive or mutilating treatment

More efficient diagnostic work up (less clinically suspicious cases)

# Unfavourable effects

Side effects of screening procedure

Earlier (knowledge of) diagnosis + side effects of treatment

Extra detection (overdiagnosis) and overtreatment

Risks of screening and assessment, and unintended detection of other diseases

Possible false reassurance (confrontation with the diagnosis, or detecting a disease, later as usual)

# How to decide if screening should be recommended?

The disease must constitute a significant public health problem with significant morbidity and mortality.

There must be demonstrable improved health outcomes related to screening, in terms of additional years of life (life-years gained).

# How to decide if screening should be recommended?

Level of overdiagnosis and adverse side-effects must be limited.

The screening procedure should have a reasonable cost; adequate resources and health services should be available to accomplish the screening and to provide the necessary interventions triggered by a positive test result.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Screening and Prostate-Cancer Mortality in a Randomized European Study

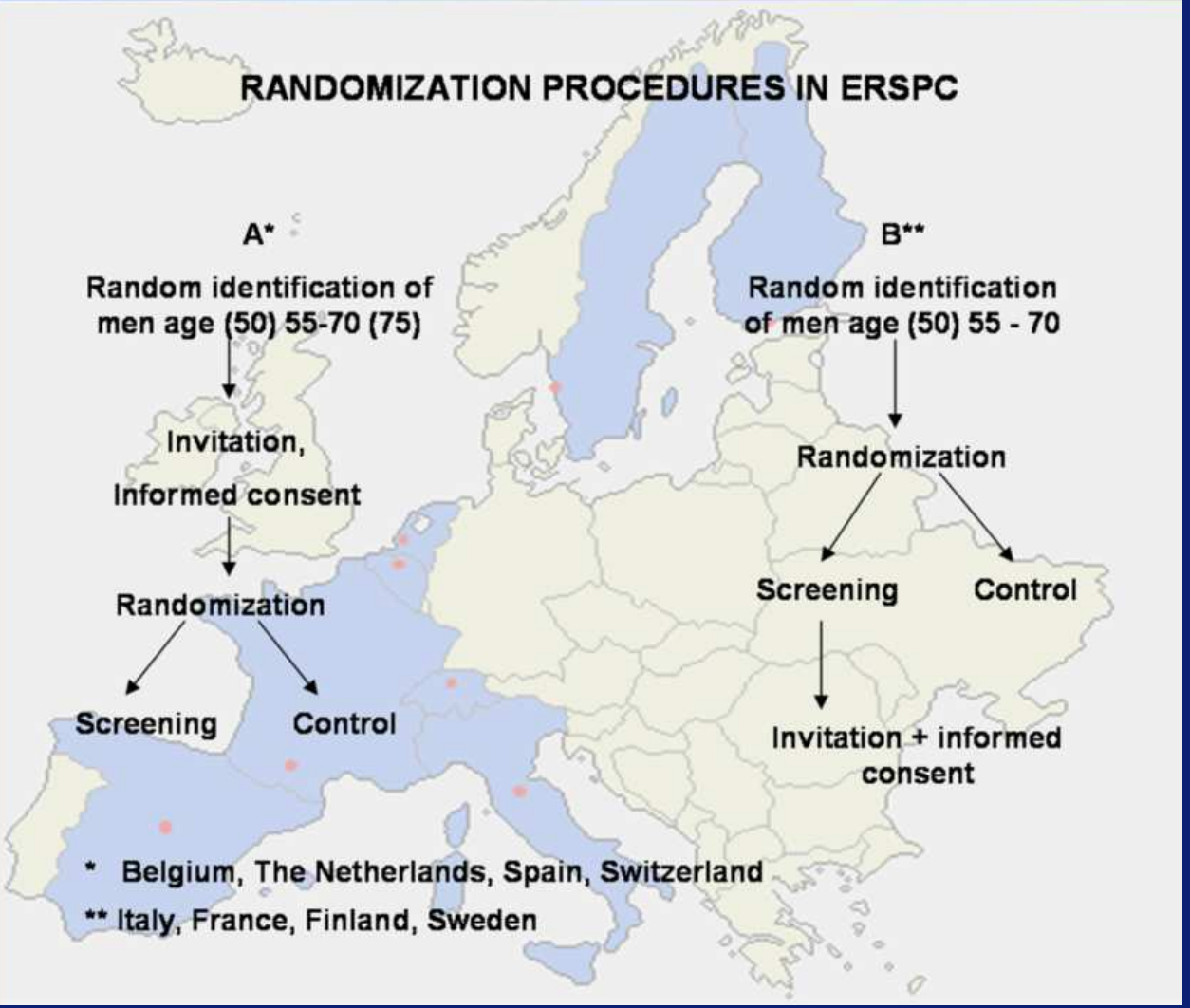
N ENGL J MED 360;13 NEJM.ORG MARCH 26, 2009

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

European Randomized Study of Screening for Prostate Cancer

ERSPC

## RANDOMIZATION PROCEDURES IN ERSPC




## Methods I
## European Randomized study of Screening for Prostate Cancer (ERSPC)

Main end point: Prostate Cancer (PC) mortality

Ages: 50-74, core age group 55-69 (N= 162,387)

Screen interval 4 years (87%) or 2 years (13%)

Sextant (lateral) biopsy recommended for PSA >= 3.0 ng/ml or >= 4.0 ng/ml. With ancillary tests (DRE, F/T ratio for PSA 3-4 ng/ml).

# Results: Cancer detection, M+ disease and death

- Follow-up: average 8.8 years, median 9.0 years
- 126.462 screens, 2.1 per subject, PPV 24.1%
- Screening arm: 5.990 PC's (8.2%), 214 PC deaths
- Control arm: 4.307 PC's (4.8%), 326 PC deaths

| T-Stage | Intervention arm N=5.990 | M1 | Control arm N=4.307 | M1 |
|---|---|---|---|---|
| T1/T1A/T1B | 190 | ( 1) | 207 | ( 4) |
| T1c | 3.086 | ( 25) | 1.346 | ( 19) |
| T2 | 1.571 | ( 32) | 984 | ( 55) |
| T3 | 456 | ( 59) | 559 | (138) |
| T4 | 60 | ( 32) | 117 | ( 79) |
| missing | 627 | ( 5) | 1.094 | ( 9) |
| Total | 5.990 | (149) | 4.307 | (304) |

*M1 disease at diagnosis 0.39 per 1000 py in C arm versus 0.23 per 1000 py in S arm, a 41% reduction ( p < 0.001)*

## Results 2: Intention to screen analysis

- Relative risk (RR) of PC death 0.80 (95% CI 0.65 – 0.98, P = 0.04), a 20% relative reduction
- Absolute risk reduction: 7 per 10.000 men screened
- Number needed to screen: 1.410 (95% CI 1.142 – 1.721)
- Number needed to treat: 48 (in excess of control group)

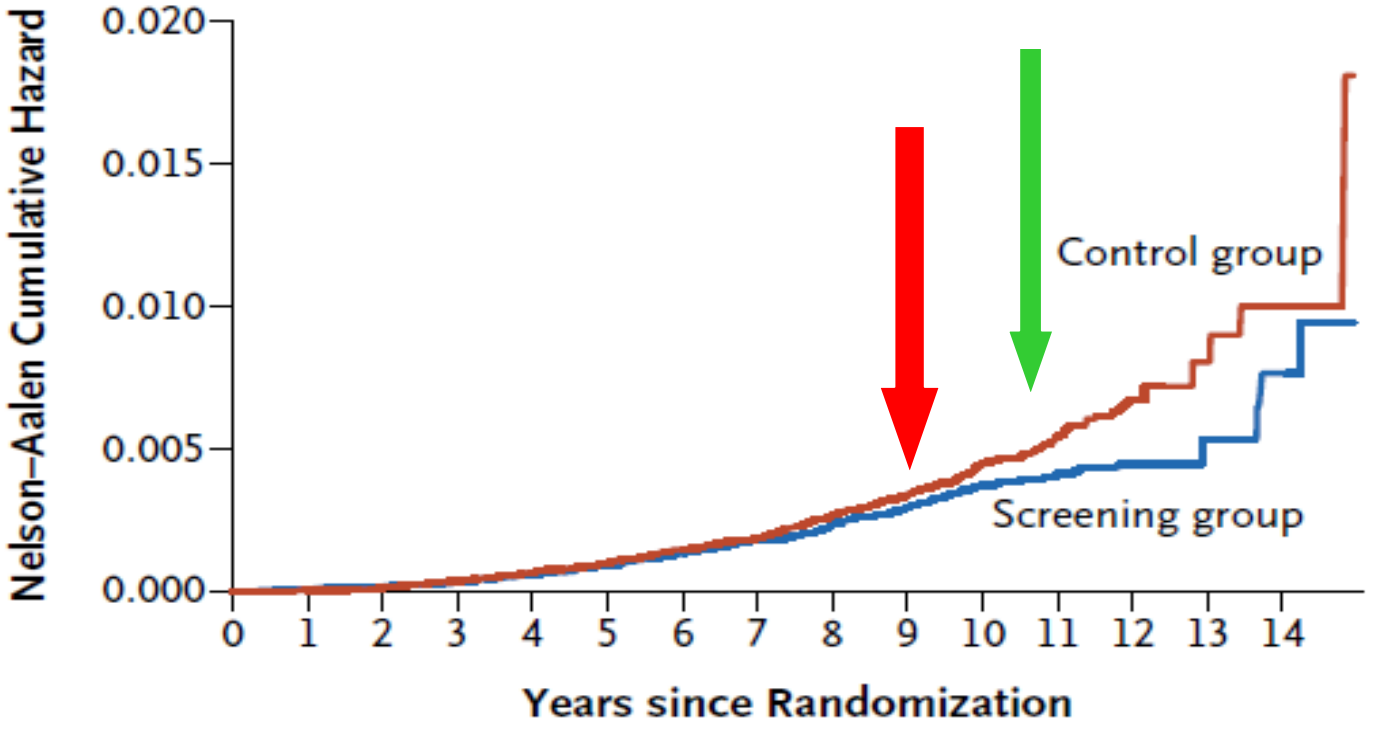
## Conclusions

- ERSPC shows a significant reduction in the relative risk of PC death for men aged 55- 69 of 20% (intention to screen analysis)*
- Adjustment for non compliance and contamination results in a relative risk reduction of 31%**

- NNS with this strategy 1410 and NNT = 48
- 52% T1C prostate cancer in S-arm
- PPV of sextant prostate biopsy triggered by a PSA cut-off of >= 3.0 ng/ml is 24%

** Schröder et al. NEJM 2009 ** Roobol et al. Eur Urol 2009*

# Cumulative risk of death from prostate cancer




| No. at Risk | | | |
|---|---|---|---|
| Screening group | 65,078 | 58,902 | 20,288 |
| Control group | 80,101 | 73,534 | 23,758 |

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Articles

D-10-00484R2

S1470-2045(10)70146-7

# Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

## Summary

**Background** Prostate cancer is one of the leading causes of death from malignant disease among men in the developed world. One strategy to decrease the risk of death from this disease is screening with prostate-specific antigen (PSA); however, the extent of benefit and harm with such screening is under continuous debate.

**Methods** In December, 1994, 20 000 men born between 1930 and 1944, randomly sampled from the population register, were randomised by computer in a 1:1 ratio to either a screening group invited for PSA testing every 2 years (n=10 000) or to a control group not invited (n=10 000). Men in the screening group were invited up to the upper age limit (median 69, range 67–71 years) and only men with raised PSA concentrations were offered additional tests such as digital rectal examination and prostate biopsies. The primary endpoint was prostate-cancer specific mortality, analysed according to the intention-to-screen principle. The study is ongoing, with men who have not reached the

Published Online July 1, 2010 DOI:10.1016/S1470-2045(10)70146-7

See Online/Reflection and Reaction DOI:10.1016/S1470-2045(10)70152-2

Department of Urology (Prof J Hugosson MD, S Carlsson MD, G Aus MD, S Bergdahl MD, A Khatami MD,

# Study Design

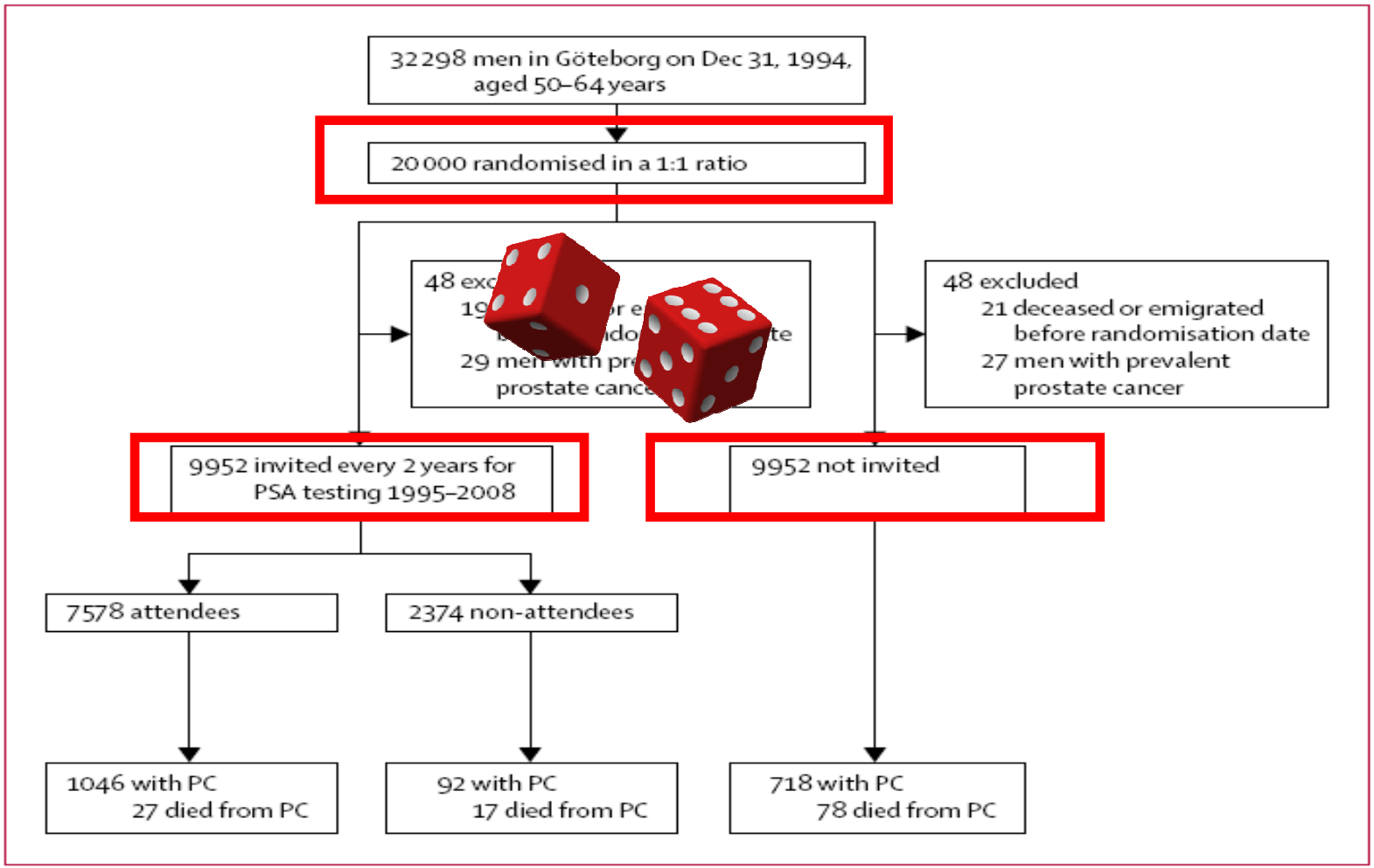



***Figure 1:*** **Trial profile**
PSA=prostate-specific antigen. PC=prostate cancer.

## Results of cancer detection and death

Screening arm:

- PC detected: 1138 (11.4%)
- PC deaths: 44 (0.44%)

Control arm:

- PC detected: 718 (7.2%)
- PC deaths: 78 (0.78%)

Follow-up: median 14.0 years

# Cumulative risk death from prostate cancer median follow up 14.0 years

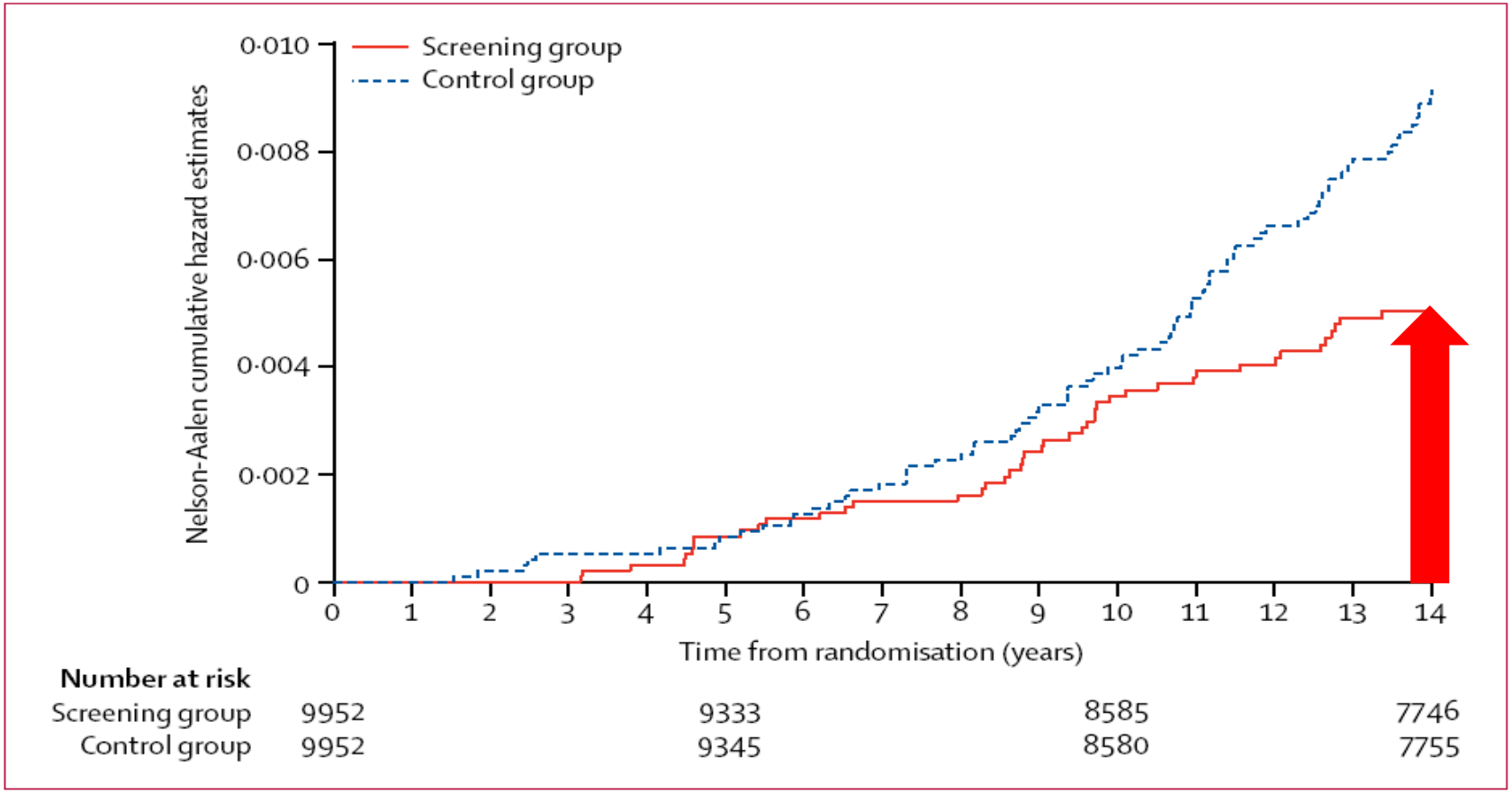



*Figure 3:* Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates

## Prostate cancer mortality - Intention to screen analysis

Relative risk (RR) of PC death 0.56 (95% CI 0.39-0.82, P=0.002), a 44% relative reduction

Absolute risk reduction: 34 per 10.000 men screened

NNS: 293 (95% CI 177-799)

NNT: 12 ( in excess of control group)

## Conclusions and recommendations

Screening reduces prostate cancer specific mortality with at least 30%

NNS and NNT have to be lowered

## The high NNS and NNT

NNS: 1 / absolute risk reduction

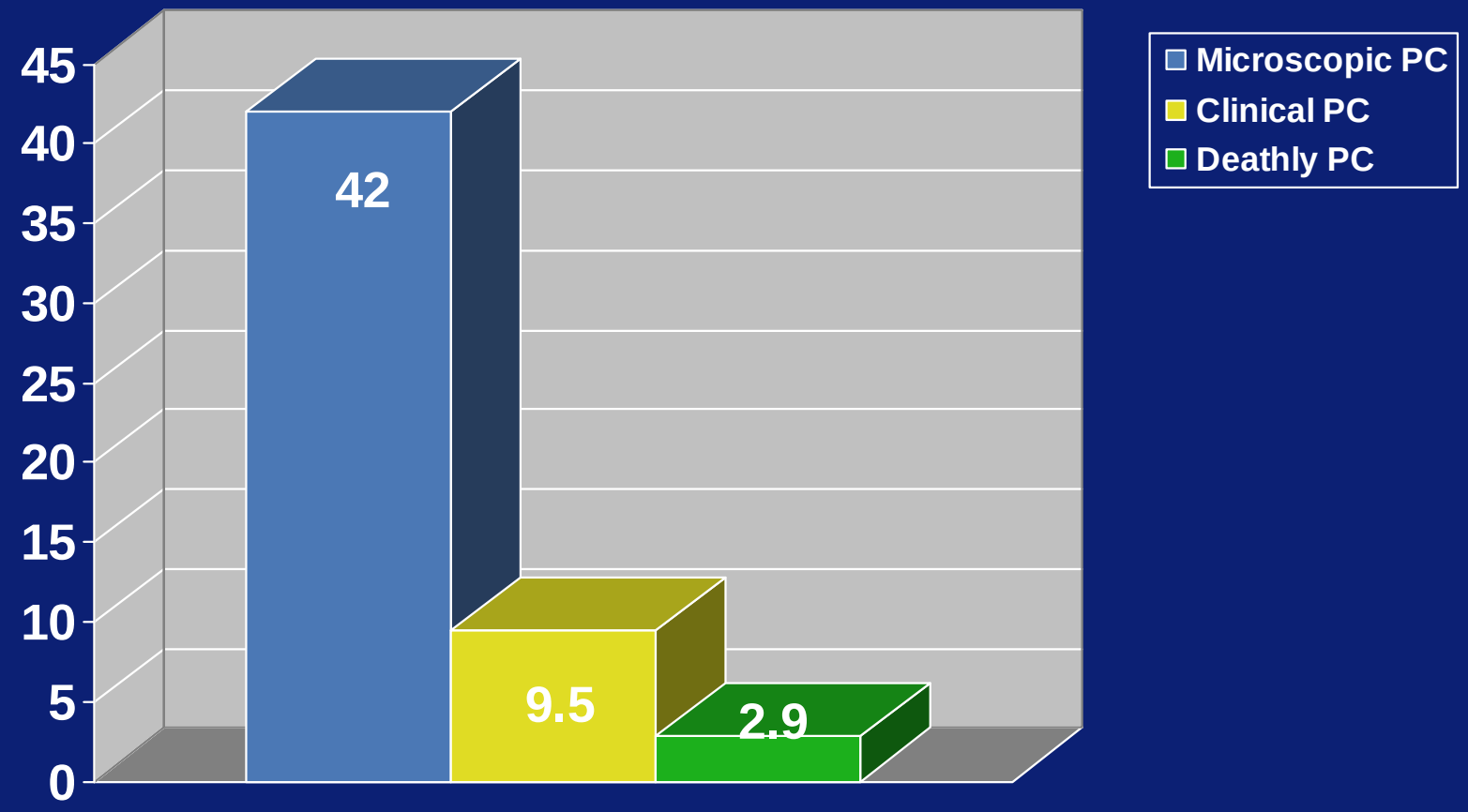
NNT: (1/absolute risk reduction) * excess incidence

## How to decrease the NNS and NNT

Increase the absolute reduction in PC mortality

Decrease the excess incidence = overdiagnosis

# The facts of prostate cancer




PC is not always a life threatening disease

## Conclusions and recommendations

**Further research should focus on:**

1. An individualised screening algorithm
2. Identification of indolent / deathly PC ( preferably before biopsy)
3. Meanwhile: Reduce overtreatment
4. Assess Q of L adjusted life years gained and cost effectiveness

**We only just have started !!!**

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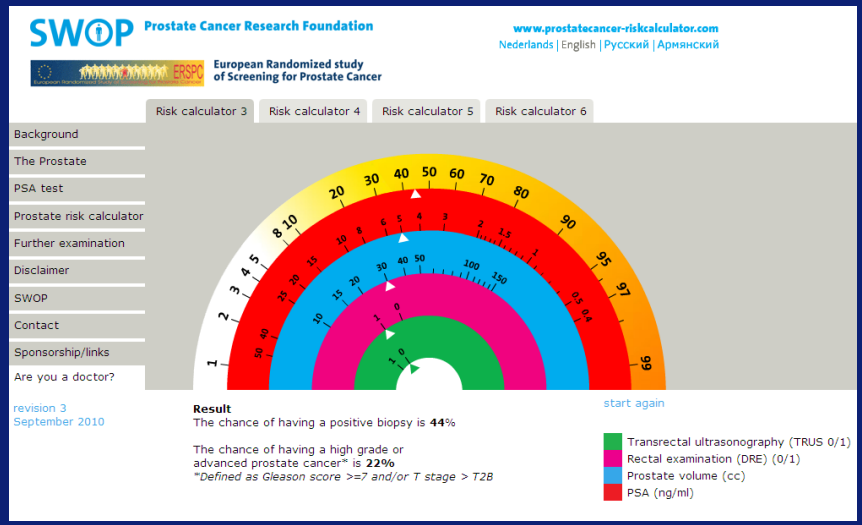

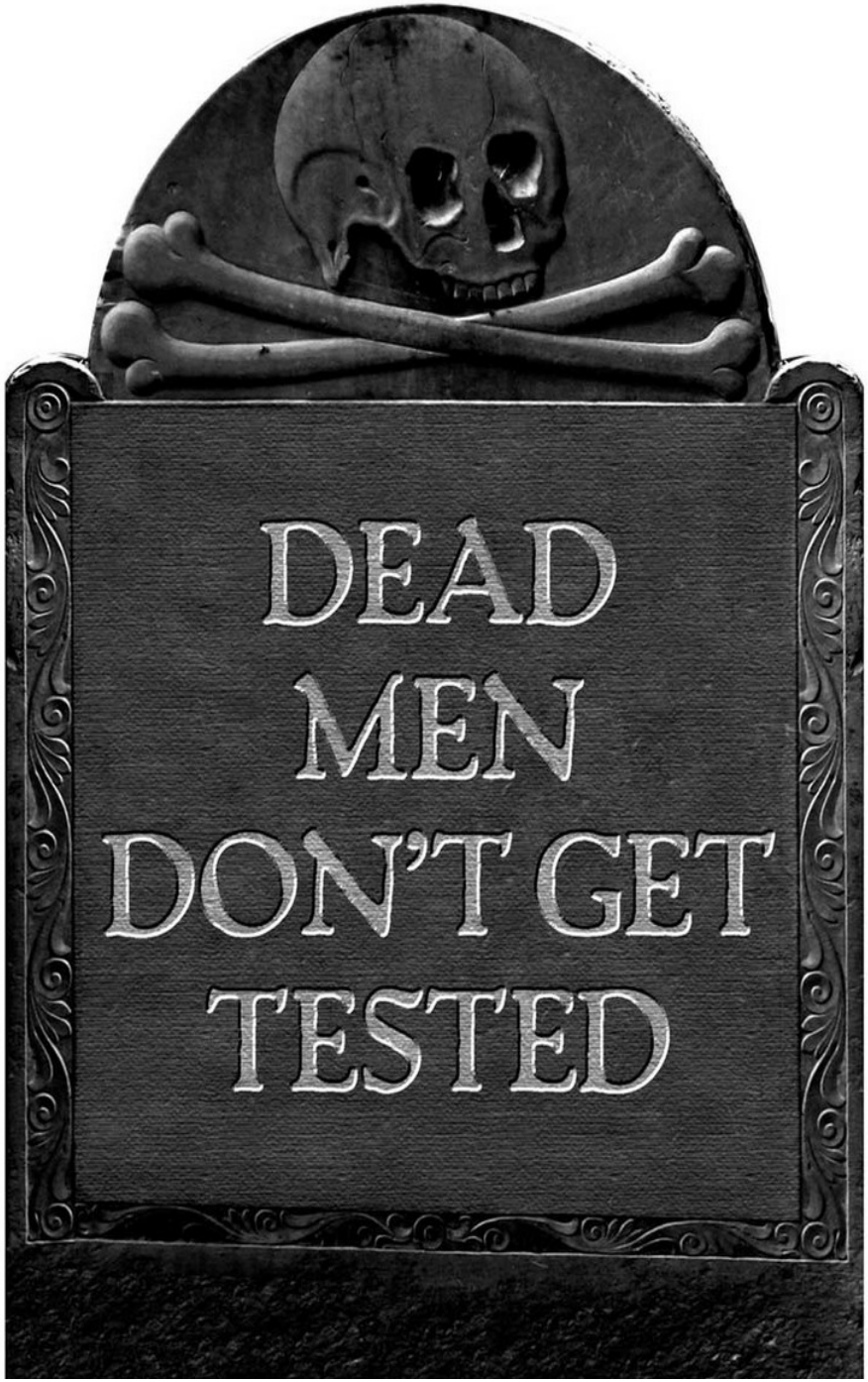


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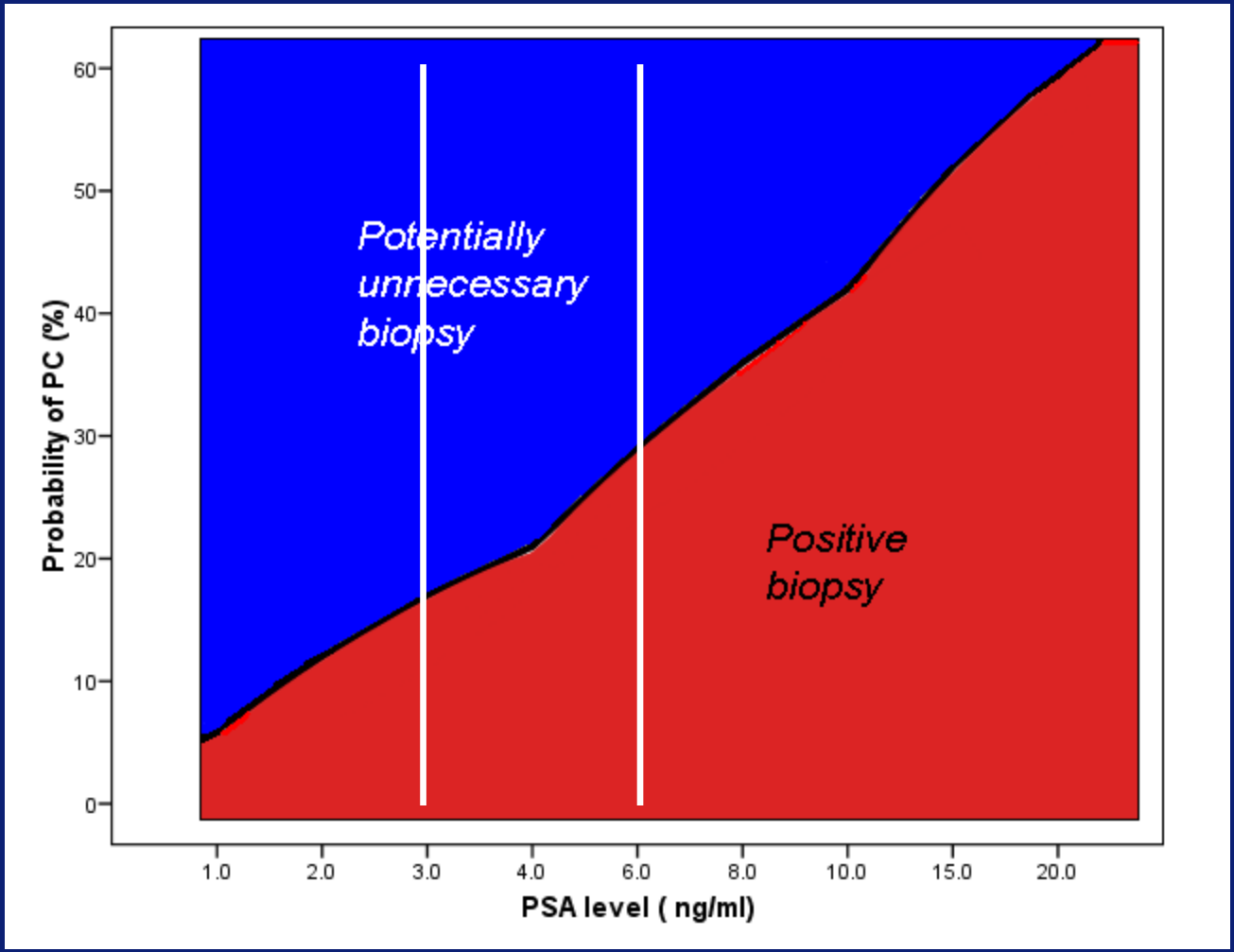
# SOME CANCER FACTS

FACT 2:

We need to know who is at an elevated risk and needs to be tested

# PSA dilemma




*Probabilities based on Riskcalculator level 2*

# An Individualized approach

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available at www.sciencedirect.com
journal homepage: www.europeanurology.com


European Association of Urology

Prostate Cancer

# A Risk-Based Strategy Improves Prostate-Specific Antigen–Driven Detection of Prostate Cancer

*Monique J. Roobol* *, *Ewout W. Steyerberg*, *Ries Kranse*, *Tineke Wolters*, *Roderick C.N. van den Bergh*, *Chris H. Bangma*, *Fritz H. Schröder*

*Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands*

*European Urology 57 (2010), pp. 79-85*

# Individual approach /Risk calculator

- Multistep decision aid based on screening data of 6,288 men.
- www.prostatecancer-riskcalculator.com
- The Riskcalculator level 1-2 use generally available information ( for lay men and GP)
- The Risk calculator level 3-5 use the outcome of DRE and TRUS examinations, prostate volume, PSA and previous biopsy.
- The risk calculator level 6 predicts characteristic of tumor after detection.
- Outcome is the probability of having a biopsy detectable prostate cancer displayed as a percentage.

# Individual approach / detection

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SWOP Prostate Cancer Research Foundation

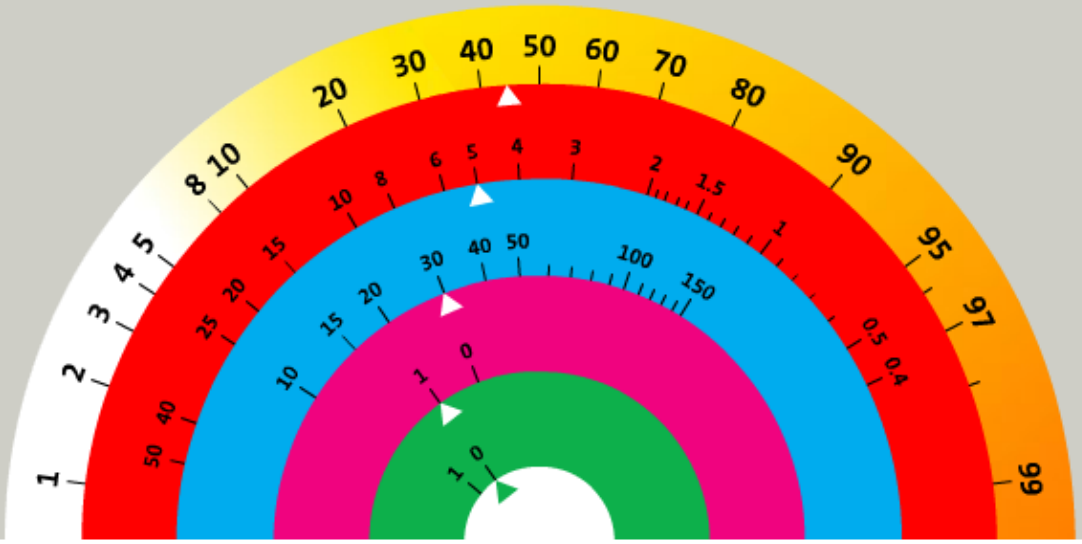
ERSPC European Randomized study of Screening for Prostate Cancer

www.prostatecancer-riskcalculator.com

Nederlands | English | Русский | Армянский

Risk calculator 3 | Risk calculator 4 | Risk calculator 5 | Risk calculator 6

- Background
- The Prostate
- PSA test
- Prostate risk calculator
- Further examination
- Disclaimer
- SWOP
- Contact
- Sponsorship/links
- Are you a doctor?




revision 3
September 2010

**Result**
The chance of having a positive biopsy is **44%**

The chance of having a high grade or advanced prostate cancer* is **22%**
**Defined as Gleason score >=7 and/or T stage > T2B*

start again

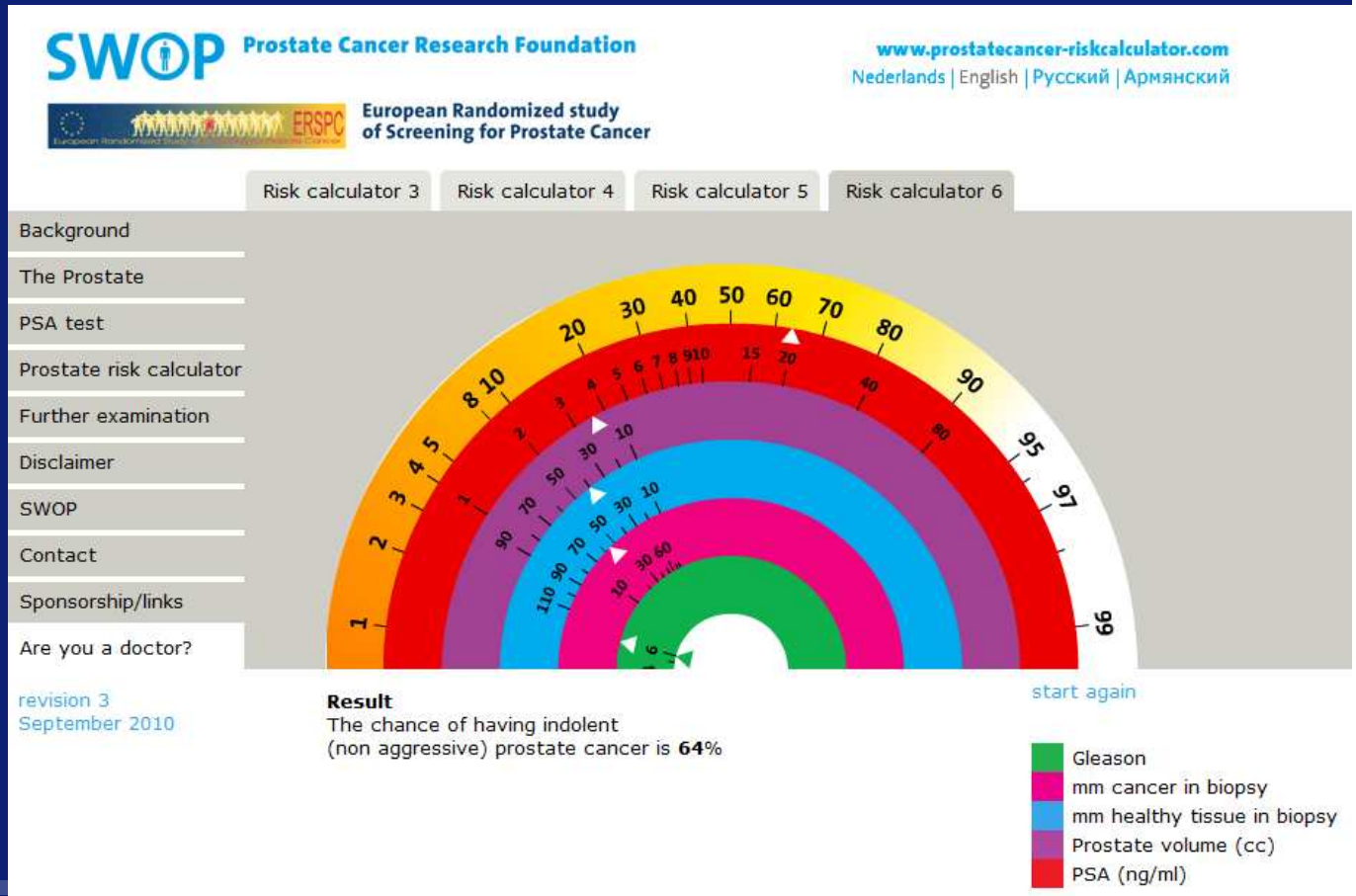
- Transrectal ultrasonography (TRUS 0/1)
- Rectal examination (DRE) (0/1)
- Prostate volume (cc)
- PSA (ng/ml)

# Individual approach / management

- Developed a nomogram to predict potentially indolent prostate cancer* on the basis of biopsy results
- Can be of aid in treatment choice.

*

- T1C or T2A disease
- Pretreatment PSA < 20 ng/ml
- Gleason grade 3 at most in any biopsy
- 50% or less positive cores



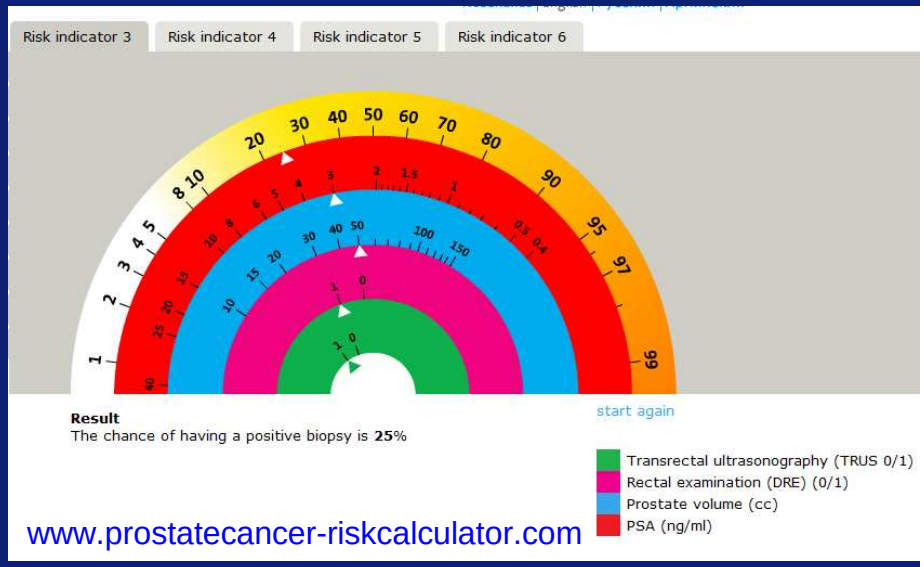
# Risk based screening strategy

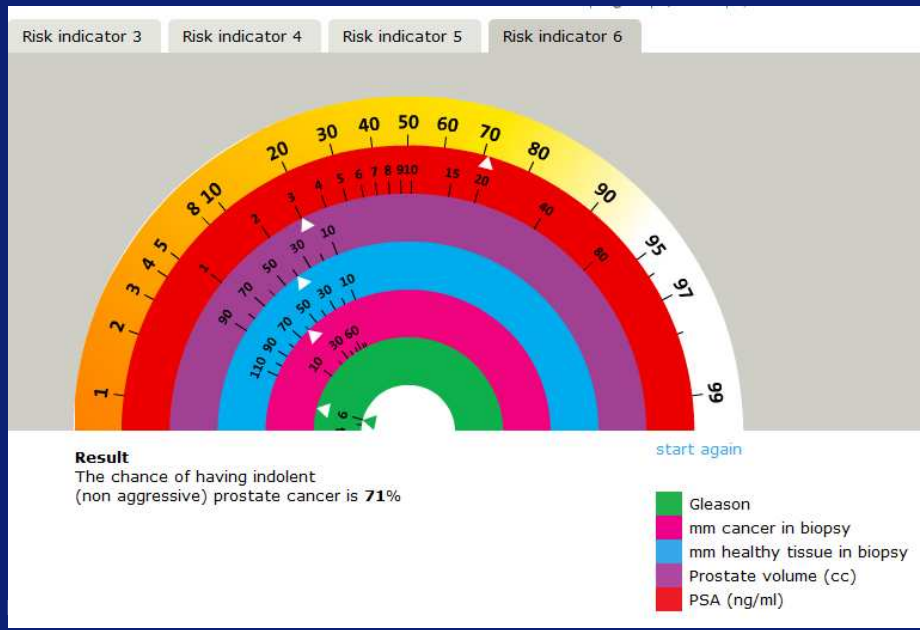
1. men, all biopsied on the basis of PSA >= 3.0

2. Calculate probability of positive biopsy with a Risk calculator

3. Asses number of biopsies if only men with an elevated risk would have been biopsied

4. Look at tumor characteristics of potentially missed PCa



## Higher PSA cut-off or risk based strategy

| | PSA >= 3.0 + Risk >= 12.5% | PSA >= 4.0 ng/ml |
|---|---|---|
| Biopsies saved | 33% | 34% |
| PC missed | 14% | 25% |
| Potentially aggressive PC missed | 10% | 36% |

*Improvement, but more needs to be done, meanwhile……*

Erasmus MC

# Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study

Andrew J Vickers, associate attending research methodologist,[1] Angel M Cronin, research biostatistician,[1] Thomas Björk, senior consultant,[2] Jonas Manjer, associate professor,[2] Peter M Nilsson, professor,[2] Anders Dahlin, data manager,[2] Anders Bjartell, professor,[2] Peter T Scardino, department chair,[3] David Ulmert, research fellow/resident,[4,5] Hans Lilja, attending research clinical chemist/professor (adjunct)[6,7]

The concentration of PSA at age 60 predicts lifetime risk of metastasis and death from prostate cancer. Though men aged 60 with concentrations below the median (≤1 ng/ml) might harbour prostate cancer, it is unlikely to become life threatening.

*BMJ 2010*

Erasmus MC

Original Article

# Balancing the Harms and Benefits of Early Detection of Prostate Cancer

Pim J. van Leeuwen, MD[1]; David Connolly, MD, PhD[2]; Teuvo L. J. Tammela, MD, PhD[3]; Anssi Auvinen, MSc, PhD[4]; Ries Kranse, MSc[5]; Monique J. Roobol, MSc, PhD[1]; Fritz H. Schroder, MD, PhD[1]; and Anna Gavin, MD, PhD[6]

For men with a low serum PSA level, the benefits of aggressive investigation and treatment may be limited because they are associated with a large increase in cumulative incidence and potential overtreatment.

*Cancer 2010*

Erasmus MC

Prostate Cancer

# Toward an Optimal Interval for Prostate Cancer Screening

*Pim J. van Leeuwen [a,*], Monique J. Roobol [a], Ries Kranse [b], Marco Zappa [c], Sigrid Carlsson [d], Meelan Bul [a], Xiaoye Zhu [a], Chris H. Bangma [a], Fritz H. Schröder [a], Jonas Hugosson [d]*

[a] *Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [b] *Dutch Cancer Registry (IKNL), Rotterdam, The Netherlands;* [c] *Unit of Clinical Epidemiology, Institute for Study and Prevention of Cancer, Florence, Italy;* [d] *Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Göteborg, Sweden*

A 2-yr screening interval significantly reduced the incidence of advanced PC; however, the 2-yr interval increased the overall risk of being diagnosed with (low-risk) PC compared with a 4-yr interval in men aged 55-64 yr. Individualized screening algorithms must be improved to provide the strategy for this issue.

*European Urology 2011, in press*

# Individual approach

- Use multivariate risk for biopsy indication including PSA, with in addition the outcome of DRE and TRUS examinations, prostate volume, and previous biopsy

- Exclude men with very low PSA values from further screening visits

- Define individualized screening intervals based on patients PSA or also based on multivariate risks

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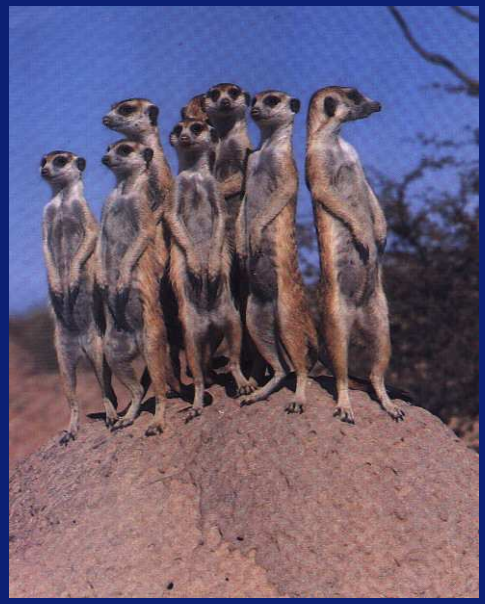


## Solution for over treatment currently available: Active Surveillance

Overdiagnosis would not matter if treatment had no adverse effects.

It would be acceptable to treat all cases, including those destined never to cause symptoms.

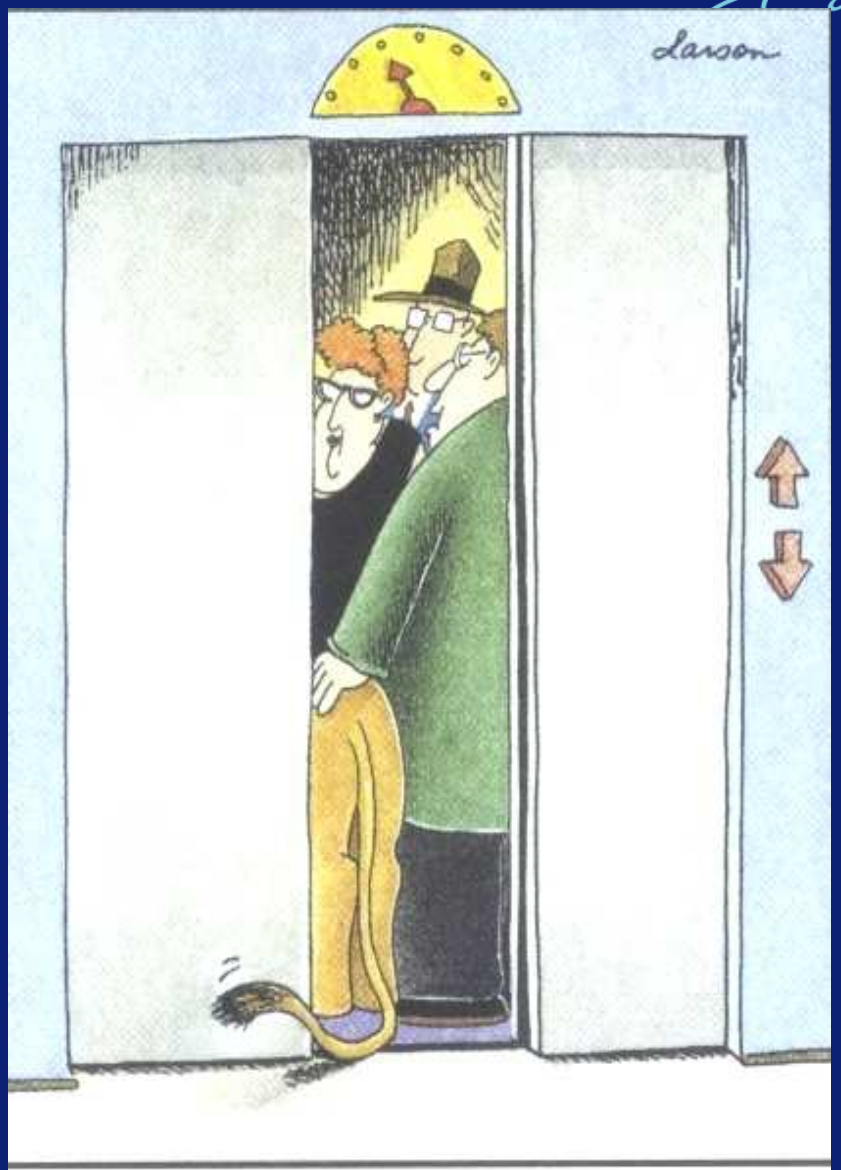
However, while radical treatment for prostate cancer may or may not improve a man's longevity, it can certainly have a big impact on his lifestyle.

Ideally, such intervention should be restricted to those who need it.

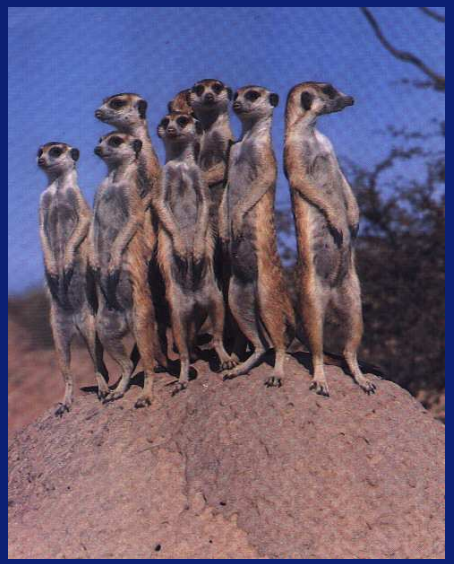

"This one was real stubborn. Had to up his medication three times before he'd agree to sign the liability waver."

# SOME CANCER FACTS

FACT 3:
We need to discriminate the ‘pussy cats’ from the ‘tigers’.



# Rationale for Active Surveillance



**Selection**

- PC with a very favorable prognosis
- Initially no radical treatment

**Follow-up**

- Strictly monitoring tumors
- Switch to (delayed) active therapy with curative intent at the moment of disease progression (biochemical/histological)

→ aim of AS is to limit the amount of overtreatment by individual management of PC

→ advantage of preserving QoL and benefiting of further advances in available therapy

## Active Surveillance

- Spin off from the European Randomized Study of Screening for Prostate Cancer (ERSPC)
- Initiative of the Department of Urology of the Erasmus Medical Centre
- Prostate Cancer Research International: Active Surveillance
- Based on available literature
- Prospective study design, ongoing evaluation, aid in decision making
- Main goal is to reduce over treatment
- It also provides an ideal setting for research to identify new markers, which, in the future, could improve our ability to determine which men need, and which men do not need, treatment for their prostate cancer.
- Web based study, accessible for urologists all over the world

# Active Surveillance

PRIAS

Erasmus MC
Universitair Medisch Centrum Rotterdam

Monday, 20 October 2008

**User menu PRIAS study**

- Edit your profile
- Private messages
- Site administration
- Extract PRIAS data
- Home (project docs)
- Include patient
- Search patients
- Logout

**User menu IMPACT study**

- Include IMPACT patient
- Search for IMPACT patients

**Information**

**Project management:**
Mrs. M.J. Roobol PhD
+31 10 7032 240
R. van den Bergh MD
+31 10 7032 242
**Site management:**
W. Roobol

**Who's Online**

1 user(s) are online (1 user(s) are browsing

**PUBLIC** : Active surveillance of early prostate cancer

*Posted by WRoobol on 2007/12/22 14:06:07 (944 reads)*

Screening has resulted in a marked increase in the number of newly diagnosed prostate cancers, while it is unclear whether the early detection of these tumors reduces the prostate cancer mortality. (1)

Up to 80% of men with PSA screen-detected prostate cancer are overdiagnosed, that is, their cancer would never have caused any symptoms. (2) Overdiagnosis would matter less if treatment had no adverse effects. (3,4)

**PRIAS** (Prostate cancer Research International: Active Surveillance) presents a program in which selected men with early prostate cancer are managed by a protocolized follow-up strategy. Candidates for this program are: men fit for curative therapy, PSA at diagnosis less than 10 ng/mL, PSA density (PSA/prostatic volume) less than 0.20, one or two biopsy cores bearing prostate cancer (using a fixed volume-dependent number of cores), Gleason score 3+3 and digital rectal examination T1c or T2.

**Participating centers include:**

1. Erasmus MC, Rotterdam, The Netherlands
2. St. Franciscus Gasthuis, Rotterdam, The Netherlands
3. Albert Schweitzer Ziekenhuis, Dordrecht, The Netherlands
4. Antoni van Leeuwenhoek Ziekenhuis (NKI), Amsterdam, The Netherlands
5. Ziekenhuisgroep Twente, Almelo, The Netherlands
6. Amphia Ziekenhuis, Breda, The Netherlands
7. Canisius-Wilhelmina Ziekenhuis, Nijmegen, The Netherlands
8. Oosterschelde Ziekenhuizen, Goes, The Netherlands
9. VUmc, Amsterdam, The Netherlands
10. Cancer agency, Vancouver, Canada British Columbia
11. VGH Prostate Centre, Vancouver, Canada
12. Sahlgrenska University Hospital, Gothenburg, Sweden
13. Helsinki University Central Hospital, Helsinki, Finland
14. University Hospital of Tampere, Tampere, Finland
15. Universitaetsklinikum, Salzburg, Austria
16. Emco Klinik, Salzburg, Austria
17. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
18. University Clinic, Münster, Germany

Contact R.vandenBergh@erasmusmc.nl for more information.

**Project protocol**

- Inclusion criteria
- Follow-up criteria
- Biopsy protocol
- Study protocol
- Pocket guide

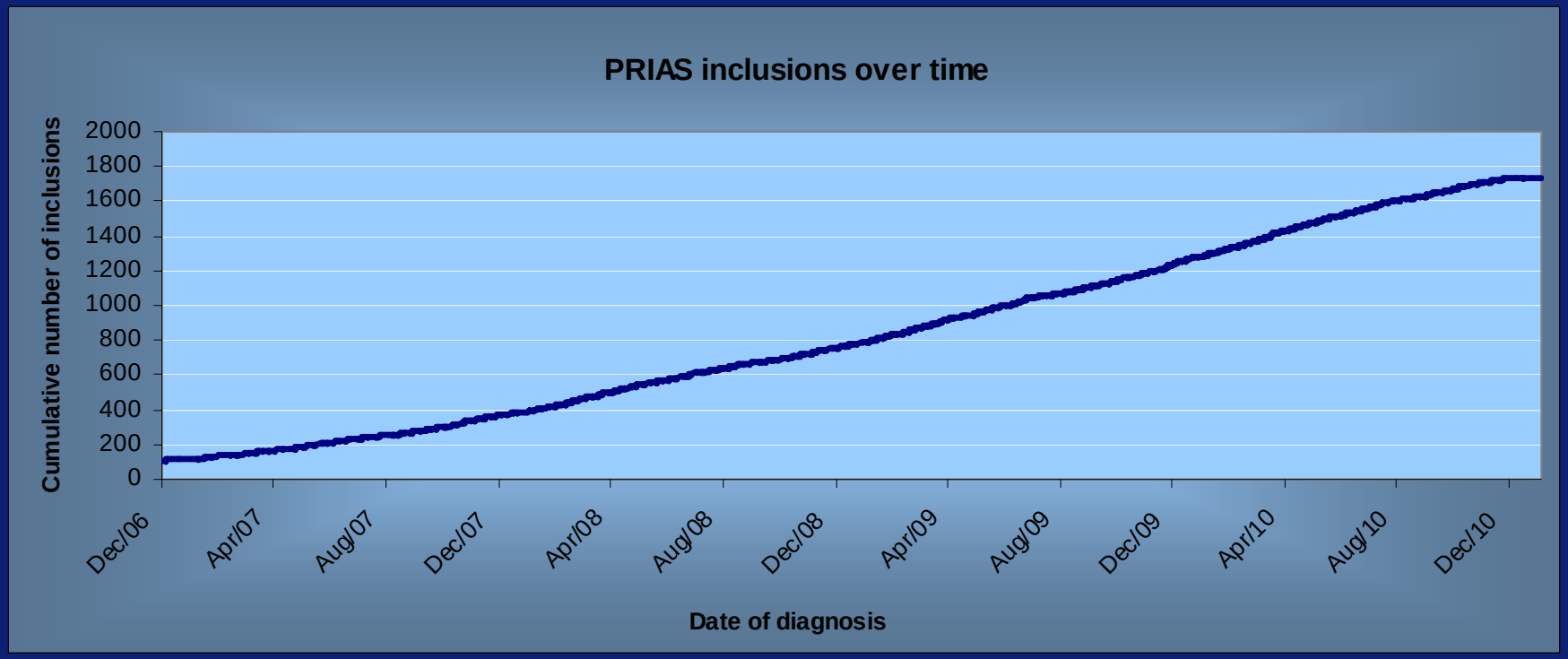
**Patient information**

- UK version PIF
- NL version PIF
- FI version PIF
- SE version PIF
- DE version PIF
- IT version PIF
- FR version PIF
- SP version PIF

**Informed consent**

- UK version consent
- NL version consent
- FI version consent
- SE version consent
- DE version consent
- IT version consent
- FR version consent
- SP version consent

# Inclusions over time for PRIAS



# Participating countries


**Inclusions Dec 2006 – Jan 2011**

**Total 1738 patients**

# Conclusions

# What does this mean for clinical practice?

- 30% of PC deaths can be avoided by PSA screening
- BUT:
- ± 50% of men with PC are overtreated

- No population based program yet
- But individual men should be well informed on the potential benefits and disadvantages

# Focus of future research

- Longer follow-up of ongoing screening trials is needed
- Data on quality of life and life-years gained is needed
- Individualized screening strategies
- Define patient individualized risk factors
- Define which cancers need to be treated and which are suitable for active surveillance
- Continue the hunt for biomarkers that can discriminate between indolent and aggressive prostate cancer


I wonder what to do, to screen or not to screen.....
Thank you!
Photo: Gunnar Aus