Epidemiologi, screening, pathology and aspects on active suveillance in Prostate Cancer

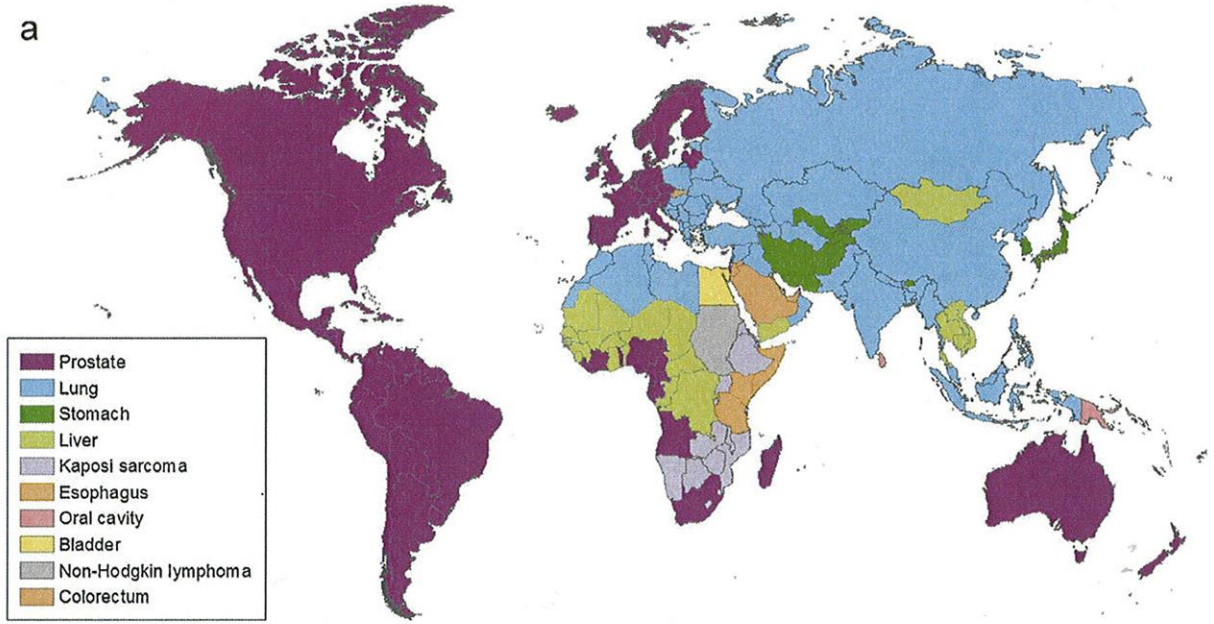
Jonas Hugosson

Professor i Urologi, Sahlgrenska akademin, Göteborgs Universitet

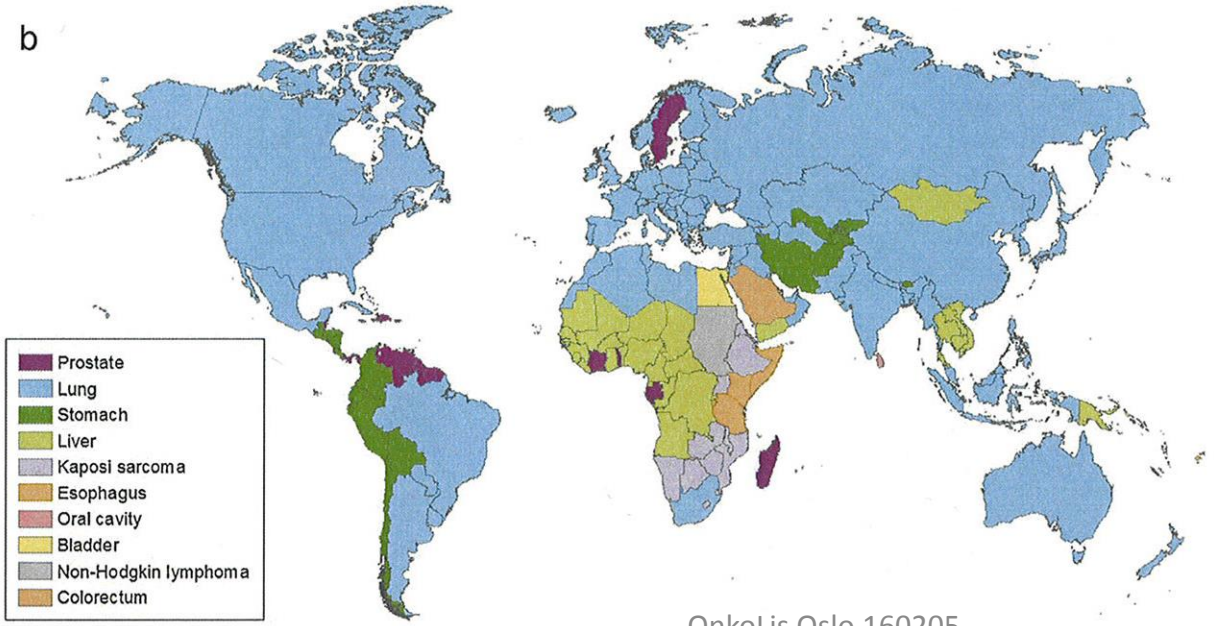
Prostate cancer: PCa

- The most common cancer among men

- Worldwide 1,1 millions new PCa cases/year (15 % of all malignancies among men)
- US: 240,000 new PCa cases/year
- Europe: 225,000 new PCa cases/year
- Sweden: 10,000 new PCa cases/year



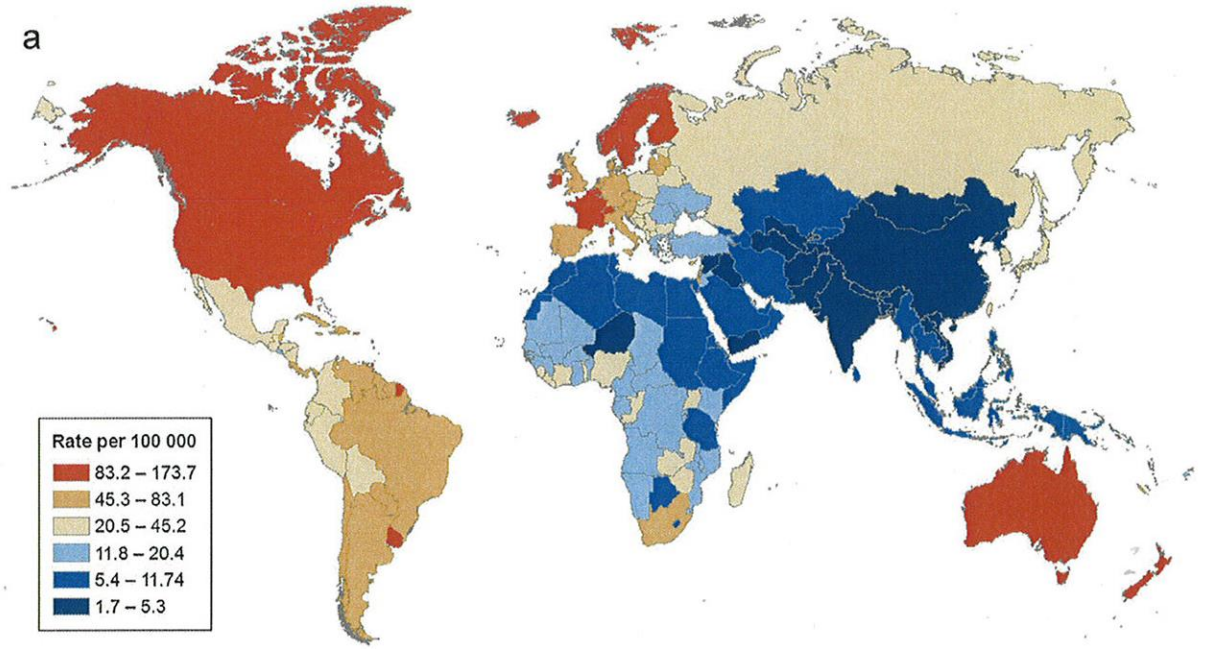
a) Most commonly diagnosed cancer among men worldwide, 2008



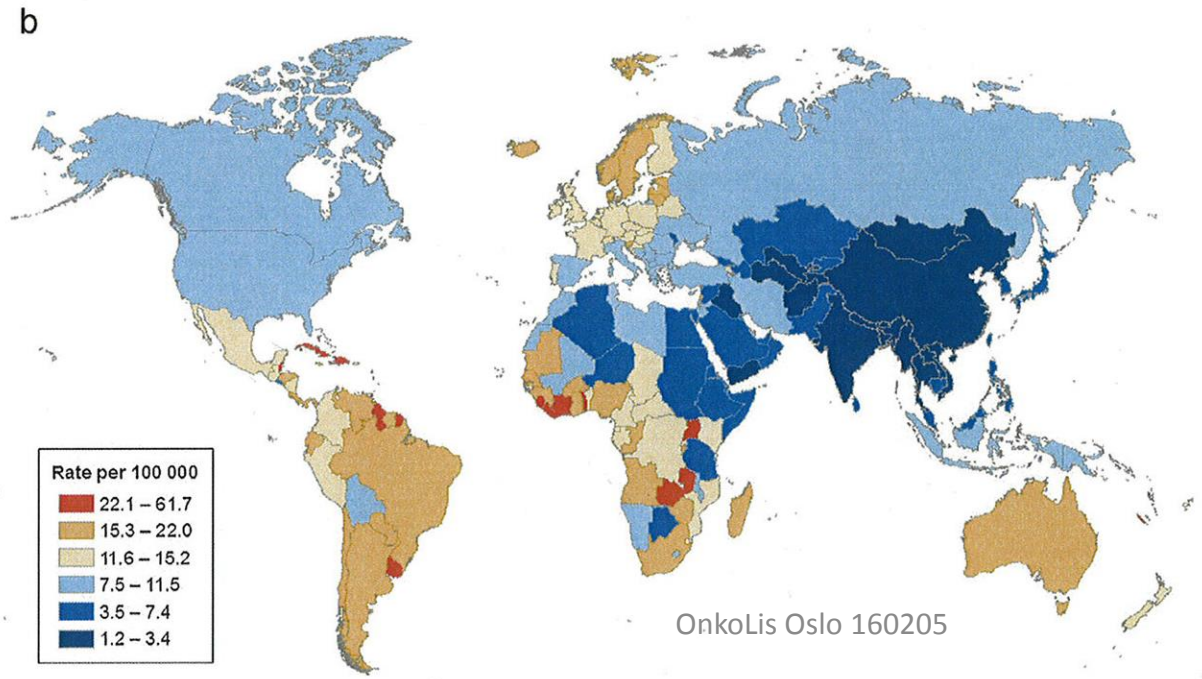
b) Leading cause of cancer deaths among men worldwide, 2008

Source: GLOBOCAN 2008 [1]

Center MM, et.al. Eur Urology 2012;61:1079-92



a) International variation in age-standardized prostate cancer incidence rates

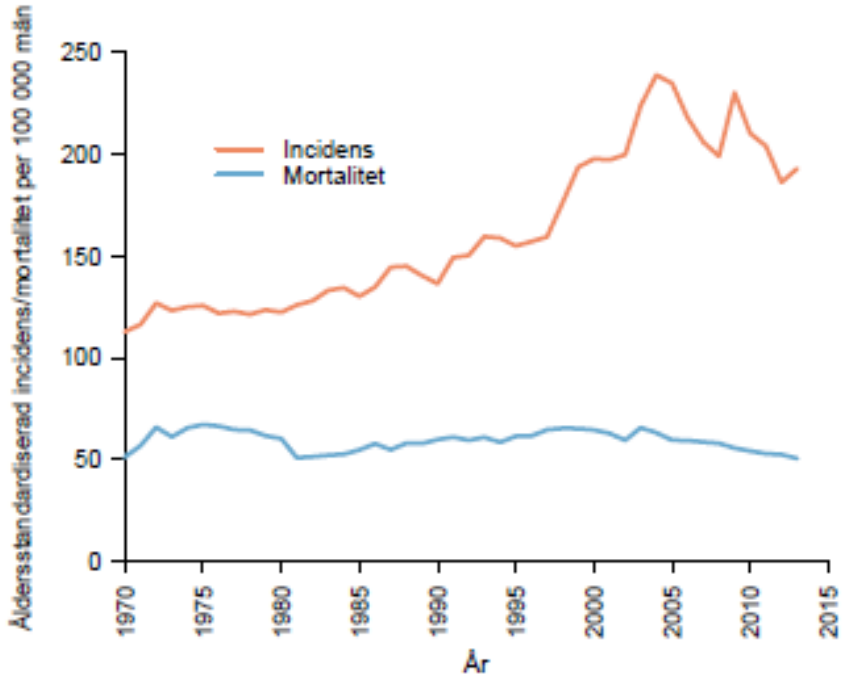


b) International variation in age-standardized prostate cancer mortality rates

Source: GLOBOCAN 2008 [1]

Center MM, et.al. Eur Urology 2012;61:1079-92

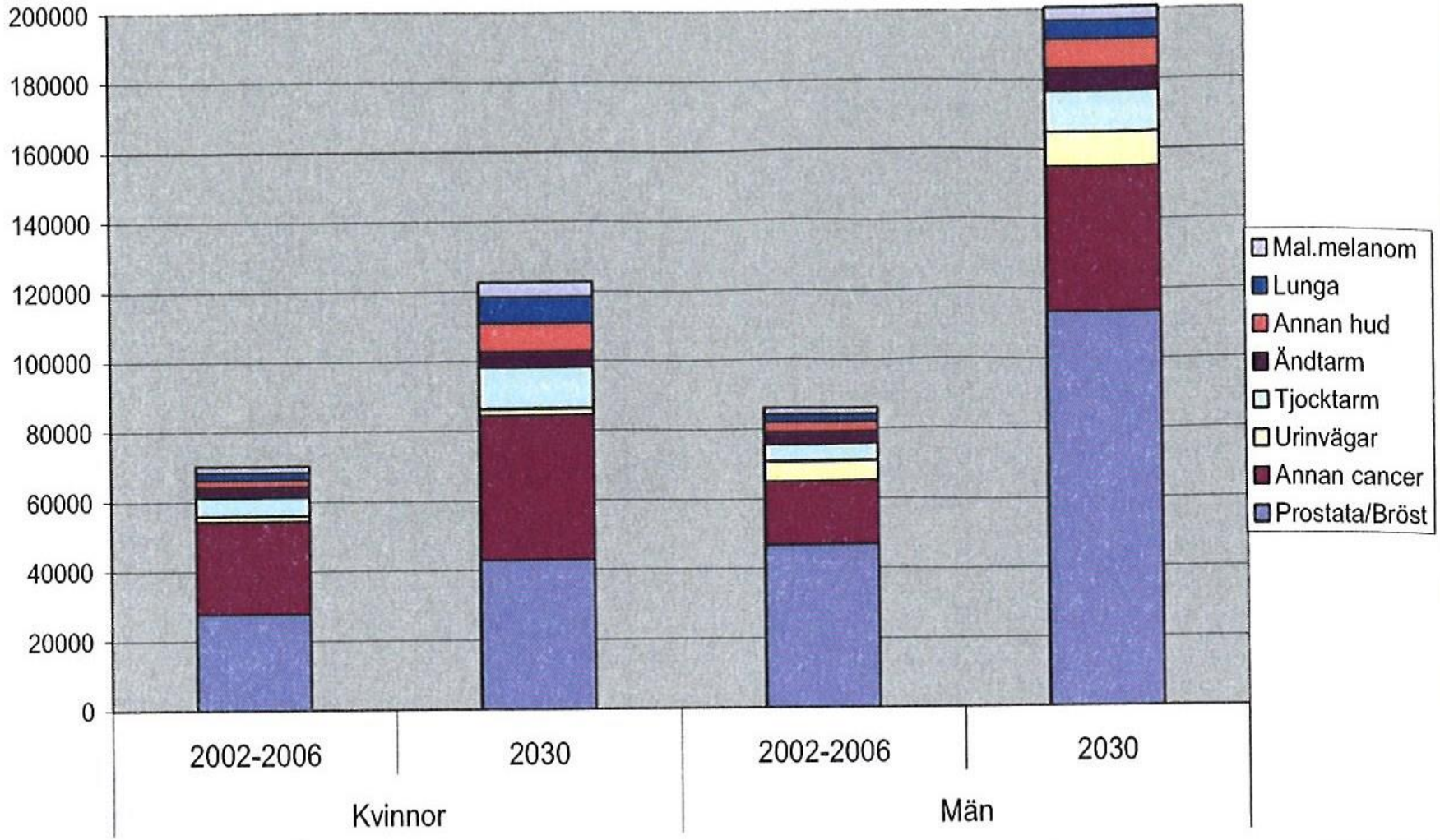
Prostatacancer i Sverige 1970 -2013



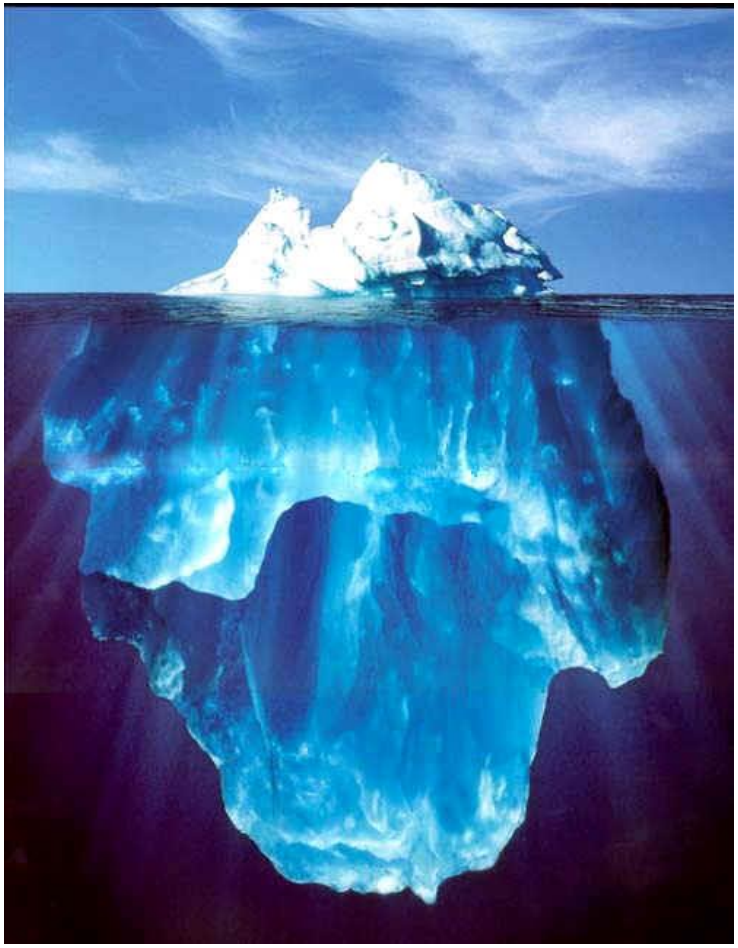
Figur 2. Åldersstandardiserad incidens och mortalitet av prostatacancer i Sverige per 100 000 män, 1970-2013.

NPCR årsrapport 2015

Figur 5.4 Prevalenspanoramat 2002-2006 och 2030

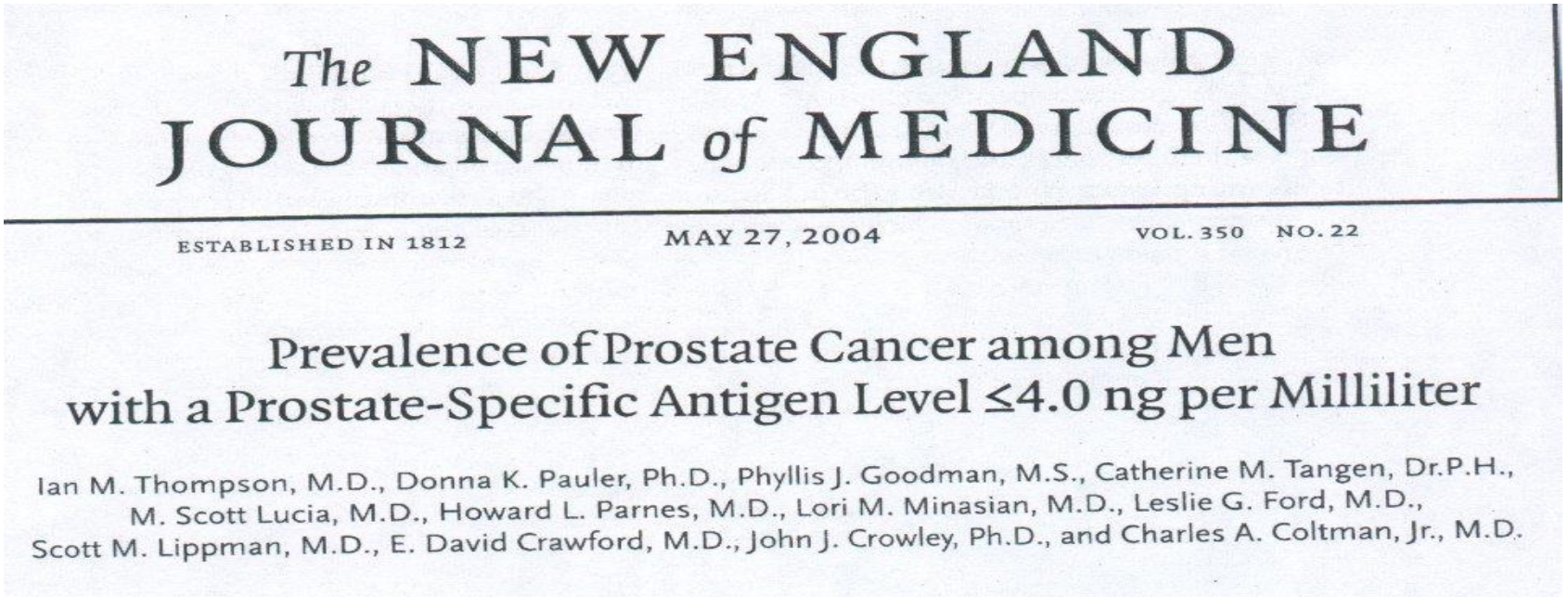


Varför ökar incidensen av PrCa?



Vi gräver oss allt djupare under vattenytan i prostatacancer-prevalensens isberg!

The prevalence of prostate cancer is high (> 23% among men with PSA > 2 ng/ml)



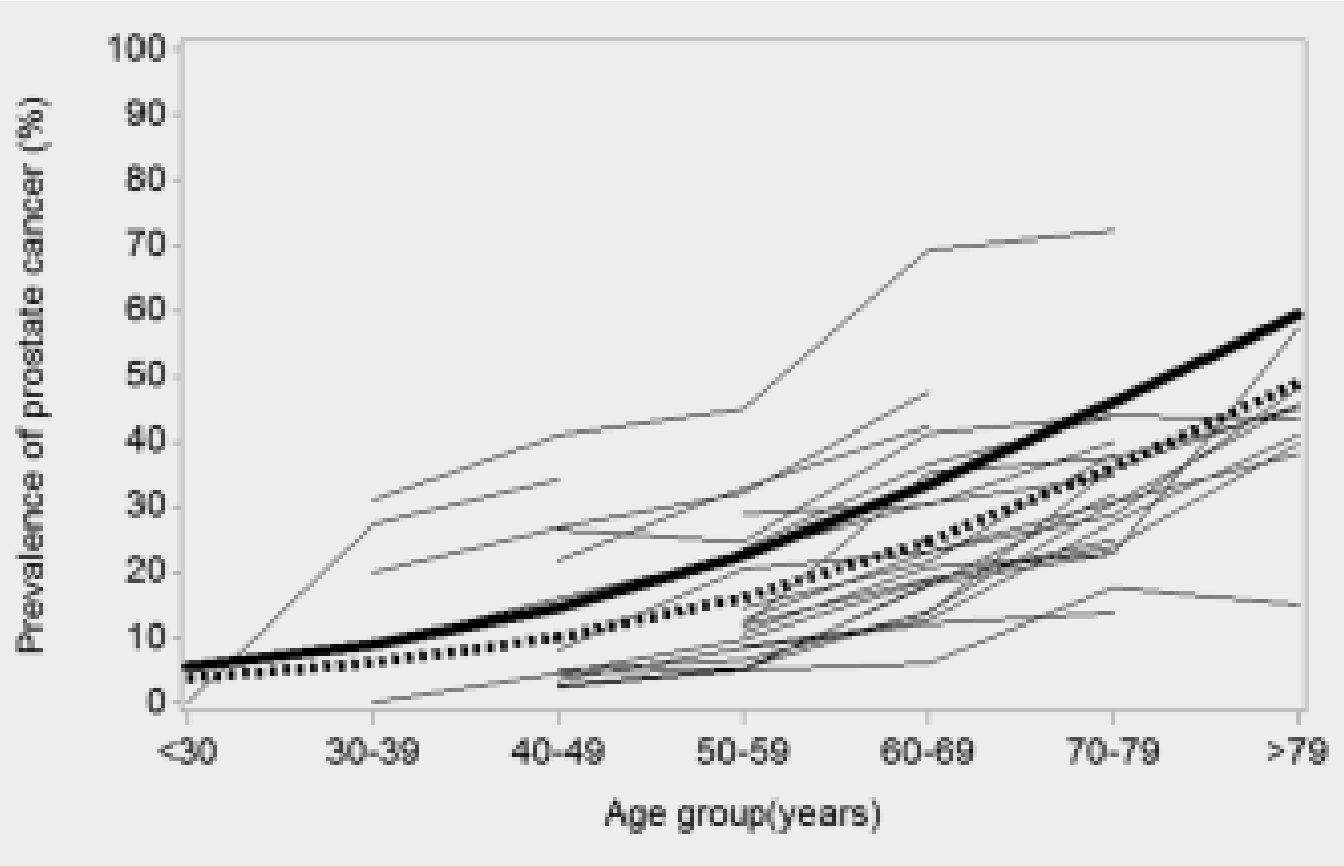
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 27, 2004 VOL. 350 NO. 22

Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤4.0 ng per Milliliter

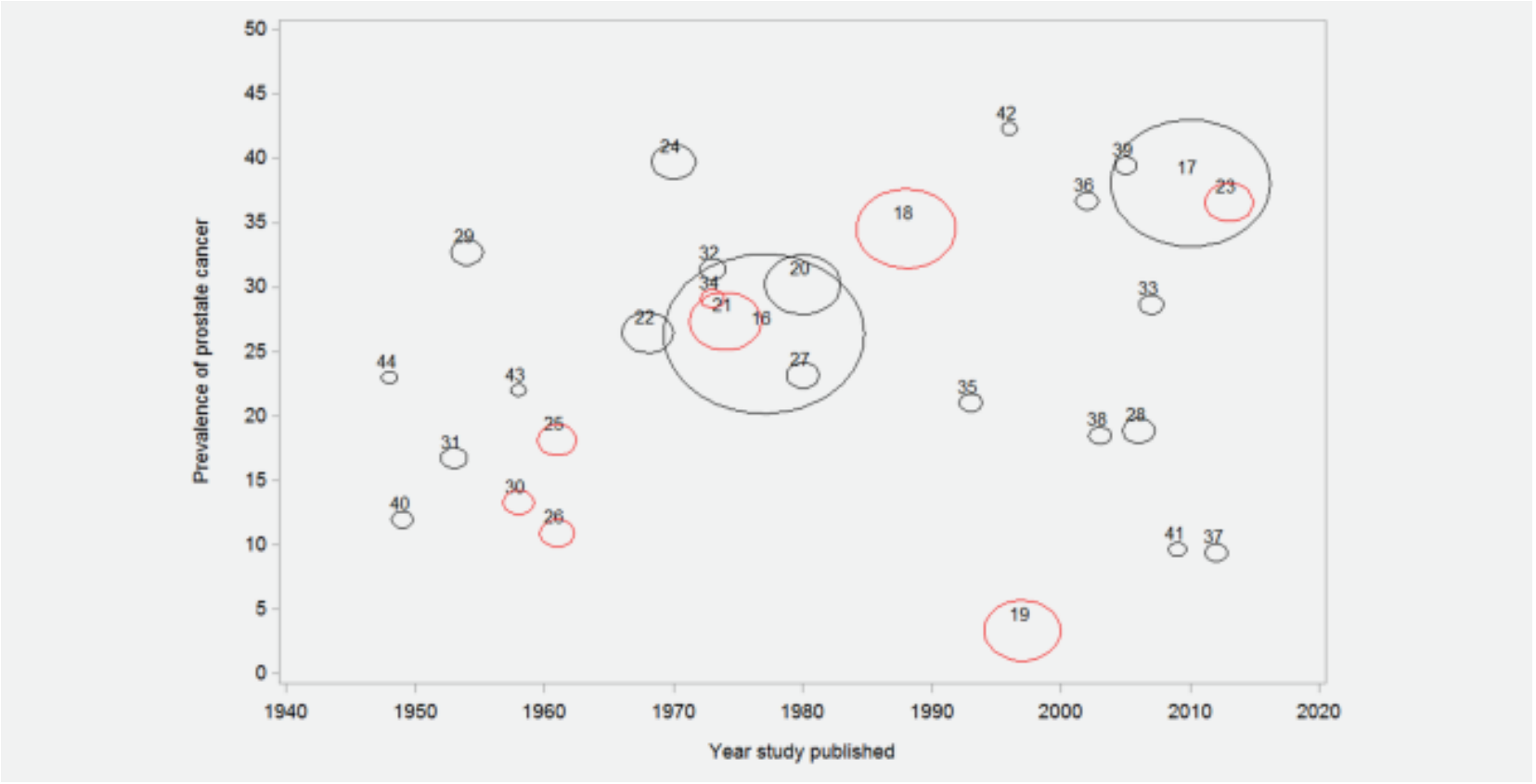
Ian M. Thompson, M.D., Donna K. Pauler, Ph.D., Phyllis J. Goodman, M.S., Catherine M. Tangen, Dr.P.H., M. Scott Lucia, M.D., Howard L. Parnes, M.D., Lori M. Minasian, M.D., Leslie G. Ford, M.D., Scott M. Lippman, M.D., E. David Crawford, M.D., John J. Crowley, Ph.D., and Charles A. Coltman, Jr., M.D.

Prevalensen av incidenta prostatacancer fall: en systematisk genomgång av obduktionsstudier

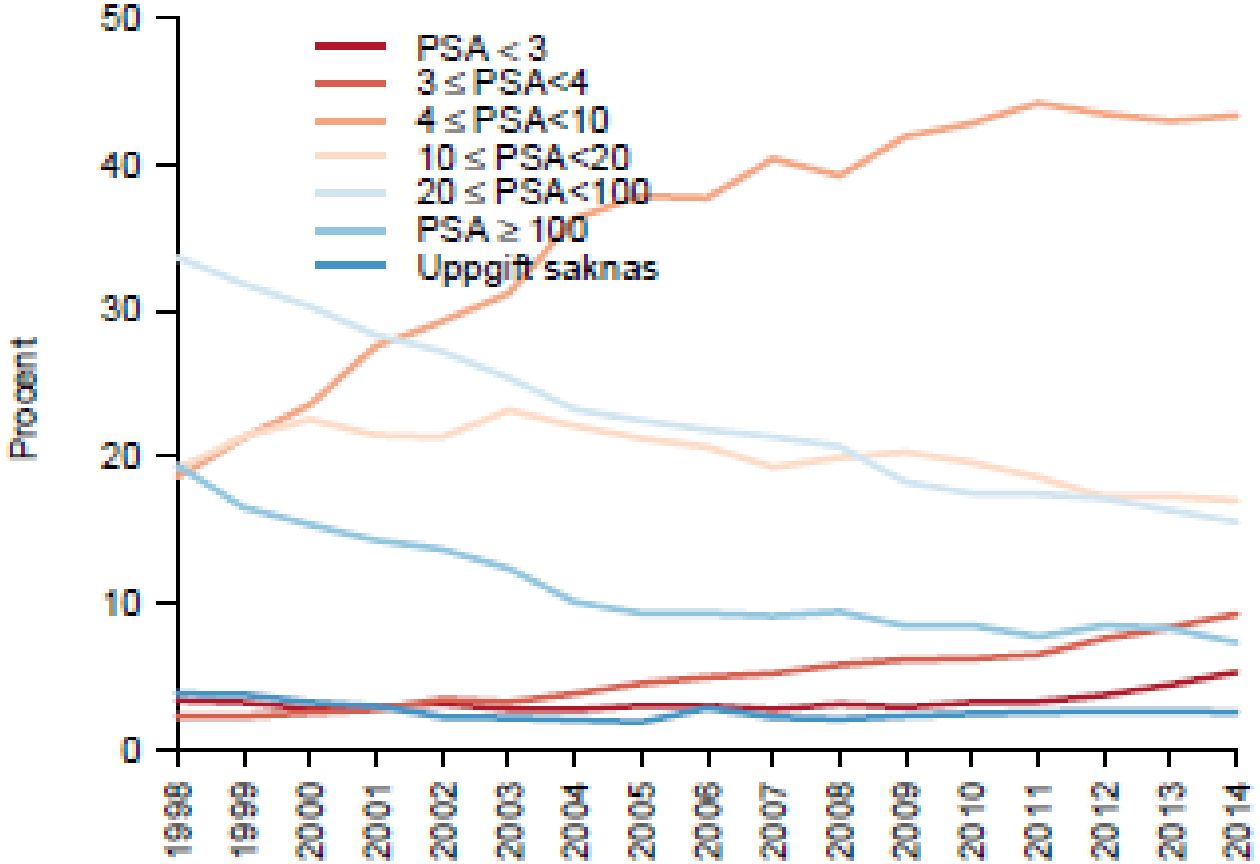


International Journal of Cancer
Volume 137, Issue 7, pages 1749-1757, 21 APR 2015 DOI: 10.1002/ijc.29538
http://onlinelibrary.wiley.com/doi/10.1002/ijc.29538/full#ijc29538-fig-0003

Prevalensen av incidenta prostatacancer fall: en systematisk genomgång av obduktionsstudier

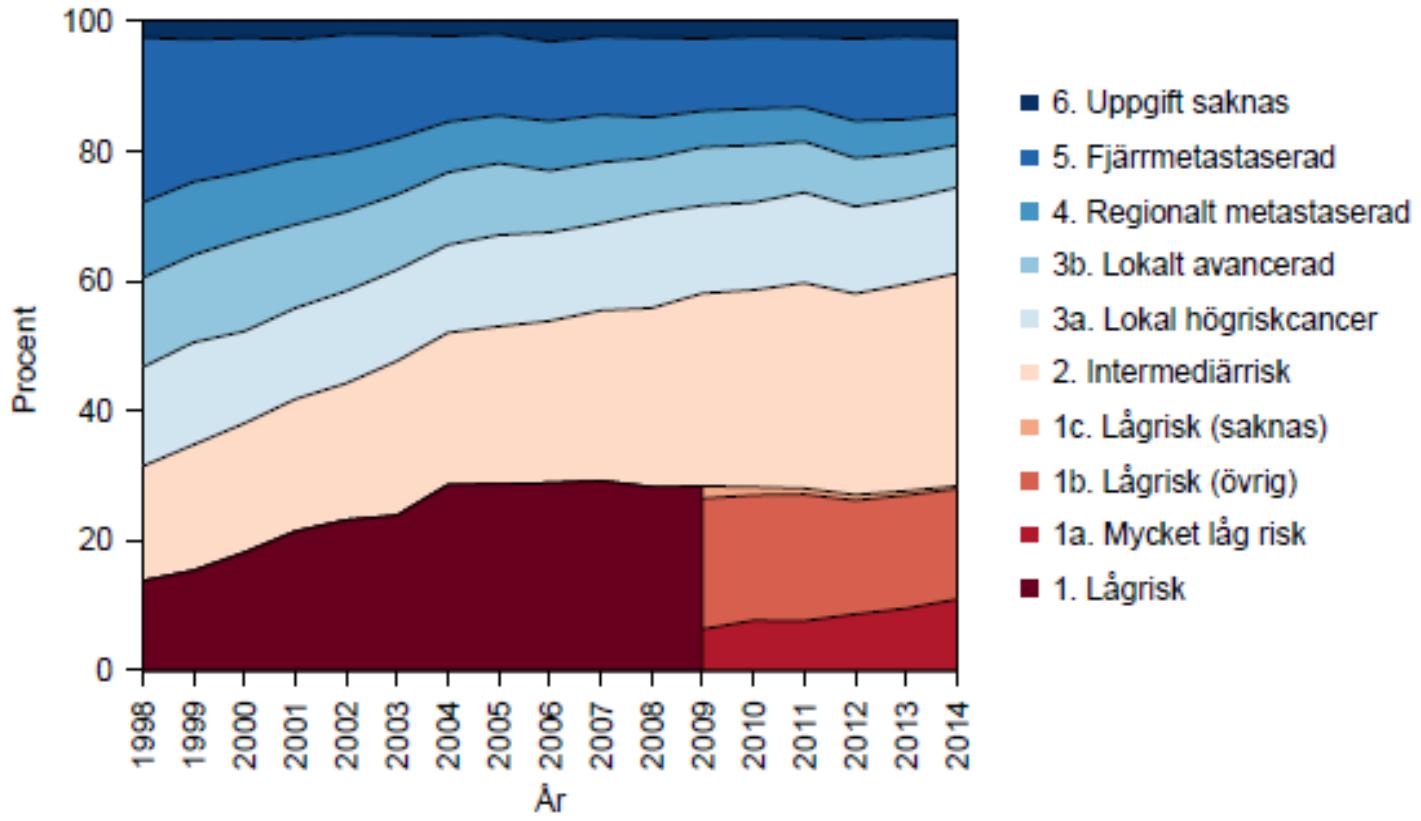


International Journal of Cancer
Volume 137, Issue 7, pages 1749-1757, 21 APR 2015 DOI: 10.1002/ijc.29538
http://onlinelibrary.wiley.com/doi/10.1002/ijc.29538/full#ijc29538-fig-0002



Figur 27. PSA-nivå (μg/L) vid diagnos per diagnosår, 1998-2014.

NPCR 2015



Figur 37. Fördelning av riskkategori per diagnosår, 1998-2014.

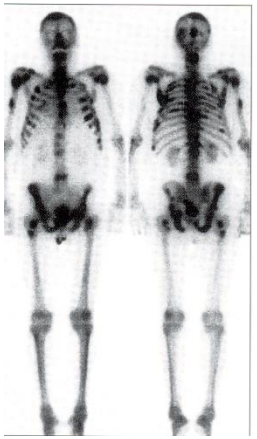
NPCR 2015

Dör man av PrCa?

Vanligaste

cancer-relaterade dödsorsaken

hos män i Sverige!

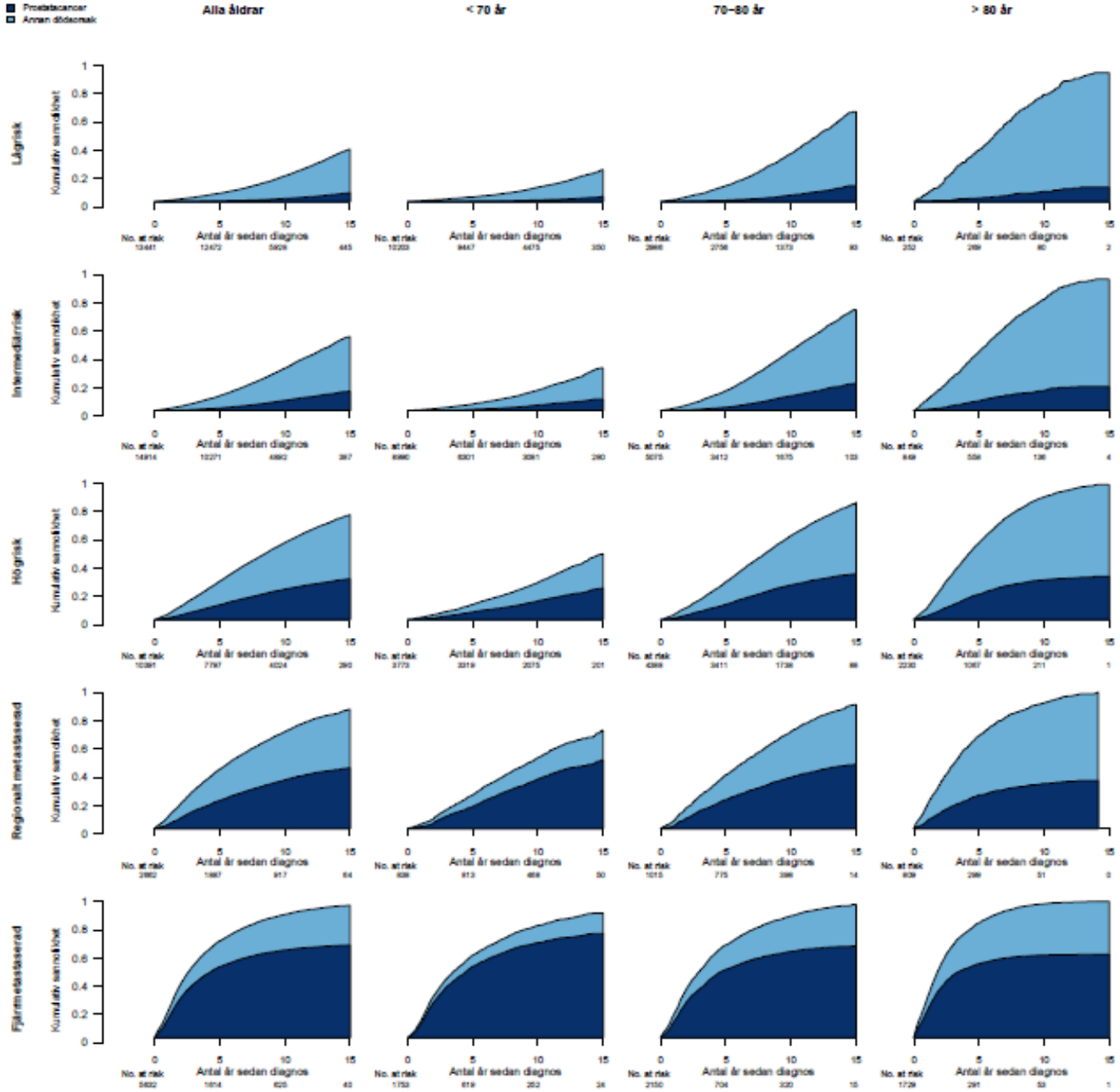


Hur många svenskar dör av PrCa?

- **5,5 %** av svenska män dog av PrCa 2014
- **2 398** dog 2014
  - Hälften var över 80 år
  - Mindre än 1,2 % att dö före 75 år

Jämför med…

- kvinnor av bröstcancer 1 505 (3,1 %)
  - Varav dock hälften < 70 år

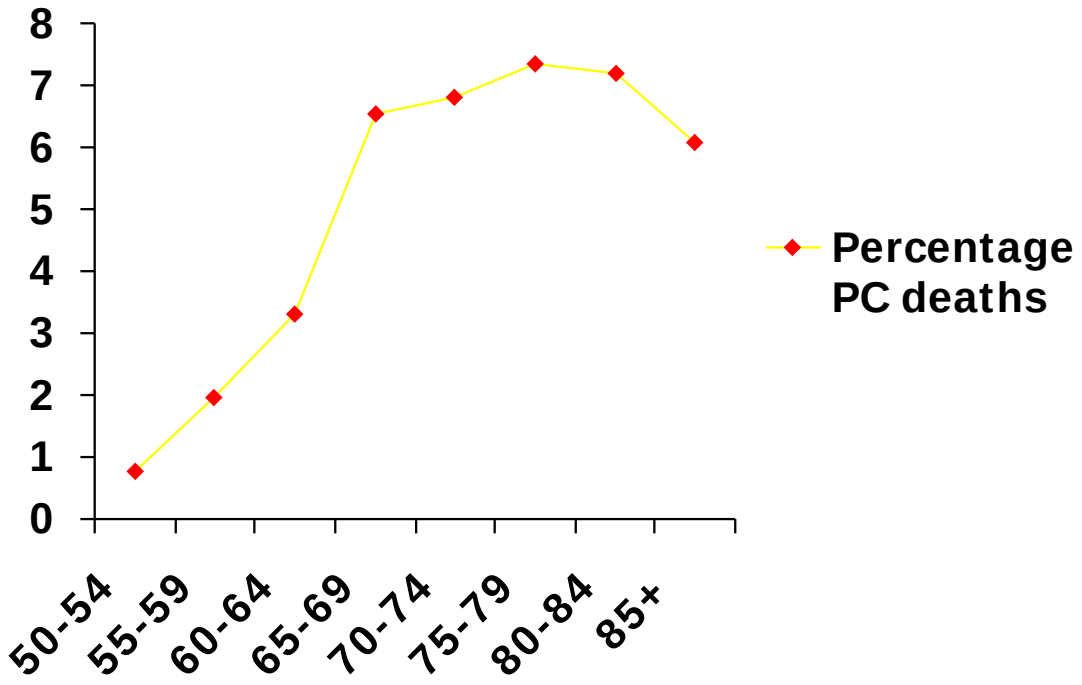


Figur 118. Kumulativ mortalitet av prostatacancer och andra orsaker, per riskkategori och åldersgrupp, periodanalys 2009-2013.

NPCR 2015

Andelen prostatacancer av samtliga dödsorsaker per ålder

%



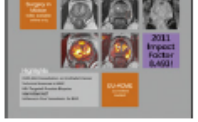
PC Prostatacancer utgör 6,2 % av alla dödsorsaker efter 50 års ålder

Sjukdomsspecifik 15-års dödlighet för prostatacancer i Sverige

- låg risk 8.9%
- intermediär risk 19.6%
- hög risk 35,5%
- regionalt metastaserade 49.1%
- Fjärrmetastaser 69,5%

Rider et al, Eur Urol, 2013

European Association of Urology



Platinum Priority – Prostate Cancer
Editorial by Urs E. Studer on pp. 436–437 of this issue

Natural History of Early, Localized Prostate Cancer: A Final Report from Three Decades of Follow-up

Marcin Popiolek[a,†], *Jennifer R. Rider*[b,c,†,*], *Ove Andrén*[a], *Sven-Olof Andersson*[a], *Lars Holmberg*[d,e], *Hans-Olov Adami*[c,f], *Jan-Erik Johansson*[a]

[a] *School of Health and Medical Sciences, Örebro University; and Department of Urology, Örebro University Hospital, Örebro, Sweden;* [b] *Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA;* [c] *Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA;* [d] *Regional Oncologic Center, University Hospital, Uppsala, Sweden;* [e] *King's College London, Medical School, Division of Cancer Studies, London, UK;* [f] *Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*

Article info

Article history:
Accepted October 5, 2012
Published online ahead of print on October 13, 2012

Keywords:
Natural history
Localized prostate cancer
Mortality

Abstract

Background: Most localized prostate cancers are believed to have an indolent course. Within 15 yr of diagnosis, most deaths among men with prostate cancer (PCa) can be attributed to other competing causes. However, data from studies with extended follow-up are insufficient to determine appropriate treatment for men with localized disease.
Objective: To investigate the long-term natural history of untreated, early-stage PCa.
Design, setting, and participants: We conducted a population-based, prospective-cohort study using a consecutive sample of 223 patients with untreated, localized PCa from a regionally well-defined catchment area in central Sweden. All subjects were initially managed with observation. Androgen deprivation therapy was administered when symptomatic tumor progression occurred.
Outcome measurements and statistical analysis: Based on >30 yr of follow-up, the main outcome measures were: progression-free, cause-specific, and overall survival, and rates of progression and mortality per 1000 person-years.
Results and limitations: After 32 yr of follow-up, all but 3 (1%) of the 223 men had died. We observed 90 (41.4%) local progression events and 41 (18.4%) cases of progression to distant metastasis. In total, 38 (17%) men died of PCa. Cause-specific survival decreased between 15 and 20 yr, but stabilized with further follow-up. All nine men with Gleason grade 8–10 disease died within the first 10 yr of follow-up, five (55%) from PCa. Survival for men with well-differentiated, nonpalpable tumors declined slowly through 20 yr, and more rapidly between 20 and 25 yr (from 75.2% [95% confidence interval, 48.4–89.3] to 25% [95% confidence interval, 22.0–72.5]). It is unclear whether these data are relevant for tumors detected by elevated prostate-specific antigen levels.
Conclusions: Although localized PCa most often has an indolent course, local progression and distant metastasis can develop over the long term, even among patients considered low risk at diagnosis.

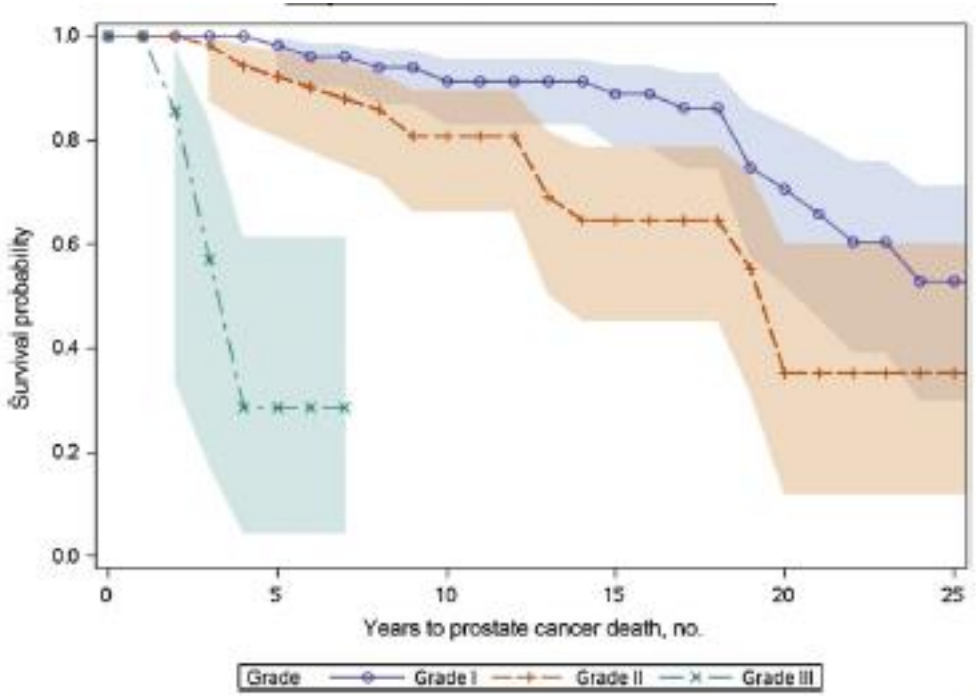
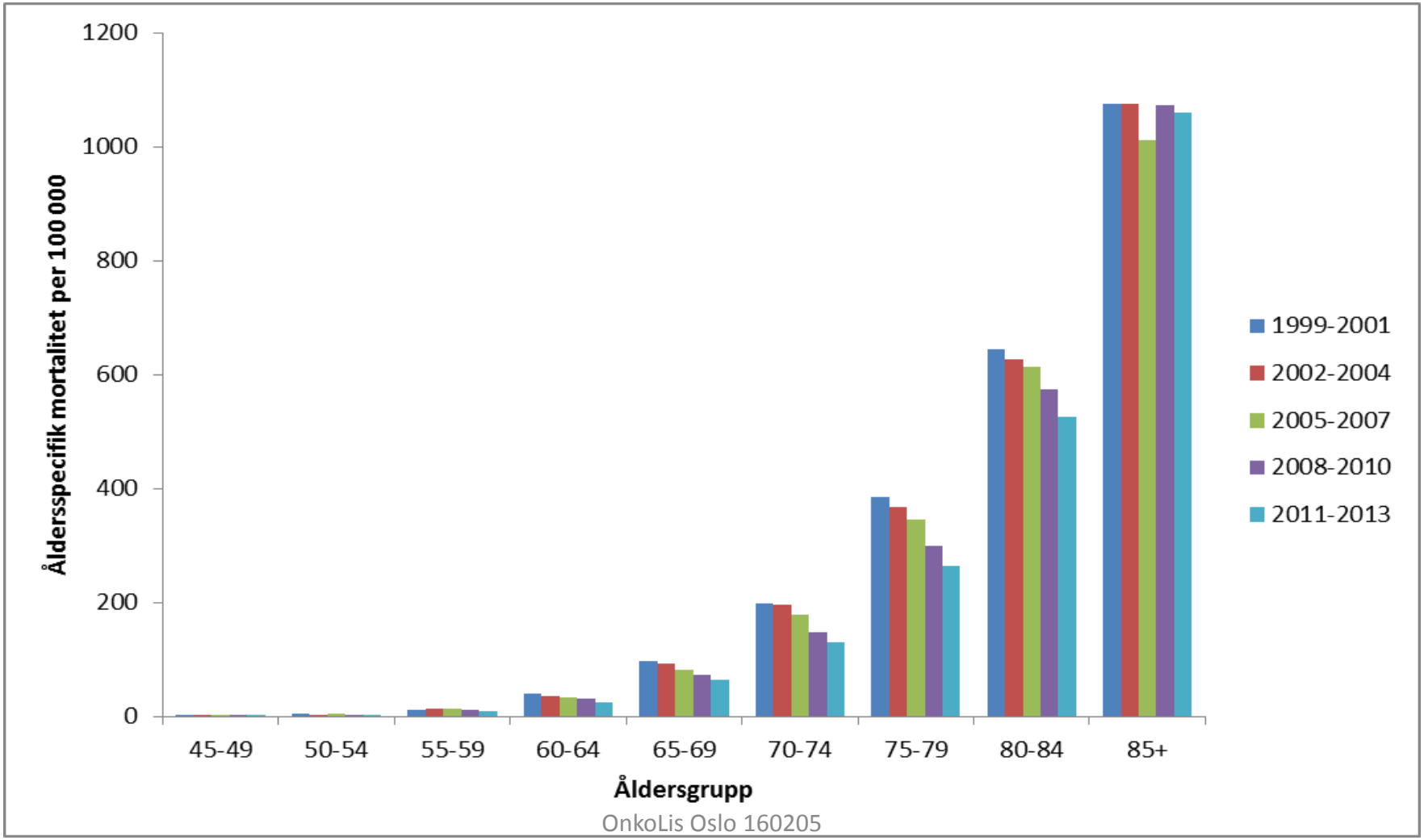


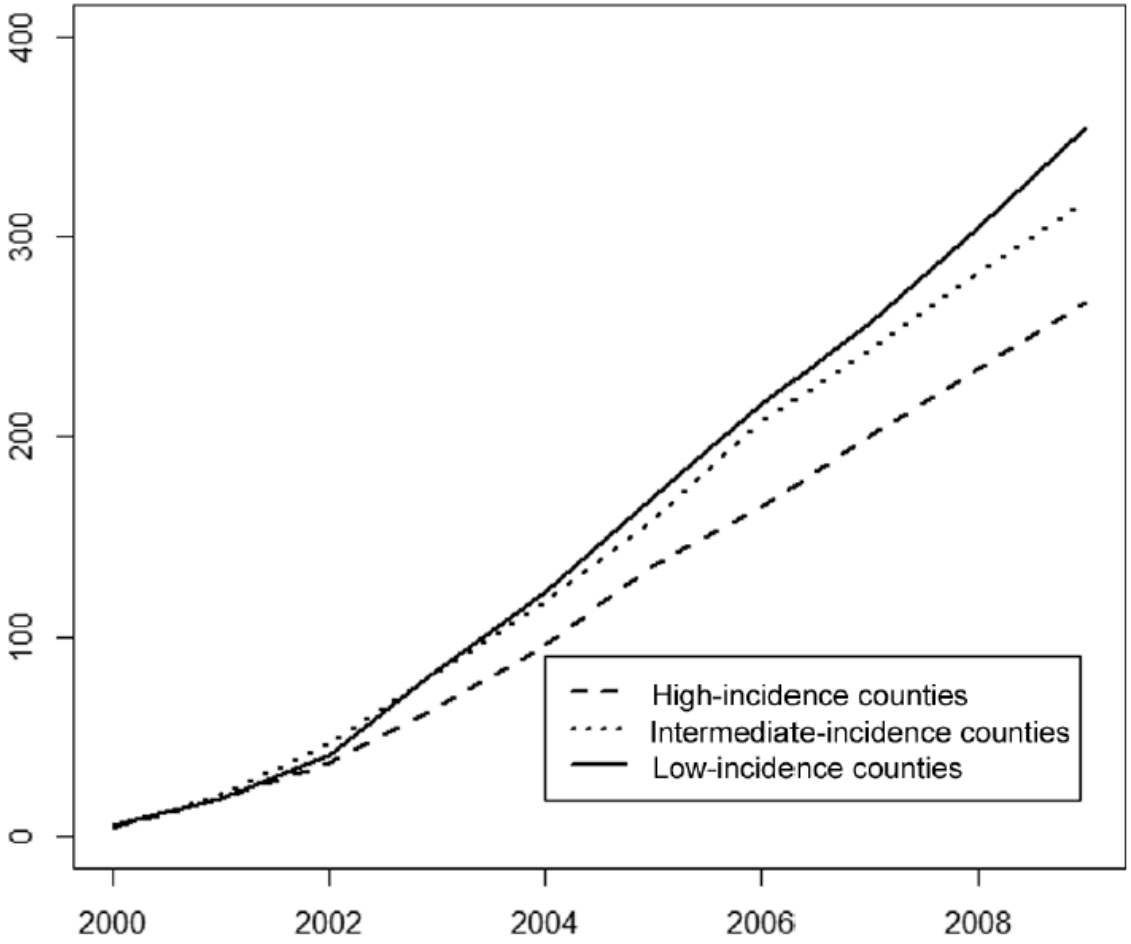
Fig. 2 – Prostate cancer-specific survival and 95% confidence intervals by stage of disease and tumor grade at diagnosis.

Minskad PrCa-mortalitet i Sverige

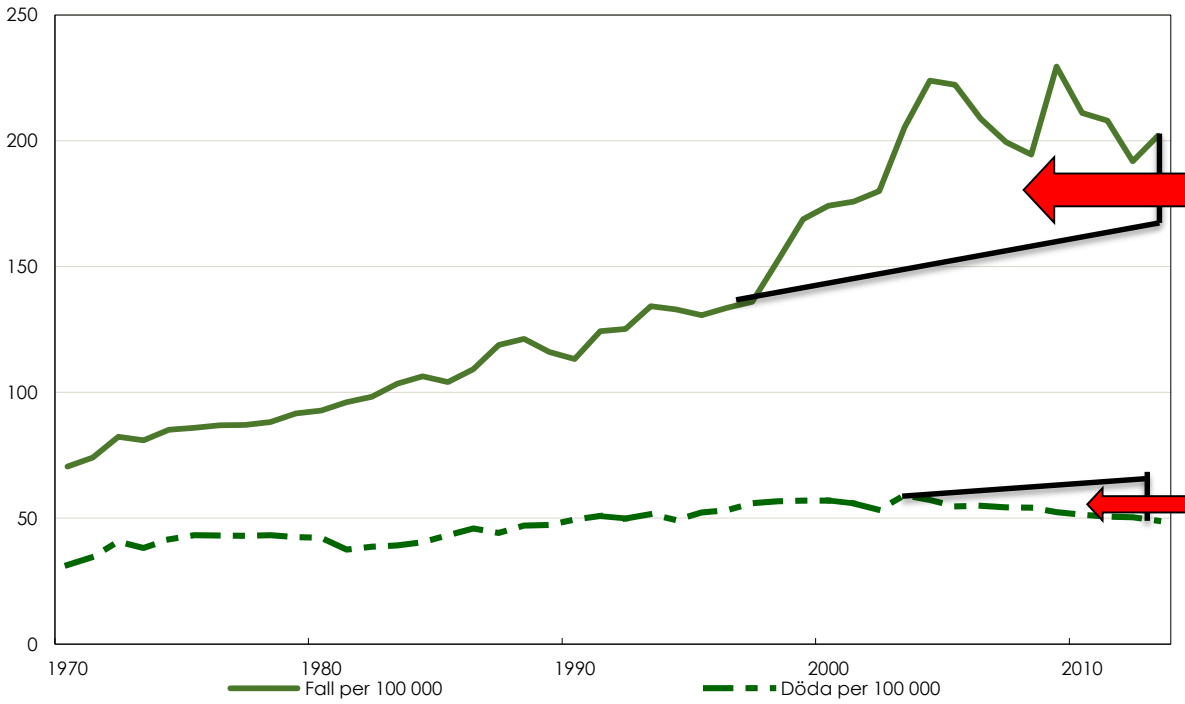


Prostatacancerdödlighet i Sverige i förhållande till PSA-testningsintensitet

(mätt som T1c) *Stattin, JNCI 2014*



Incidens och mortalitet för prostatacancer i Sverige



Omkring 75 000 extra cancerfall pga PSA-test

Omkring 4000 färre dödsfall efter PSA infört

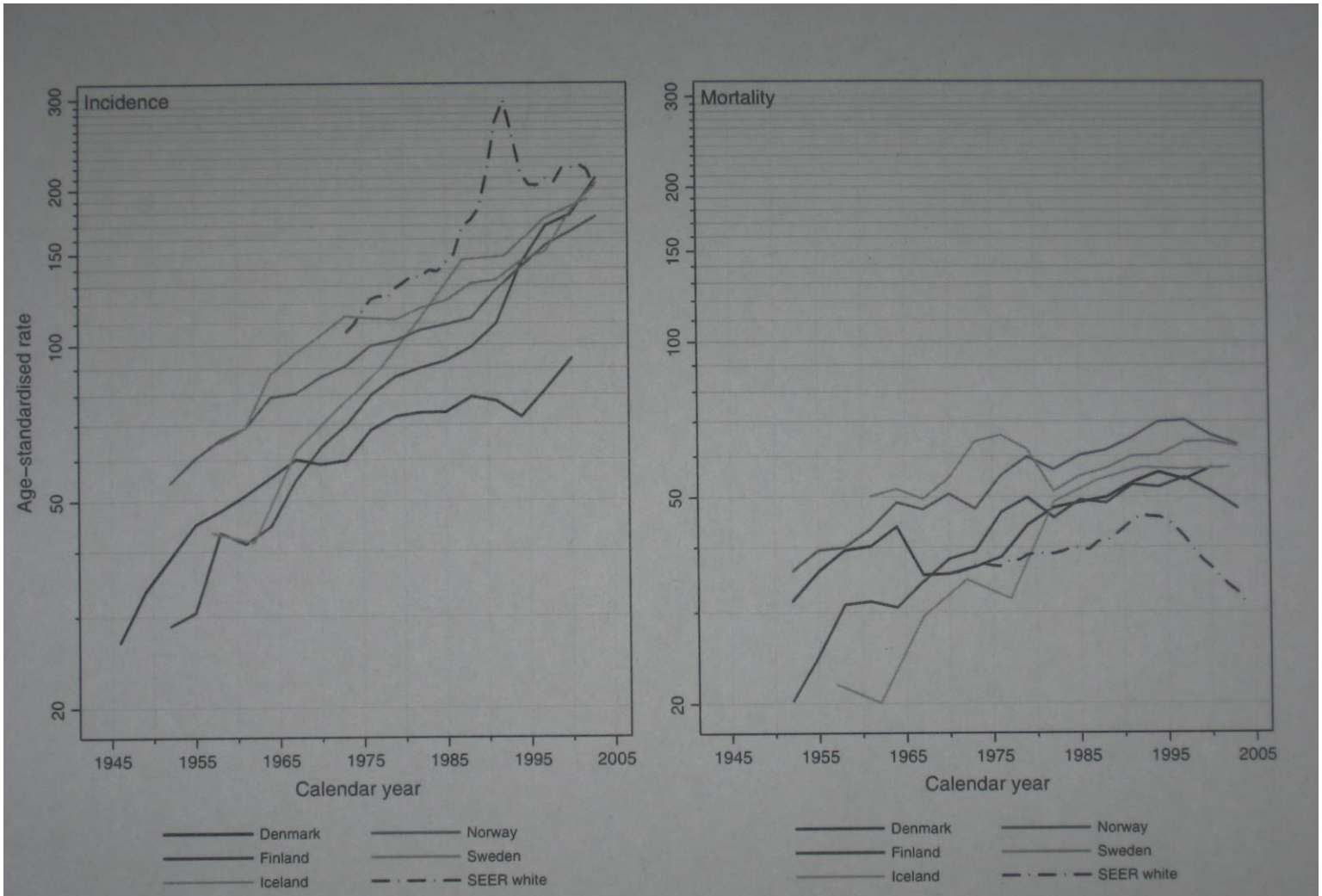
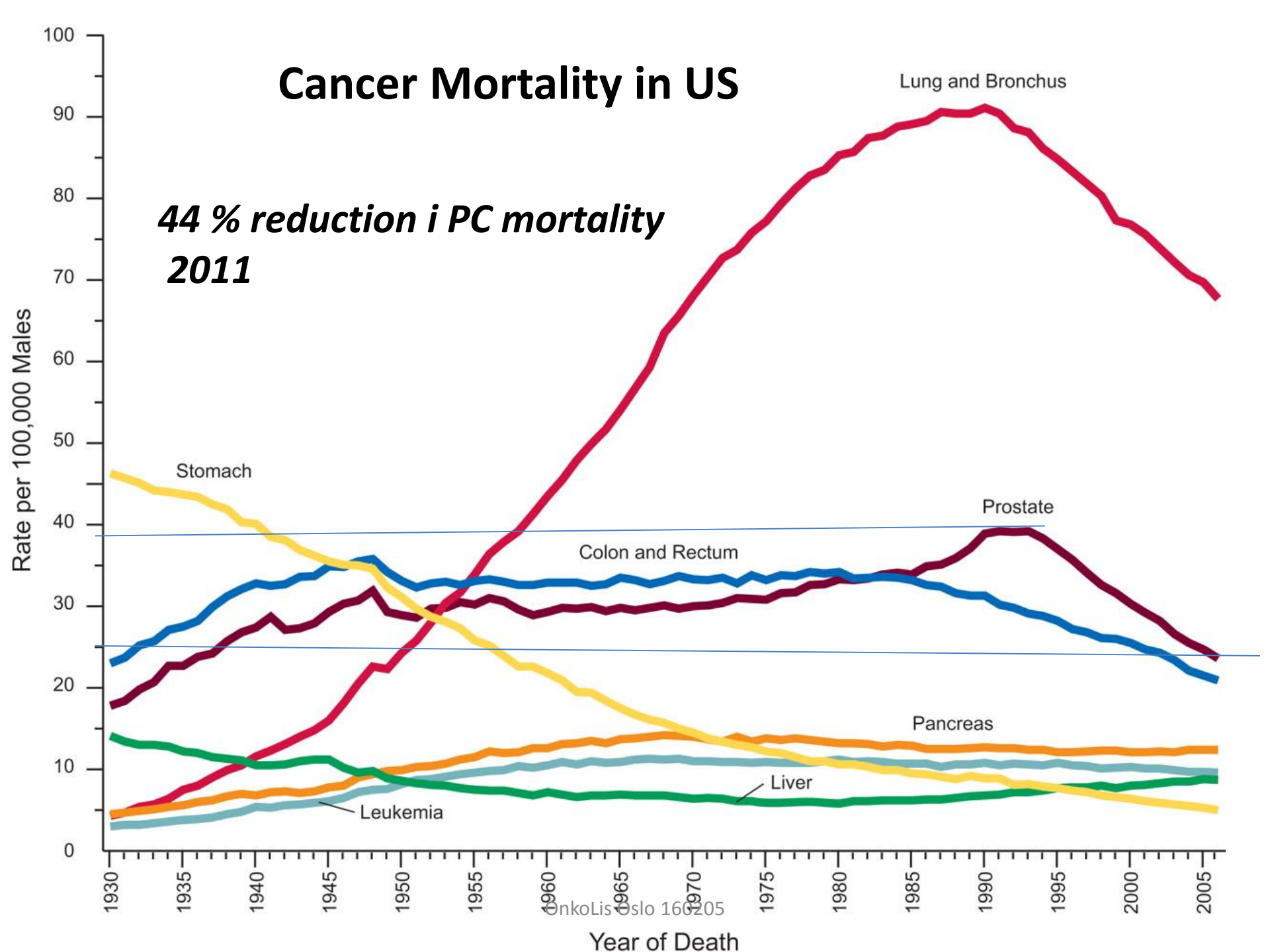


Fig. 1. Observed age-standardized rates (Nordic standard 2000) of prostate cancer incidence and mortality in the Nordic countries and the United States (all ages).


Cancer Mortality in US
44 % reduction i PC mortality
2011
Lung and Bronchus
Stomach
Prostate
Colon and Rectum
Pancreas
Liver
Leukemia
Rate per 100,000 Males
Year of Death
100
90
80
70
60
50
40
30
20
10
0
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005

A balance between Benefits and Harms

”At the heart of the screening debate lies the ethics of information”

Ian S Markham. Brittish Medical Bulletin.

1998; 54 (4): p.1012.

Review

Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force

Roger Chou, MD;
Jennifer M. Croswell, MD, MPH;
Tracy Dana, MLS;
Christina Bougatsos, BS;
Ian Blazina, MPH;
Rongwei Fu, PhD;
Ken Gleitsmann, MD, MPH;
Helen C. Koenig, MD, MPH;
Clarence Lam, MD, MPH;
Ashley Maltz, MD, MPH;
J. Bruin Rugge, MD, MPH; and
Kenneth Lin, MD

Published on-line Annals of Internal Medicine Oct 2011

Conclusion: Prostate-specific antigen–based screening results in small or no Reduction in prostate cancer–specific mortality and is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary.

Starka argument för screening

- Prostatacancer är ett stort hälsoproblem speciellt i Skandinavien, 5 % av alla dödsfall i Sverige
- Ju äldre man är desta större är risken
- Endast tidig upptäckt prostatacancer är botbar med operation eller strålning om man har symptom så är cancern ofta för långt gången
- Behandling med hormoner är effektivt men förr eller senare kommer sjukdomen tillbaks.
- Biverkningarna av operation och strålning har blivit väsentligen mycket mindre de senaste 20 åren.

Starka argument mot screening

- Risken för överdiagnostik är hög, hälften av alla män som får diagnosen genom PSA testning kommer inte utveckla symptom under den återstående livstiden
- Tiden mellan PSA diagnos och symptom debut är lång, 5-15 år dvs män får byta många symptomfria levnadsår mot år med ev biverkningar av behandlingen och leva med vetskapen att de har cancer
- Behandlingen ger ibland biverkningar, inkontinens, impotens och tarmbesvär
- Få diagnosen prostatacancer är psykiskt belastande

Randomised screening studies

	Published	Number invited	Weakness
Stockholm	2009	1800	Small study, one time screening, few men treated with curative intent
Quebec	1999 (2004)	31 133	Only 24 % participated, not evaluated according to ”intention to screen”
Norrköping	2011	1494	Small study, not designed to evaluate mortality, PSA was included from 3rd round and only 895 men PSA tested
ERSPC	2009, 2012	82816	8 centers with different protocols
PLCO	2009, 2012	37285	52 % contamination, very low mortality in controls, low biopsy rate, no up-front power calculation, only 6 years of screening

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

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*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 15, 2012 VOL. 366 NO. 11

Prostate-Cancer Mortality at 11 Years of Follow-up

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., Alvaro Páez, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Sigrid Carlsson, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Paula M. Kujala, M.D., Bert G. Blijenberg, Ph.D., Ulf-Hakan Stenman, M.D., Andreas Huber, M.D., Kimmo Taari, M.D., Matti Hakama, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

Articles

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

Fritz H Schröder, Jonas Hugosson, Monique J Roobol, Teuvo LJ Tammela, Marco Zappa, Vera Nelen, Maciej Kwiatkowski, Marcos Lujan, Liisa Määttänen, Hans Lilja, Louis J Denis, Franz Recker, Alvaro Paez, Chris H Bangma, Sigrid Carlsson, Donella Puliti, Arnauld Villers, Xavier Rebillard, Matti Hakama, Ulf-Hakan Stenman, Paula Kujala, Kimmo Taari, Gunnar Aus, Andreas Huber, Theo H van der Kwast, Ron H N van Schaik, Harry J de Koning, Sue M Moss, Anssi Auvinen, for the ERSPC Investigators*

Summary

Background The European Randomised study of Screening for Prostate Cancer (ERSPC) has shown significant reductions in prostate cancer mortality after 9 years and 11 years of follow-up, but screening is controversial because of adverse events such as overdiagnosis. We provide updated results of mortality from prostate cancer with follow-up to 2010, with analyses truncated at 9, 11, and 13 years.

Published Online August 7, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60525-0

See Online/Comment

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.

Lancet Oncol 2010; 11: 725–32

Published Online July 1, 2010

DOI:10.1016/S1470-2045(10)70146-7

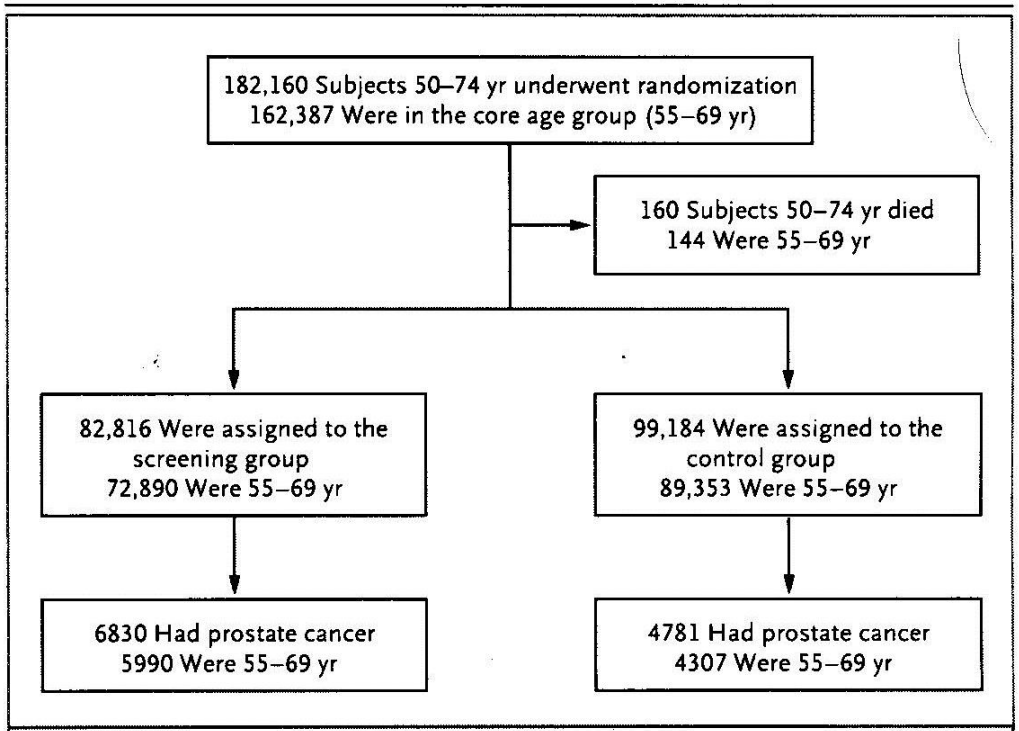


Figure 1. **Enrollment and Outcomes, According to Age Group at Randomization.**
The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years.

ERSPC

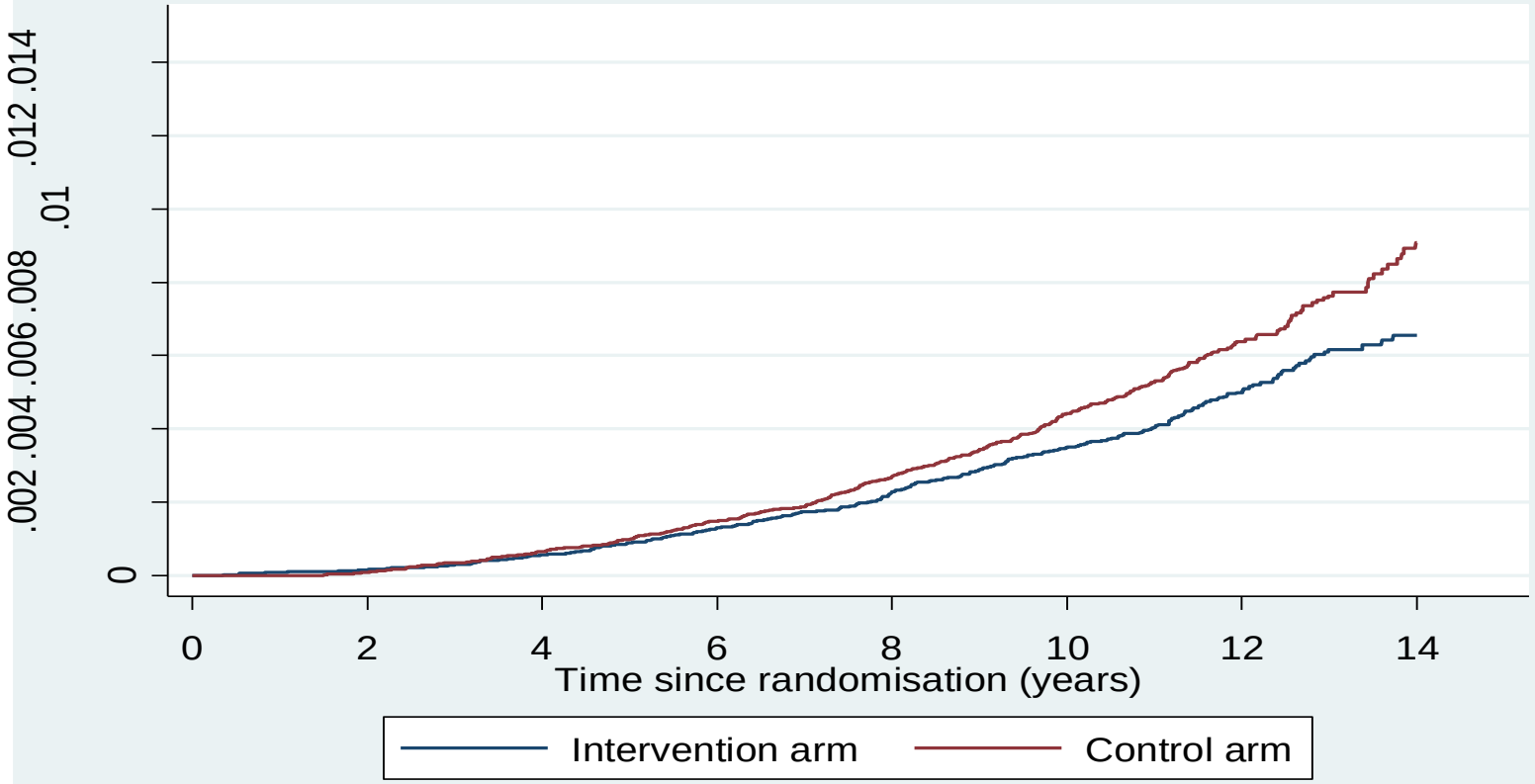
- Startades 1992
- 182,000 män i 8 oilka Europeiska länder har lottats mellan organiserad PSA testning respektive ej
- Världens största studie i sitt slag
- Hög kvalitet. Quality control programs during the entire study (PSA, Pathology, Epidemiology, International COD)
- Oberoende central databas i London
- Oberoende utvärdering av dödsorsaker
- Återkommande möten 2 ggr per år

Table 7. Key characteristics of the study protocols in the ERSPC and PLCO trials.

	ERSPC								PLCO
	Finland	Netherlands	Sweden	Belgium	Italy	Spain	Switzerland	France	
Age at entry	55/59/63/67	55-74	51-66	55-74	55-70	45-70	55-70	55-69	55-74
Screening interval	4	4	2	7	4	4	4	2	1
Recruitment	Population-based	Volunteers	Population-based	Volunteers	Population-based	Volunteers	Population-based	Population-based	Volunteers
Randomization	Before consent	After consent	Before consent	After consent	Before consent	After consent	After consent	Before consent	After consent
Target sample size*	80,000	42,000	20,000	10,000	15,000	4,300	10,000	101,000	74,000
PSA threshold (µg/l)†	4.0	3.0	2.54	3.0	4.0	3.0	3.0	3.0	4.0
Supplemental screening criteria‡	%FPSA	-	-	DRE	DRE/ TRUS	%FPSA	%FPSA	-	DRE

Crude. †, ‡ Current protocol.

Cumulative risk of death from prostate cancer after 11years of follow-up (Relative risk reduction 21%)



Schröder et al. 2012

Prostate cancer mortality for individual centers

Center (FU)	Rate ratio (95%)	Relative risk reduction	
			P-value
Netherlands (11.1 ys)	0.71 (0.52-0.96)	29%	0.003
Belgium (12.1 ys)	0.86 (0.48-1.52)	14%	NS
Sweden (14 ys)	0.56 (0.38-0.83)	44%	0.001
Finland (11.0 ys)	0.89 (0.72-1.09)	11%	NS
Italy (10.7 ys)	0.86 (0.46-1.58)	14%	NS
Spain (10.7 ys)	2.15 (0.20-23.77)	-	-
Switzerland (8.2 ys)	0.89 (0.36-2.20)	11%	NS

D-10-00484R2

S1470-2045(10)70146-7

Articles

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

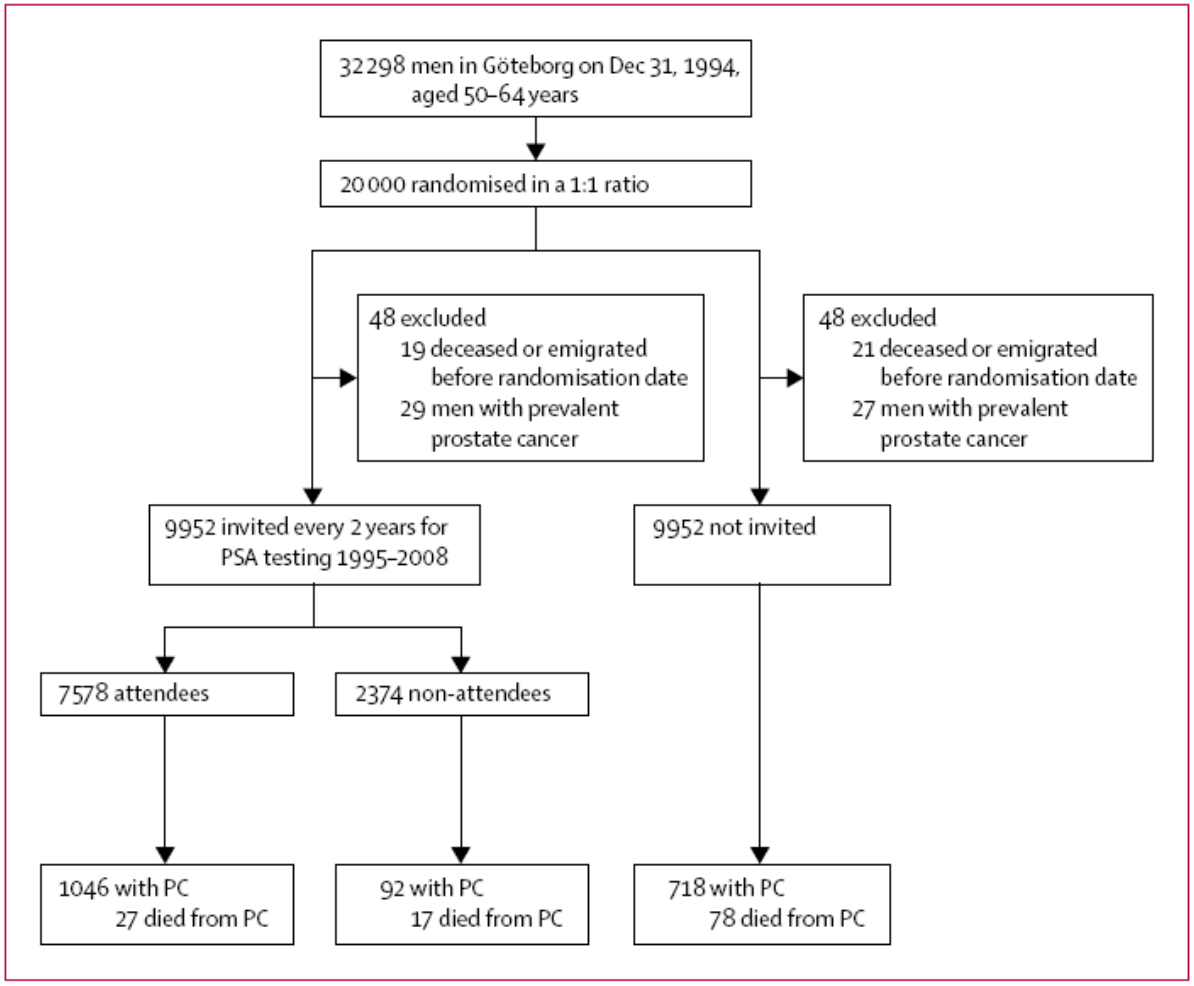


Figure 1: **Trial profile**
PSA=prostate-specific antigen. PC=prostate cancer.

Prostatacancer dödlighet I Göteborgsstudien

- 44 % om man mäter hos alla män som inbjudits(n=9952)
- 56 % hos de som inbjudits och deltagit (n=7578)
- 77 % hos de som inbjudits och deltagit och var under 60 år vid första inbjudan (n=5514)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 16, 2012 VOL. 367 NO. 7

Quality-of-Life Effects of Prostate-Specific Antigen Screening

Eveline A.M. Heijnsdijk, Ph.D., Elisabeth M. Wever, M.Sc., Anssi Auvinen, M.D., Jonas Hugosson, M.D., Stefano Ciatto, M.D.,* Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Arnauld Villers, M.D., Alvaro Páez, M.D., Sue M. Moss, Ph.D., Marco Zappa, M.D., Teuvo L.J. Tammela, M.D., Tuukka Mäkinen, M.D., Sigrid Carlsson, M.D., Ida J. Korfage, Ph.D., Marie-Louise Essink-Bot, Ph.D., Suzie J. Otto, Ph.D., Gerrit Draisma, Ph.D., Chris H. Bangma, M.D., Monique J. Roobol, Ph.D., Fritz H. Schröder, M.D., and Harry J. de Koning, M.D.

RESULTS

Per 1000 men of all ages who were followed for their entire life span, we predicted that annual screening of men between the ages of 55 and 69 years would result in nine fewer deaths from prostate cancer (28% reduction), 14 fewer men receiving palliative therapy (35% reduction), and a total of 73 life-years gained (average, 8.4 years per prostate-cancer death avoided). The number of QALYs that were gained was 56 (range, −21 to 97), a reduction of 23% from unadjusted life-years gained. To prevent one prostate-cancer death, 98 men would need to be screened and 5 cancers would need to be detected. Screening of all men between the ages of 55 and 74 would result in more life-years gained (82) but the same number of QALYs (56).

Key Results

- Mortality Reduction 35 %
- Every man saved from PC death have an average lengthening of life with 8 years
- 23 % of life years gained are lost due to impaired QoL
- The main QoL loss is due to permanent side-effects of treatment
- Number needed to treat is 5

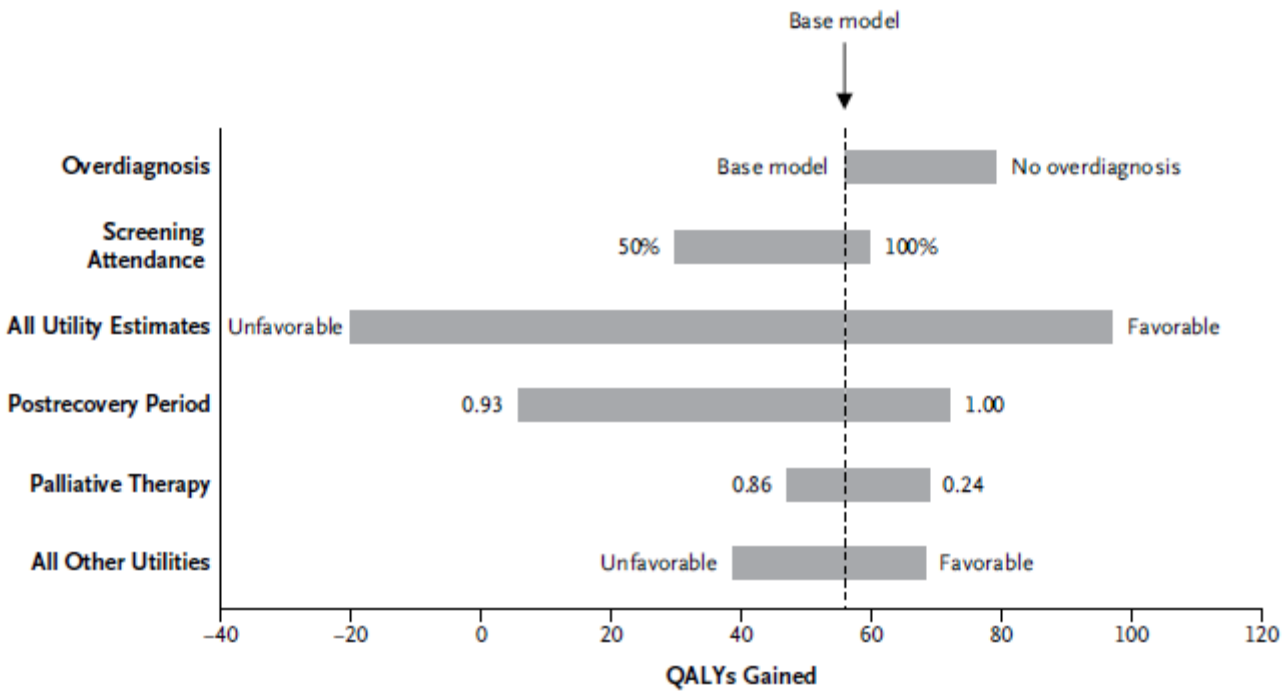


Figure 1. Effect of Various Modeling Assumptions on Quality-Adjusted Life-Years (QALYs) Gained by Prostate-Cancer Screening in Comparison with the Base Model.

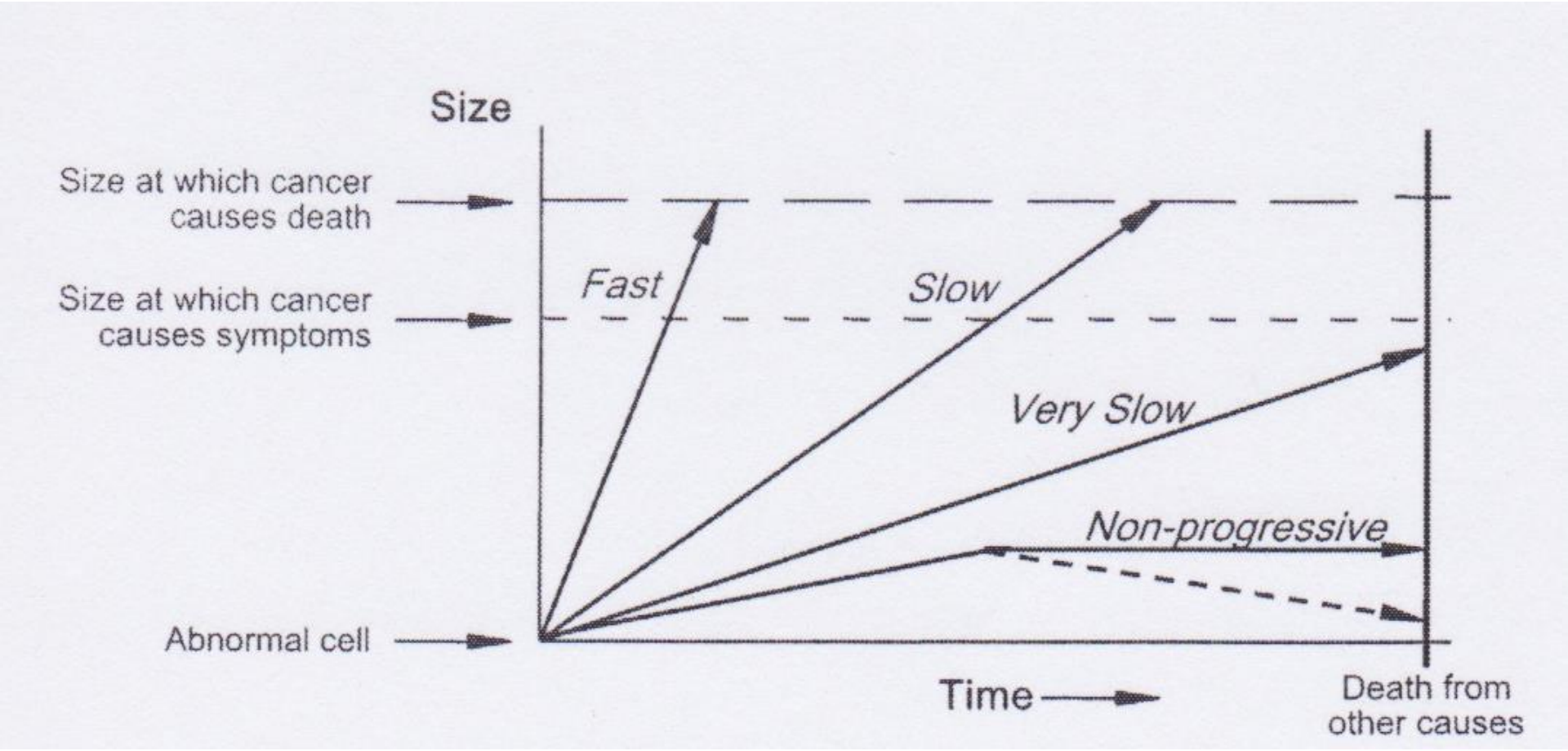
The base model predicted a gain of 56 QALYs (range, −21 to 97) for men between the ages of 55 and 69 years who underwent prostate-cancer screening, which means that 23% of the unadjusted life-years gained by screening would be counterbalanced by a loss in quality of life because of follow-up biopsies and procedures. In the base model, sensitivity analyses considered various assumptions, including the effects of overdiagnosis, screening attendance of 50% and 100%, all unfavorable and favorable utility estimates, utility estimates of 0.93 and 1.00 for the lifetime postrecovery period, utility estimates of 0.86 and 0.24 for palliative therapy, and utility estimates for the postrecovery period (0.95) and palliative therapy (0.60) as used in the base model combined with the unfavorable and favorable utility estimates of all other health states.

Problems with current diagnostic pathway

- Overdiagnosis
- Underdiagnosis
- Undergrading
- Understaging

Över-diagnostik och överbehandling

- Diagnos av en cancer som aldrig skulle gett symptom under livstiden
- Behandling av en cancer som aldrig skulle gett symptom


Size
Size at which cancer causes death
Size at which cancer causes symptoms
Abnormal cell
Fast
Slow
Very Slow
Non-progressive
Time
Death from other causes

Over-treatment is common in Medicine

- Treating men aged 49-65 with Statins because of mild hyper cholesterolemia, NNT is 26 to avoid one cardiovascular event (McEldluff, Heart 2006, 92; 1213-18)
- Treating hypertension and hypercholesterolemia in patients with type 2 diabetes result in a NNT of 7 to avoid cardio-vascular events

Over-diagnosis, background

- 30-50 % of all men in the age 50-70 years have histological cancer in the prostate
- Only 20 % of these cancers have volume > 0,5 cc (Stamey and McNeal 1991)
- At least 30 % of cancers found in a PSA based screening program have a volume < 0.5 cc (Hugosson et al 2010)
- Many patients with a cancer volume > 0.5 cc will not progress due to short survival

How large is the risk of over-diagnosis in a PSA based screening program?

- The life-time risk of being diagnosed with PC have doubled, in Sweden from 10 % in the pre PSA era to 20 % in our screeningstudy
- This is in line with simulation models where 49 % of PSA detected cancers were classified as over-diagnosed (Steyerberg 2003)

Current diagnostic pathway with systematic biopsies in all men with elevated PSA result in over-diagnosis

- Current diagnostic pathway is based upon systematic biopsies aiming to cover the whole peripheral zone
- PSA has a low specificity, PPV in a screening study is around 25 %, but only 15 % have a significant cancer (Hugosson et al 2010)
- Every time a man with elevated PSA undergo systematic biopsies there is 10 % risk of diagnosing an insignificant cancer

Pre biopsy MRI and only targeted directed biopsies??

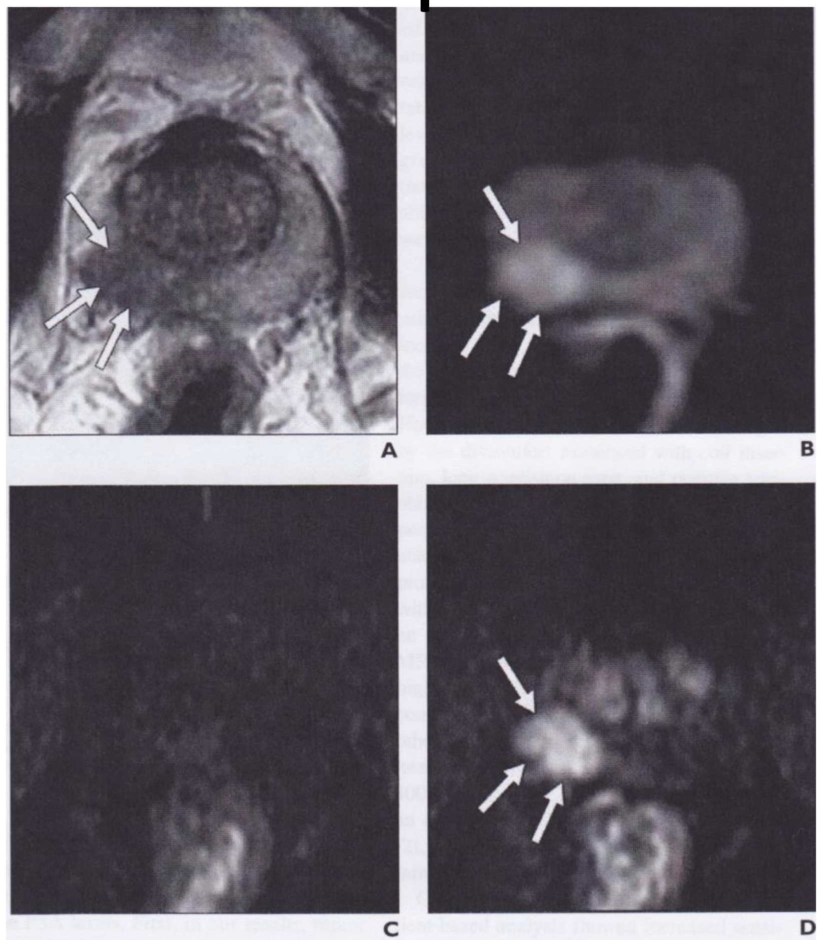


Fig. 2—72-year-old man with prostate-specific antigen level of 4.22 ng/mL and positive results of transrectal biopsy. Transverse MRI of prostate indicated Gleason score of 9 in middle right and transition zone (TZ) right regions.
A, T2-weighted fast spin-echo image (3600/102) shows peripheral zone (PZ) cancer (*arrows*) in middle right region as homogeneous hypointense lesion with mass effect.
B, Diffusion-weighted image shows PZ cancer (*arrows*) as focal hyperintensity.
C and **D,** PZ cancer is seen as focal early enhancement on dynamic contrast-enhanced MRI using liver acquisition with volume acceleration sequence in first (unenhanced; **C**) and fourth (*arrows*, **D**) phases. Cancer lesion in TZ right region could not be detected by any of three MRI techniques.

Is mpMRI of the prostate the solution of current diagnostic problems?

- Is the risk of over-diagnosis decreased?
- What is the sensitivity of significant cancers?
- What is the features of these cancers missed with mpMRI
- What is the equipment needed? 1.5 T or 3T?
- How large is the interobserver variation in reading the MRI?
- How are biopsies best guided towards MRI lesions?

BJUI
BJU INTERNATIONAL

Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection

Jérémie Haffner*, Laurent Lemaitre†, Philippe Puech†, Georges-Pascal Haber§, Xavier Leroy‡, J. Stephen Jones§ and Arnauld Villers*

*Department of Urology, †Department of Radiology and ‡Department of Pathology, Université Lille Nord de France, F-59000 Lille, France; INSERM, U703, F-59120 Loos, France; CHU Lille, F-59000 Lille, France, and §Glickman Urological & Kidney Institute CCF, USA

Accepted for publication 26 November 2010

Haffner et al BJUI 2011

- 555 pts who had a pre biopsy mpMRI
- All had 12 systematic + possible targeted bx
- 302 PC detected
- 249 (82%) were classified as significant

- 63 % had pos MRI
- Systematic biopsies detected 237 significant and 53 non significant cancers
- Targeted biopsies detected 236 significant and none of the non significant cancers

Studies using systematic biopsies as a reference test

- The most accepted definition of indolent disease is:
- less than 3 or 4 positive biopsy cores with
- no Gleason pattern 4 or 5 and
- ≤3 to 5 mm involvement of any biopsy core.
- MRI negative predictive value (NPV) for Gleason score 7 or greater was ranging from 91 to 97%.

Vargas, J Urol 2012

Studies using transperineal template mapping biopsies as a reference test.

- Almost all authors reporting series of TTMP use the same significant cancer definition as those using 12-core systematic biopsy

- MRI NPV for Gleason score 7 or greater ranged from 79 to 89%

Arumainayagam N Radiology 2013

Studies using RP histopathology as a reference test

- On ROC analysis AUC value for MRI tumor volume in estimating tumors larger than 0.5 cc at histopathology was 0.949.
- In patients eligible for active surveillance, those with non-suspicious MRI had decreased likelihood of Gleason ≥7 disease or stage ≥pT3 compared to those with suspicious MRI (7.7% vs. 47.6%, respectively p= 0.01)

Turkbey B J Urol 2012

Borofsky MS Urology 2013

Prostate MRI findings with radical prostatectomy

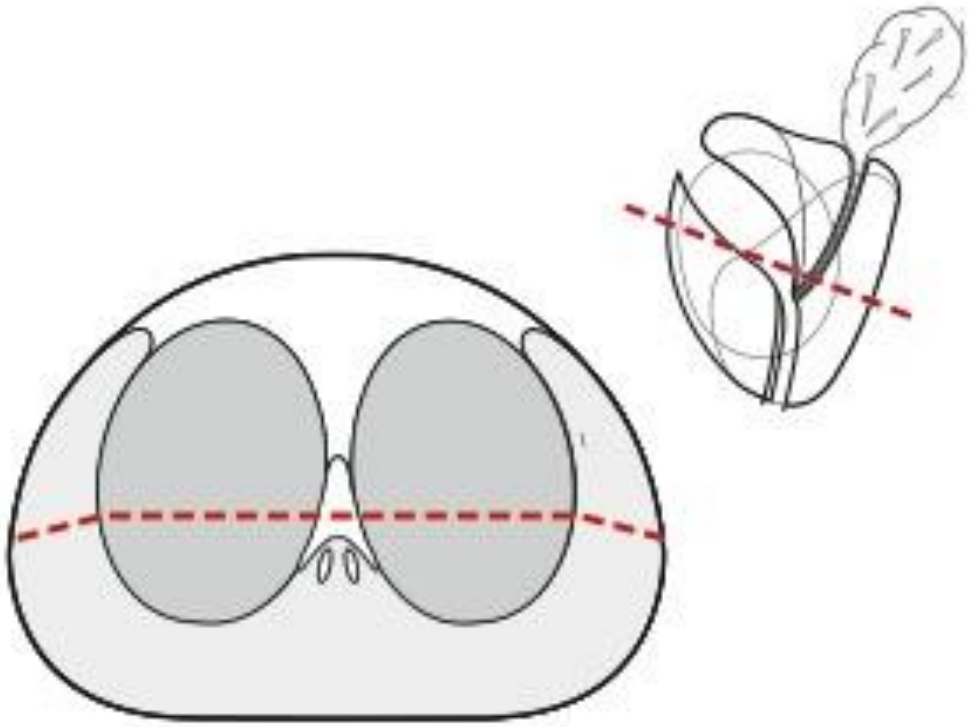
- 3T MP-MRI (N=133).
- Lesions were identified on MRI in 126 (95%) cases.
- MRI showed sensitivity of 93%, PPV of 57%, and overall accuracy of 92% in predicting insignificant pathologic disease (defined as tumour volume <0.5 ml, no Gleason pattern 4) outperforming Epstein, d'Amico and CAPRA criteria

Turkbey Radiology. 2013

19% of cancers are anterior, not sampled by posterior systematic biopsies

The anterior region starts 17mm (biopsy core length) from the prostatic posterior surface (red dotted line)

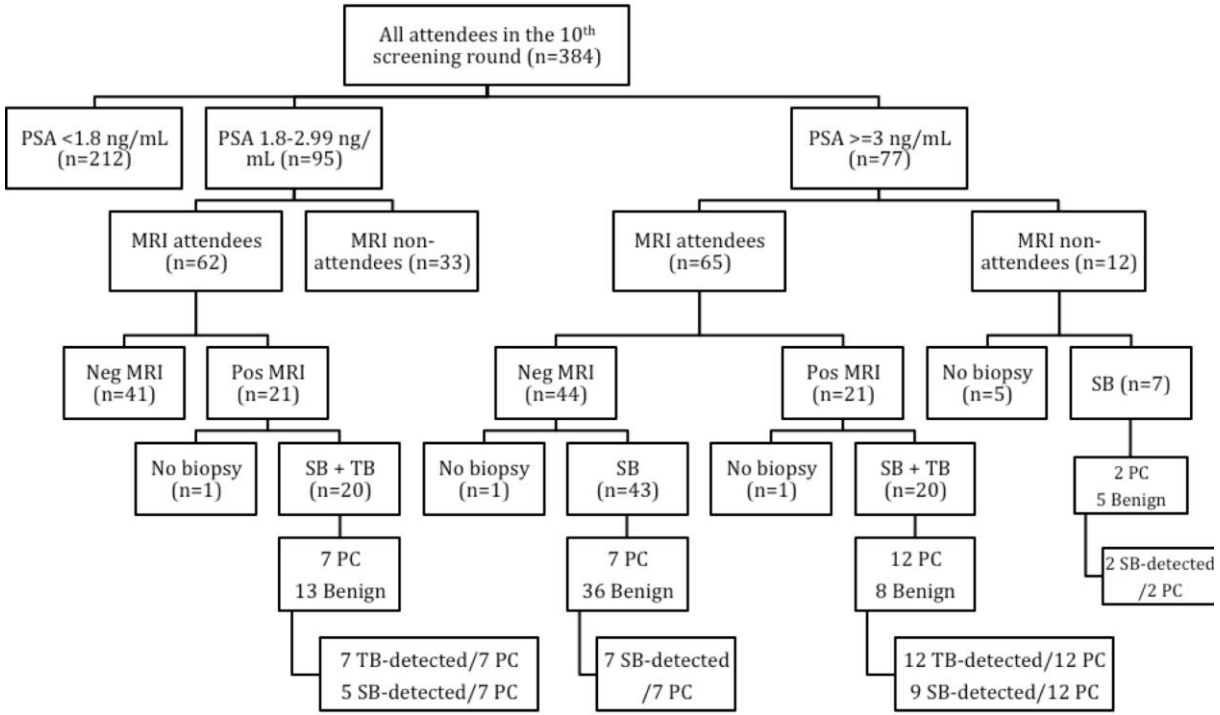
A 12-core extended biopsy scheme would be expected to sample only the 12 posterior sectors



Dickinson L Eur Urol 2011
Ouzzane A, Villers BJUI 2012

Göteborg study (Grenabo et al 2015)

Figure 1.



Cancers detected with mpMRI and targeted bx in the PSA range 1.8-2.99

A)

	PSA	T-stage	Gleason	Biopsy mode	No. of sectors with cancer	Modified Epstein criteria
1	2.32	T2a	3+4=7	SB + TB	5/ 10	S
2	2.57	T2a	3+4=7	SB + TB	6/10	S
3	1.82	T1c	3+4=7	SB + TB	5/10	S
4	1.94	T2a	3+3=6	SB + TB	2/10	S
5	2.04	T1c	3+3=6	SB + TB	2/10	IS
6	2.94	T1c	3+3=6	TB	2/10	S
7	2.89	T1c	3+3=6	TB	1/10	IS

B)

Cancers detected with systematic bx and a normal mpMRI

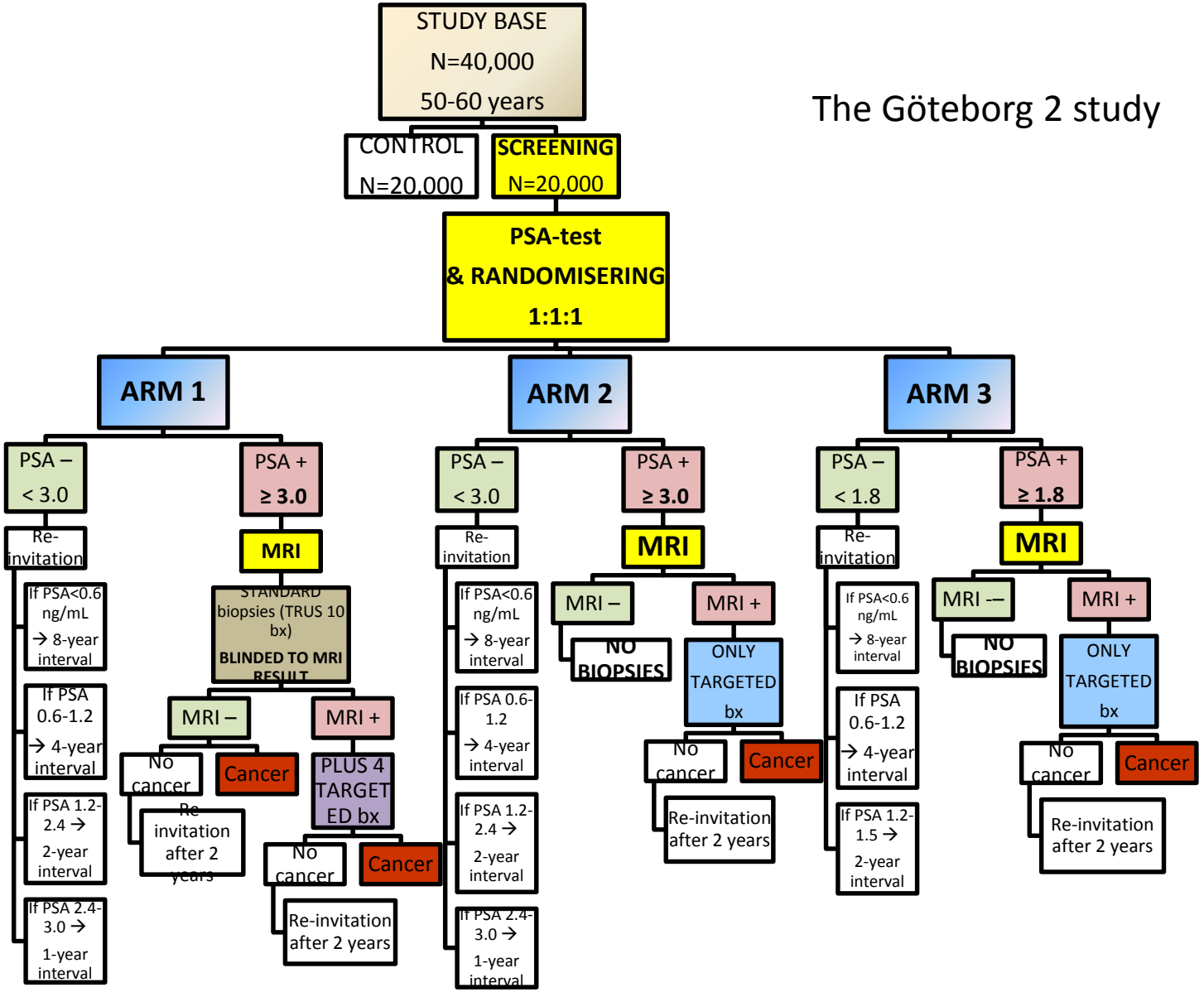
B)

	PSA	T-stage	Gleason	Biopsy mode	No. of sectors with cancer	Modified Epstein criteria
1	3.47	T1c	3+3=6	SB	1/10	IS
2	4.05	T1c	3+3=6	SB	3/10	S
3	3.53	T1c	3+3=6	SB	1/10	IS
4	3.32	T1c	3+4=7	SB	1/10	S
5	6.83	T1c	3+4=7	SB	4/10	S
6	4.04	T1c	3+3=6	SB	1/10	S
7	3.03	T1c	3+3=6	SB	1/10	IS

Conclusions

- Both systematic and targeted bx miss significant cancers
- The “risk” of detecting non significant cancers is much lower if only targeted bx are performed
- Large randomised studies are needed to confirm the safety before changing from systematic to targeted biopsies only

The Göteborg 2 study



mpMRI in FU of Active Surveillance patients

- At the moment there is increasing evidence that mpMRI is of value in patients on AS
- We still lack long-term longitudinal studies comparing progression on biopsies and on mpMRI (Moore et al Eur Urol 2014)

Cost benefit analys (JNCI 2014)

- Kostnaden för att rädda en man från att dö av prostatacancer är relativt billig , lägre än för bröstcancer
- Men…Det som driver kostnaden och orsakar sänkt livskvalitet är risken för att bli behandlad i onödan.

European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Outcome Following Active Surveillance of Men with Screen-detected Prostate Cancer. Results from the Göteborg Randomised Population-based Prostate Cancer Screening Trial

Rebecka Arnsrud Godtman [a,*], *Erik Holmberg* [b], *Ali Khatami* [a], *Johan Stranne* [a], *Jonas Hugosson* [a]

[a] *Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Göteborg, Göteborg, Sweden;* [b] *Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Göteborg, Göteborg, Sweden*

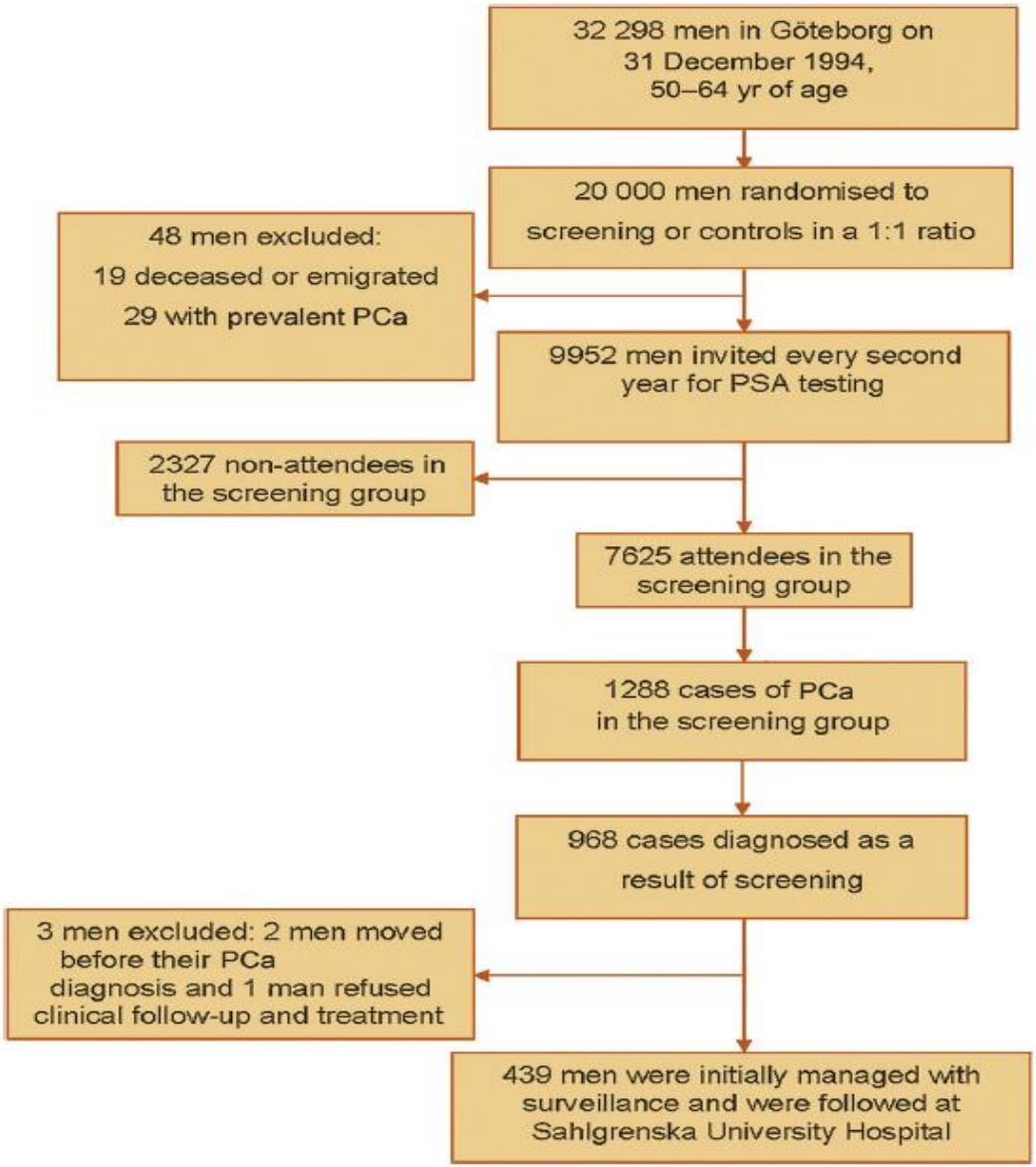


Fig. 1 – Consolidated Standards of Reporting Trials diagram of the Göteborg randomised, population-based prostate cancer screening trial.
PCa = prostate cancer; PSA = prostate-specific antigen.
*** Treatment strategy was chosen at the discretion of the treating physician and patient.**

Fördelning riskgrupper screeningstudien Göteborg

Risk grupp	Samtliga med PC diagnos	De som ej fått aktiv behandling primärt
Låglåg	224	180 (80%)
Låg	357	161 (45%)
Mellan	309	95 (31%)
Hög	62	6 (10%)
Avancerad	13	0
Totalt	965	442 (46%)

För att optimera behandling till de som behöver behandling

- Avvakta med behandling hos de med väldigt liten och långsamväxande tumör
- Intensifiera behandlingen hos patienter med aggressiv tumör

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

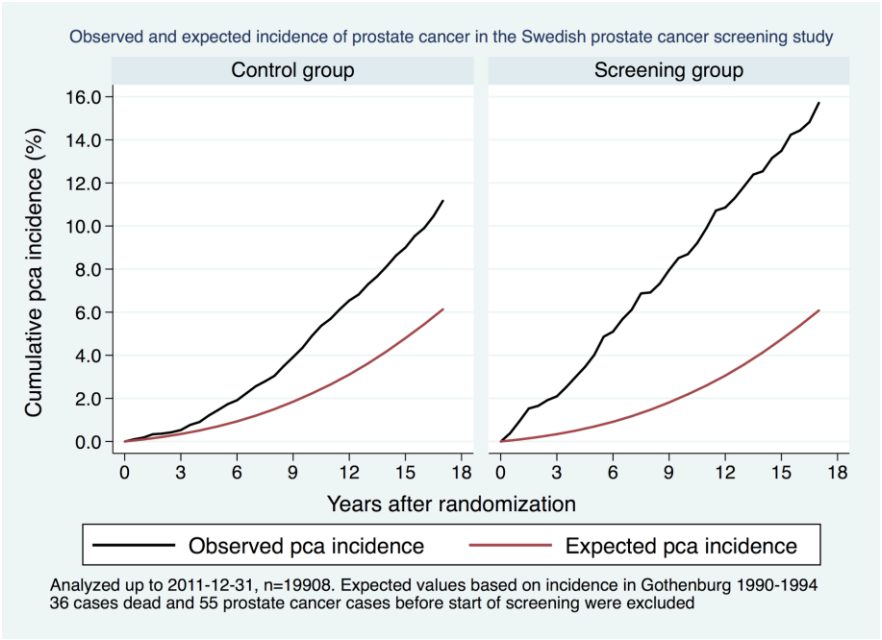
Department of Urology (Prof J Hugosson MD, S Carlsson MD, G Aus MD, S Bergdahl MD, A Khatami MD,

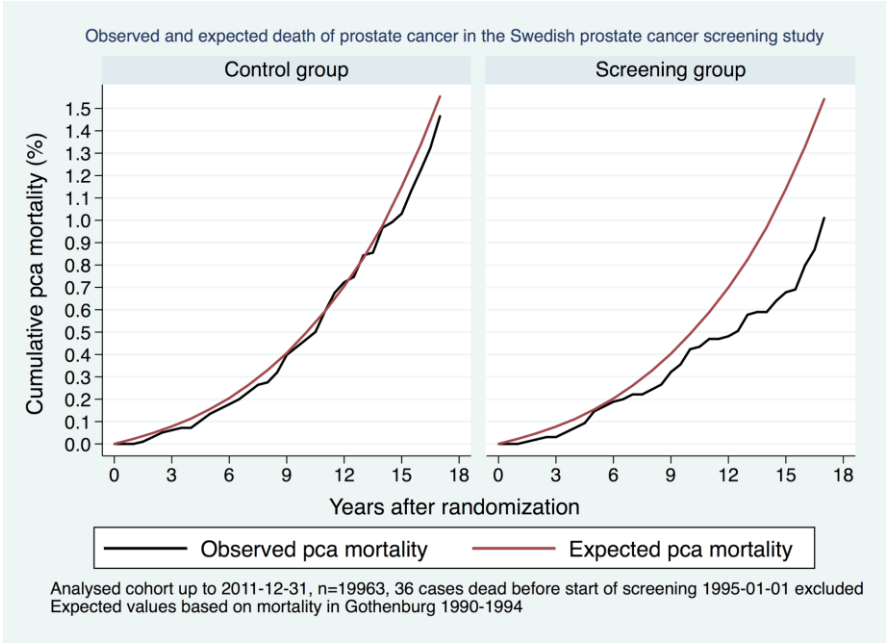
In dec 1994 10,000 were randomised (before consent) to screenig and 10,000 to controls
Invitation every 2 year
PSA cut-off 3.4 (95-98)
PSA cut off 2.9 (98-04)
Psa cut off 2.5 (05 and onwards)

	2008	2010
Median FU	14 years	16 years
Number of PC deaths CG	78	98
Number of PC detahs SG	44	60
Absolute risk reduction	0.34 %	0.38 %
Relative risk reduction	44%	39%
NNI	293	208
NND	12	9

The Gothenburg Screening Trial, 16 years FU

Observed Incidence and Mortality compared to expected pre PSA (1990-94)





Cumulative incidence screening group = 14.4%
Cumulative incidence control group = 9.9%
Expected incidence rate = 5.4%

Cumulative mortality screening group = 0.77%
Cumulative mortality control group = 1.25%
Expected Mortality rate = 1.45%

NNS (SG vs CG)= 208
NNS (SG vs exp)=147
NNS (CG vs exp)=500

NND (SG vs CG)= 9
NND (SG vs exp)=13
NND (CG vs exp)=23

Ny smartare screening

- Bättre markörer än PSA
- Involvera Magnetkamera i diagnostiken
- Screena män med hög risk intensivt och män med låg risk betydligt mer sällan

Konklusioner

- En man som regelbundet testar sitt PSA minskar sin risk att dö av prostata cancer med cirka hälften
- Samtidigt fördubblar han sin risk att få diagnosen prostatacancer
- Bara en fjärdel av de män som idag får diagnosen prostatcancer pga PSA testning skulle dö av sin cancer om man lämnade den obehandlad
- Oorganiserad screening är betydligt mindre effektiv än organiserad screening.
- Många män som får diagnosen prostatcancer bör rekommenderas att inte behandlas med strålbehandling eller operation

Konklusioner

- Om man överväger behandling bör man välja rätt kirurg
- Innan man bestämmer sig för att kolla sitt PSA värde bör man vara medveten om risken för över diagnostik och att bli behandlad i onödan med de biverkningar som kan följa
- Magnetkamera undersökning kan vara en framtida metod att minska risken för överdiagnostik

Konklusion

- Alla män borde få chansen att bestämma själv om man vill delta i ett hälsoprogram (screening) för tidig diagnostik av prostatacancer. Varje man över 50 års ålder borde få information om fördelar respektive de nackdelar som finns med att testa sig.