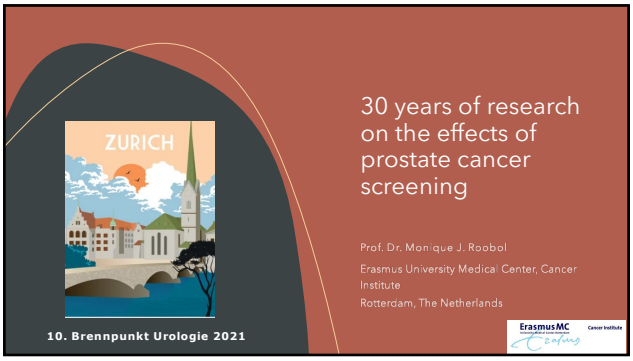
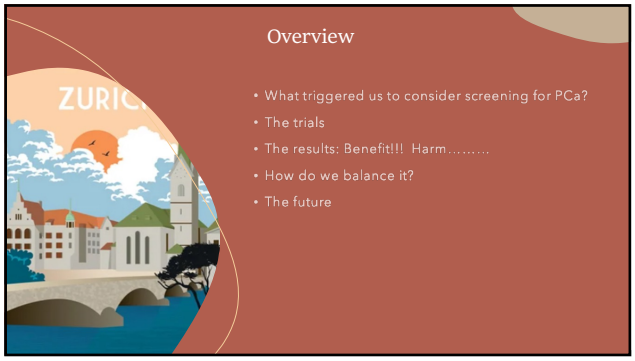
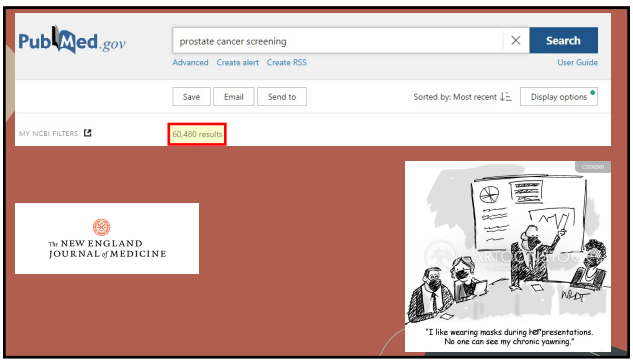

ZURICH
30 years of research on the effects of prostate cancer screening
Prof. Dr. Monique J. Roobol
Erasmus University Medical Center, Cancer Institute
Rotterdam, The Netherlands
10. Brennpunkt Urologie 2021

1


Overview
• What triggered us to consider screening for PCa?
• The trials
• The results: Benefit!!! Harm……
• How do we balance it?
• The future

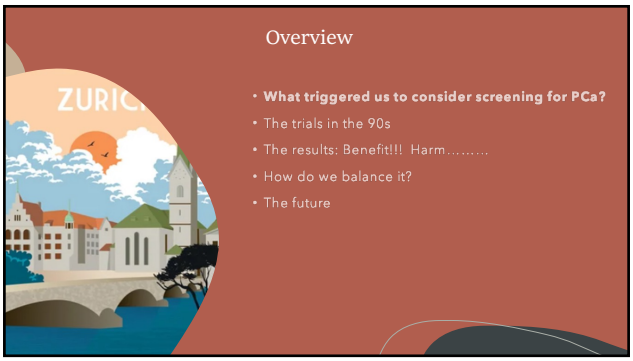
2


PubMed.gov
prostate cancer screening
Search
Advanced Create alert Create RSS
User Guide
Save Email Send to
Sorted by: Most recent
Display options
MY NCBI FILTERS
60,480 results
The NEW ENGLAND JOURNAL of MEDICINE
"I like wearing masks during HCP presentations. No one can see my chronic yawning."

3


Before we start…
The founders of ERSPC
Fritz Schröder
Louis Denis † 2021
ERSPC
European Randomized Study of Screening for Prostate Cancer

4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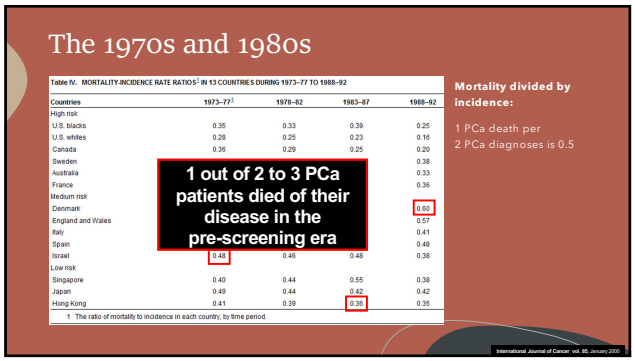

The 1970s and 1980s
Table IV. MORTALITY-INCIDENCE RATE RATIOS[1] IN 13 COUNTRIES DURING 1973–77 TO 1988–92
Countries
1973–77[1]
1978–82
1983–87
1988–92
High risk
U.S. blacks 0.35 0.33 0.39 0.25
U.S. whites 0.28 0.25 0.23 0.16
Canada 0.36 0.29 0.25 0.20
Sweden 0.38
Australia 0.33
France 0.36
Medium risk
Denmark 0.60
England and Wales 0.57
Italy 0.41
Spain 0.48
Israel 0.48 0.46 0.48 0.38
Low risk
Singapore 0.40 0.44 0.55 0.38
Japan 0.49 0.44 0.42 0.42
Hong Kong 0.41 0.39 0.36 0.35
1. The ratio of mortality to incidence in each country, by time period.
1 out of 2 to 3 PCa patients died of their disease in the pre-screening era
Mortality divided by incidence:
1 PCa death per 2 PCa diagnoses is 0.5
International Journal of Cancer: vol. 85, January 2000

6

Beyond cure…

- 1984: With the DRE as the only method of diagnosis, 30-35% of men had bone metastases, and 40-45% had nodal disease

The Journal of Urology
Volume 132, Issue 4, October 1984, Pages 690-692

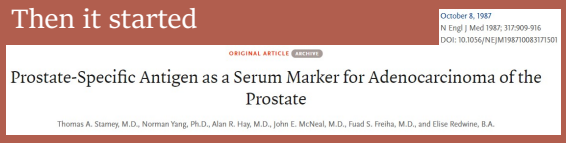
Adenocarcinoma of the Prostate: Results of Routine Urological Screening

Ian M. Thompson Jr., Joseph J. Ernst, Mauro P. Gangai, C. Ritchie Spence

The use of adjunctive screening tools for detection of adenocarcinoma of the prostate is suggested.

7

Then it started



October 8, 1987
N Engl J Med 1987; 317:909-916
DOI: 10.1056/NEJM198710083171501

ORIGINAL ARTICLE ARCHIVE

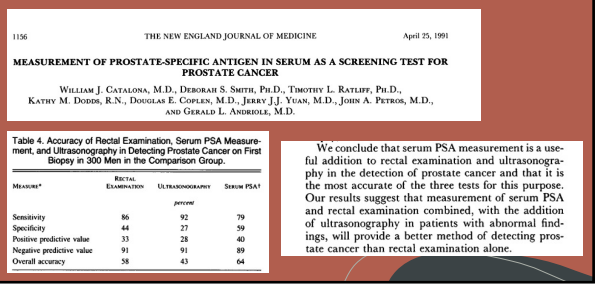
Prostate-Specific Antigen as a Serum Marker for Adenocarcinoma of the Prostate

Thomas A. Stamey, M.D., Norman Yang, Ph.D., Alan R. Hay, M.D., John E. McNeal, M.D., Fuad S. Freiha, M.D., and Elise Redwine, B.A.

We conclude that PSA is more sensitive than PAP in the detection of prostatic cancer and will probably be more useful in monitoring responses and recurrence after therapy. However, since both PSA and PAP may be elevated in benign prostatic hyperplasia, neither marker is specific. (N Engl J Med 1987; 317:909-16.)

8

1991, 30 years ago in the NEJM



1156 THE NEW ENGLAND JOURNAL OF MEDICINE April 25, 1991

MEASUREMENT OF PROSTATE-SPECIFIC ANTIGEN IN SERUM AS A SCREENING TEST FOR PROSTATE CANCER

William J. Catalona, M.D., Deborah S. Smith, Ph.D., Timothy L. Ratliff, Ph.D., Kathy M. Dodds, R.N., Douglas E. Coplen, M.D., Jerry J.J. Yuan, M.D., John A. Petros, M.D., and Gerald L. Andriole, M.D.

Table 4. Accuracy of Rectal Examination, Serum PSA Measurement, and Ultrasonography in Detecting Prostate Cancer on First Biopsy in 300 Men in the Comparison Group.

Measure*	Rectal Examination	Ultrasonography	Serum PSA†
	percent		
Sensitivity	86	92	79
Specificity	44	27	59
Positive predictive value	33	28	40
Negative predictive value	91	91	89
Overall accuracy	58	43	64

We conclude that serum PSA measurement is a useful addition to rectal examination and ultrasonography in the detection of prostate cancer and that it is the most accurate of the three tests for this purpose. Our results suggest that measurement of serum PSA and rectal examination combined, with the addition of ultrasonography in patients with abnormal findings, will provide a better method of detecting prostate cancer than rectal examination alone.

9

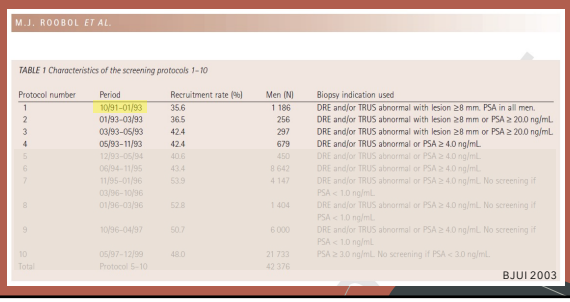
1990
Visiting Professor W. Catalona

Prof. Catalona visits Erasmus MC Urology headed by Prof. Schroder.

The basis for an European screening trial

10

1991 in Rotterdam



M.J. ROOBOL *ET AL.*

TABLE 1 Characteristics of the screening protocols 1–10

Protocol number	Period	Recruitment rate (%)	Men (N)	Biopsy indication used
1	10/91–01/93	35.6	1 186	DRE and/or TRUS abnormal with lesion ≥8 mm, PSA in all men.
2	01/93–03/93	36.5	256	DRE and/or TRUS abnormal with lesion ≥8 mm or PSA ≥ 20.0 ng/mL
3	03/93–05/93	42.4	297	DRE and/or TRUS abnormal with lesion ≥8 mm or PSA ≥ 20.0 ng/mL
4	05/93–11/93	42.4	679	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL
5	12/93–05/94	40.6	450	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL
6	06/94–11/95	43.4	8 642	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL
7	11/95–01/96 03/96–10/96	53.9	4 147	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL. No screening if PSA < 1.0 ng/mL
8	01/96–03/96	52.8	1 404	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL. No screening if PSA < 1.0 ng/mL
9	10/96–04/97	50.7	6 000	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL. No screening if PSA < 1.0 ng/mL
10	05/97–12/99	48.0	21 733	PSA ≥ 3.0 ng/mL. No screening if PSA < 3.0 ng/mL
Total	Protocol 5–10		42 376	

BJUI 2003

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Overview

- What triggered us to consider screening for PCa?
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- The future

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Screening trials initiated in the 90s

Study	Setting, country	Enrolment criteria	Study conducted	No of men randomised (intervention/control)	Screening method	Screening frequency	Primary outcomes	Secondary outcomes
ERSPC (core)[31]	RCT, multicentre, 9 European countries	Men aged 55-69 years	1993-2003, 13 year follow-up	72 891/89 352	PSA ± DRE. If PSA ≥3 ng/mL standardised prostate biopsy	Screening every 2-4 years	Prostate cancer-specific mortality	All-cause mortality, prostate cancer incidence, clinical stage, quality of life, harms
Labrie (Quebec)[33]	RCT, Quebec, Canada	Men aged 45-80 years	1988-1999, 11 year follow-up	31 133/15 353	PSA ± DRE. If PSA ≥3 ng/mL standardised prostate biopsy	Annual screening	Prostate cancer-specific mortality	Prostate cancer incidence, clinical stage
Lundgren (Stockholm)[32]	RCT, Stockholm, Sweden	Men aged 55-70 years	1988-2003, 20 year follow-up	2400/25 081	PSA, DRE, TRUS. Biopsy depended on DRE and TRUS findings, PSA >10 ng/mL	One-time screening	Prostate cancer-specific mortality	All-cause mortality, prostate cancer incidence
PLCO[32]	RCT, multicentre, US	Men aged 55-74 years	1993-2001, 15 year follow-up	38 340/38 343	PSA, DRE	Annual screening	Prostate cancer-specific mortality	All-cause mortality, prostate cancer incidence, clinical stage, Gleason grade, harms

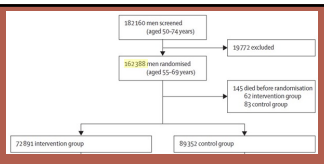
RCT=randomised controlled trial. PSA=prostate-specific antigen. DRE=digital rectal examination. TRUS=transrectal ultrasound.

To assess the effect of PSA based screening on prostate cancer-specific mortality more than 300,000 men were included in studies

13

ERSPC

Started in 1993 In 8 European countries
www.erspc.org



- Screening interval: 4 years in 87%, 2 years in 13% (Sweden)
- Biopsy indication (sextant lateral): PSA >= 3.0 ng/ml
- Standardized causes of death evaluation
- Quality control by independent committees (e.g. pathology, PSA)

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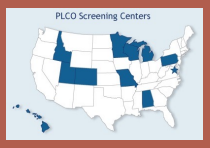
PLCO



- From 1993 through 2001, **76,693** men were randomly assigned at 10 U.S. study centers
- They received either annual screening (38,343 men) or usual care as the control group (38,350 men)
- Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years.
- Diagnostic evaluation was decided by the patients and their primary physicians.

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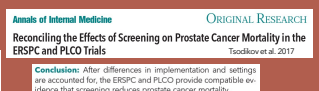
Results…… Debate, debate and debate….

ERSPC:

- Rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% CI: 0.65 to 0.98)
- Reduction in M+ advanced disease 30-40% (Eur Urol 2012)

And clarity



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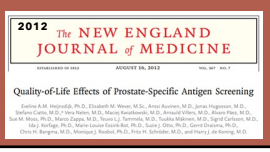
Confirmation of results: harm <> benefit



ERSPC:

- Rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.79 (95% CI: 0.68 to 0.91)

Adjusting for harm:

- The benefit of screening was diminished by loss of QALYs owing to postdiagnosis long-term effects **(overdiagnosis and subsequent overtreatment)**

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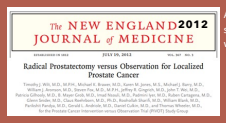
Should we treat all screen-detected PCa?


The NEW ENGLAND JOURNAL of MEDICINE 2012

Radical Prostatectomy versus Observation for Localized Prostate Cancer

Among screen detected localized PCa, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up.


The NEW ENGLAND JOURNAL of MEDICINE 2016

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

At a median of 10 years, prostate-cancer–specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments.

No, certainly not , **Active Surveillance** is the way to go

Even better:

AVOID the diagnosis and stop making men cancer patients

19

Reflection on what we had learned..


2017 SOUNDING BOARD

Prostate Cancer Screening — A Perspective on the Current State of the Evidence

There is a critical need for strategies to reduce the burdens associated with the diagnosis of **indolent disease**, through a combination of **not diagnosing** it in the first place and accurately classifying it as **not needing any further follow-up or treatment**, while still maintaining any mortality benefits for men with aggressive disease. Perhaps that is the **most pressing research challenge** going forward.


2020 MEDICINE AND SOCIETY

Reconsidering Prostate Cancer Mortality — The Future of PSA Screening

We have learned that the conventional goal of screening – to maximize cancer detection – is wrong. The appropriate goal is more complex: **identify the few cancers that matter**, while not disturbing the rest of the population.


2020 SOUNDING BOARD

Reconsidering the Trade-offs of Prostate Cancer Screening

Based on long-term FU and **new developments**: As clinicians who screen, diagnose, and treat patients with prostate cancer and as statisticians who are devoted to understanding the effects of cancer screening, we suggest that the **balance of benefits and harms of screening may be more favorable than is generally appreciated.**

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mpMRI in clinical and screening setting


The NEW ENGLAND JOURNAL of MEDICINE 2018

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

PRECISION trial: MRI, with or without targeted biopsy, led to **fewer men undergoing biopsy**, more clinically significant cancers being identified, **less overdetection of clinically insignificant cance**r, and fewer biopsy cores being obtained than did standard transrectal ultrasonography–guided biopsy.


2020 ORIGINAL ARTICLE

MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis

Among patients with MRI-visible lesions, **combined biopsy** led to more detection **of all** prostate cancers. However, MRI-targeted biopsy alone **underestimated** the histologic grade of some tumors.


2021 ORIGINAL ARTICLE

MRI-Targeted or Standard Biopsy in Prostate Cancer Screening

STHLM3MRI trial: MRI with **targeted and standard biopsy** in men with MRI results suggestive of prostate cancer was noninferior to standard biopsy for detecting clinically significant prostate cancer in a population-based screening-by-invitation trial and resulted in **less detection of clinically insignificant cancer.**

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Overview

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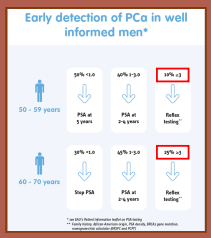
Population based screening



12,750 men enrolled → 1,532 randomized with PSA ≥ 3 ng/ml

STHLM3MRI trial : 12% directly referred for mpMRI

Proportion MRI-negative correlates to disease risk distribution

	STHLM3MRI Main Study n=1,532	Göteborg-2 n=551	Precision n=500	MRI-First n=251	STHLM3MRI Phase 1 n=532
Cohort	Screening	Screening	Clinical	Clinical	Clinical
Age, yrs (median)	66	57	64	64	64
PSA, ng/ml (median)	4.3	3.3	6.7	6.5	6.3
MRI not suggestive of significant cancer	56%	77%	28%	21%	19%

In Europe: 55 Million men aged 55-75 yr, with a PSA cut-off as only risk stratification step:
6.6 Million men eligible for MRI , 60% unnecessary?

23

First step …

Lancet Oncol 2021; 22: 1240–49

Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial

Tobias Nordström, Andrea Discacciati, Martin Bergman, Mark Clements, Markus Aly, Magnus Annerstedt, Axel Glaessgen, Stefan Carlsson, Fredrik Jiderling, Martin Eklund*, Hans-Olov Adami, Henrik Grönberg*, on behalf of the STHLM3 study group

Stockholm3 test:
Clinical variables (age and previous prostate biopsy), plasma protein concentrations (PSA, free PSA, human kallikrein 2, β-microseminoprotein, and growth-differentiation factor-15), and a polygenic risk score derived from single-nucleotide polymorphisms.
Result:
A percentage risk of clinically significant prostate cancer (>= Gleason score 3 + 4)

Standard biopsies in men with PSA of ≥3 ng/mL
MRI-targeted biopsies in men with PSA of ≥3 ng/mL
MRI- targeted biopsies in men with Stockholm3 of ≥0·11
MRI-targeted biopsies in men with Stockholm3 of ≥0·15

The results from this trial show that replacing PSA with the Stockholm3 test in a screening setting, in which MRI and targeted biopsies are used, **decreases the number of MRIs** done by 36% and biopsy procedures done by 8%, while **maintaining the ability to detect clinically significant prostate cancer.**

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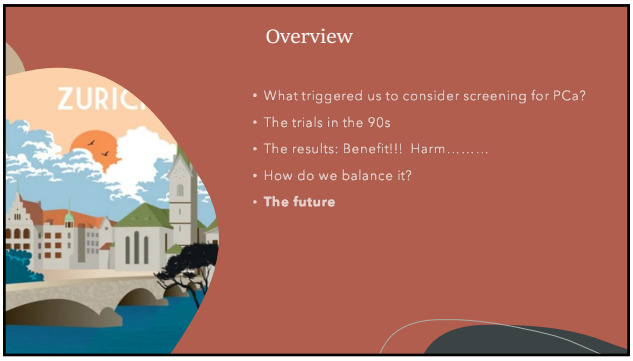
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ZURICH
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Trials, trials, trials.
• Prostate cancer screening is a dynamic field of research
• What are we waiting for?
Hogenhout et al. Eur Urol Oncol 2021

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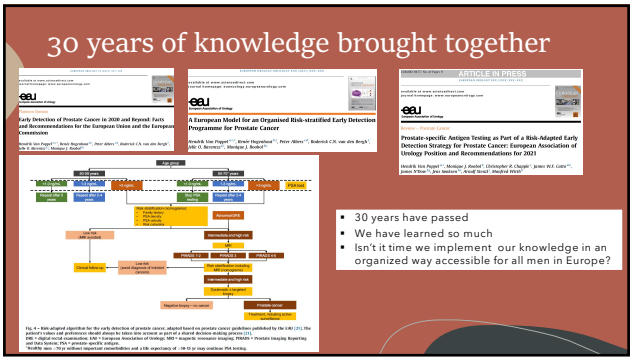
30 years of knowledge brought together
A European Model for an Organised Risk-stratified Early Detection Programme for Prostate Cancer
Prostate-specific Antigen Testing as Part of a Risk-Adapted Early Detection Strategy for Prostate Cancer: European Association of Urology Position and Recommendations for 2021
• 30 years have passed
• We have learned so much
• Isn't it time we implement our knowledge in an organized way accessible for all men in Europe?

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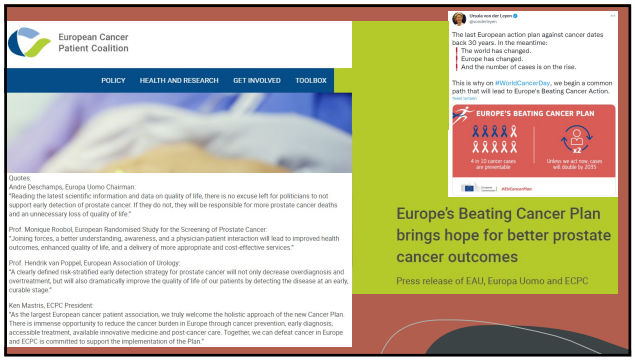
European Cancer Patient Coalition
POLICY
HEALTH AND RESEARCH
GET INVOLVED
TOOLBOX
EUROPE'S BEATING CANCER PLAN
Europe's Beating Cancer Plan brings hope for better prostate cancer outcomes
Press release of EAU, Europa Uomo and ECPC

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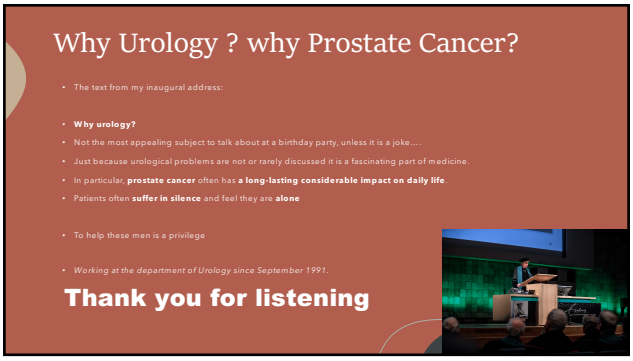
Why Urology ? why Prostate Cancer?
• The text from my inaugural address:
• Why urology?
• Not the most appealing subject to talk about at a birthday party, unless it is a joke….
• Just because urological problems are not or rarely discussed it is a fascinating part of medicine.
• In particular, prostate cancer often has a long-lasting considerable impact on daily life.
• Patients often suffer in silence and feel they are alone
• To help these men is a privilege
• Working at the department of Urology since September 1991.
Thank you for listening

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