Prostate Cancer Screening: What We've Learned and Where we should go

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Disclosures

- Consultant/Advisor – Augmenix, Bayer, Blue Earth Diagnostics, Genomic Health, Myriad Genetics
- Investigator – Johnson & Johnson, Medivation, Traxxsson
- Funding: NCI and NIDDK

Outline

- Overview of Screening
- Results and limitations of randomized trials (US PLCO and European ERSPC)
- Current Specialty Society Guidelines
  - American Urologic Association
  - European Association of Urology
- Potential future improvements
  - New Biomarkers
  - Better Biopsy

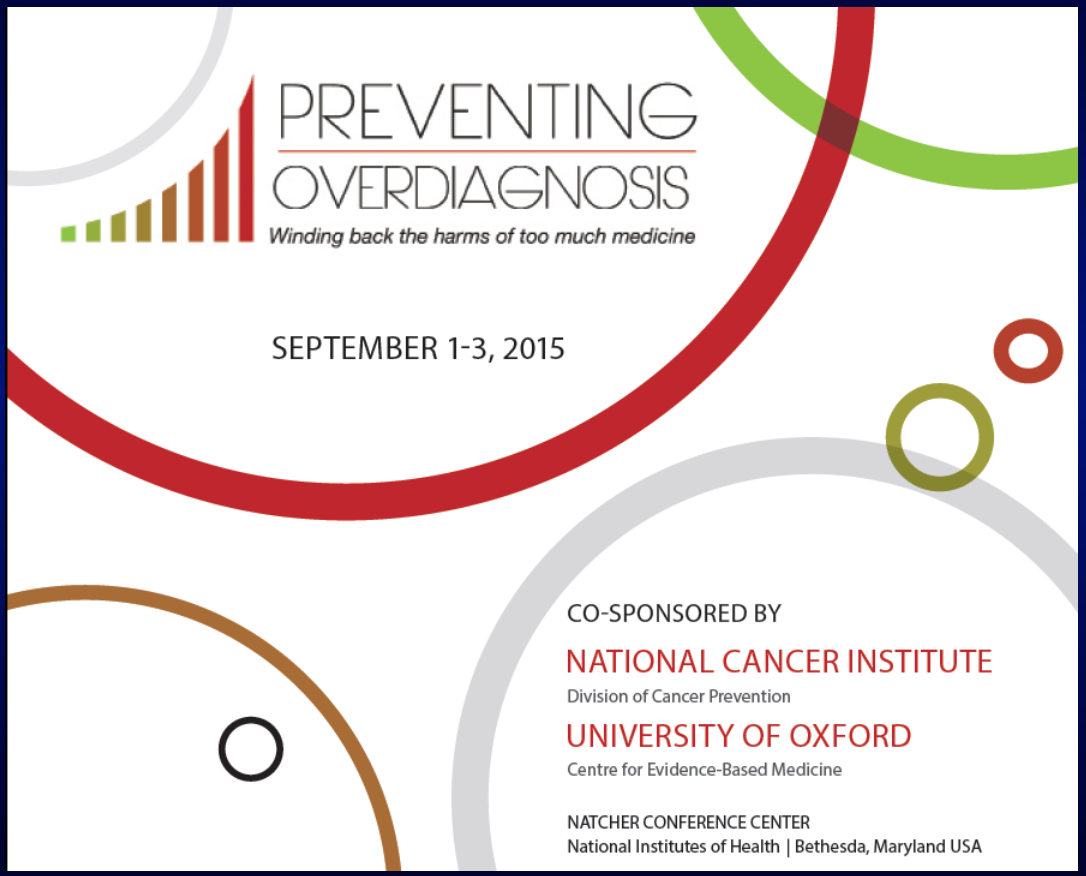
Prostate Cancer Screening: What We've Learned

- "Mass" population screening has a small effect on CaP mortality: 0-0.9% ARR (~3% → 2.1%)
  - PLCO: no benefit for entire group
  - ERSPC: 20-30% RRR in subgroup
    - 2 sites (Goteborg and Rotterdam) drive results
    - all sites have not reported
    - all patients not reported
    - treatment differences between arms may explain some of the effect
- Significant risk of "overdiagnosis"
- Significant risk of "overtreatment"
- Treatment has side effects
- Costly in human and economic terms

Factors promoting overdiagnosis of cancer

- Existence of a silent disease reservoir
- Activities leading to its detection (particularly screening)
- Long natural history and hence limited cancer-specific mortality

G. Welch and W. Black, JNCI, 2010


PREVENTING
OVERDIAGNOSIS
Winding back the harms of too much medicine
SEPTEMBER 1-3, 2015
CO-SPONSORED BY
NATIONAL CANCER INSTITUTE
Division of Cancer Prevention
UNIVERSITY OF OXFORD
Centre for Evidence-Based Medicine
NATCHER CONFERENCE CENTER
National Institutes of Health | Bethesda, Maryland USA

Prevalence of CaP on Autopsy

Age Range	Black (%)	White (%)
20-29	8	11
30-39	31	31
40-49	43	38
50-59	46	44
60-69	72	68
70-79	77	68

Powell et al: J Urol 183: 1792-6, 2010

Prevalence of Prostate Cancer on Autopsy: Cross-Sectional Study on Unscreened Caucasian and Asian Men

Alexandre R. Zlotta, Shin Egawa, Dmitry Pushkar, Alexander Govorov, Takahiro Kimura, Masahito Kido, Hiroyuki Takahashi, Cynthia Kuk, Marta Kovylina, Najla Aldaoud, Neil Fleshner, Antonio Finelli, Laurence Klotz, Jenna Sykes, Gina Lockwood, Theodorus H. van der Kwast

J Natl Cancer Inst

Table 1. Baseline characteristics of patients*

Characteristics	Mean (range) ASI n = 100	CAU n = 220
Age, years	68.5 (24–89)	62.5 (22–80)
History of cancer, non-PCa	59 (59.0)	26 (11.8)
Prostate weight, g	31.9 (10.2–144.5)	40.0 (13.2–150.6)
Prostate cancer	35 (35)	82 (37.3)
Gleason score		
4	0 (0.0)	4 (4.9)
5	1 (2.9)	10 (12.2)
6	16 (45.7)	49 (59.8)
7	14 (40.0)	16 (19.5)
8	2 (5.7)	3 (3.7)
9	2 (5.7)	0 (0.0)
7–10	18 (51.4)	19 (23.2)
8–9	4 (11.4)	3 (3.6)
Focality§		
Unifocal	24 (68.6)	59 (72.0)
Multifocal	9 (25.7)	18 (22.0)
Tumor volume		

Prevalence of Prostate Cancer on Autopsy: Cross-Sectional Study on Unscreened Caucasian and Asian Men

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Table 3. Prevalence of Gleason score 7 or greater cancers in Asian and Caucasian men (core group aged 50–80 years)

	Asian men		Caucasian men		
Age, years	HG*, No.	% HG	HG*, No.	% HG	*P*
51–60	0/1	0	4/13	30.8	.99
61–70	2/8	25	4/25	16.0	.62
51–70	2/9	22.2	8/38	21.1	.99
71–80	9/16	56.3	10/34	29.4	.12

* HG = high grade/ Gleason score of 7 or greater.

RR of screen-detected cancer v. 25 year risk of various CaP Endpoints

PSA (ng/ml)	PCPT (repeat screening) (Sextant Bx.)		
	Clinical diagnosis	Distant metastasis	Cancer-specific mortality
<1.0	2.7 (1.9, 4.2)	21.6 (9.6, 69.5)	64.9 (18.2, 72.9)
0.5	2.7 (1.8, 4.5)	38.0 (15.2, 192.3)	153.4 (48.2, 219.7)
1.0	2.8 (2.3, 3.5)	14.5 (9.7, 27.2)	28.8 (15.4, 92.1)
2.0	1.6 (1.5, 2.0)	4.7 (4.2, 6.1)	5.7 (5.1, 7.5)
3.0	1.3 (1.1, 1.5)	3.4 (2.6, 4.0)	4.0 (3.0, 4.7)
4.0	1.2 (0.8, 1.3)	2.7 (1.8, 3.2)	3.2 (2.0, 3.9)
5.0	1.1 (0.7, 1.2)	2.3 (1.3, 2.8)	2.7 (1.5, 3.4)
7.5	0.9 (0.4, 1.1)	1.7 (0.8, 2.1)	2.0 (0.8, 2.7)
10.0	0.8 (0.3, 1.0)	1.3 (0.5, 1.8)	1.6 (0.5, 2.3)

Vickers *et al. BMC Medicine* 2014, 12:26

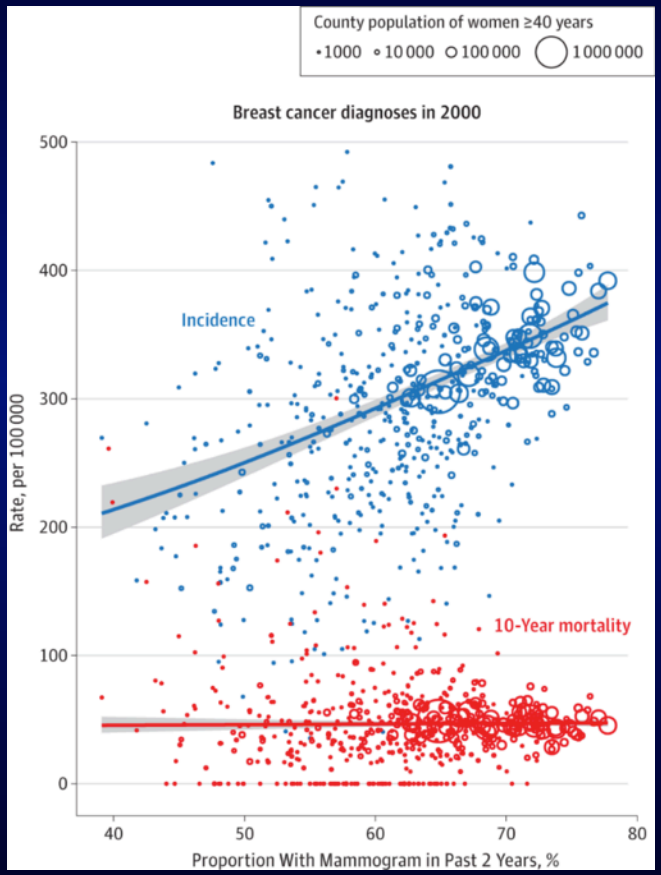
Breast Cancer Screening: Benefits and Harms

JAMA December 17, 2014 Volume 312, Number 23 2585

60% False+

10% Unnecessary Bx

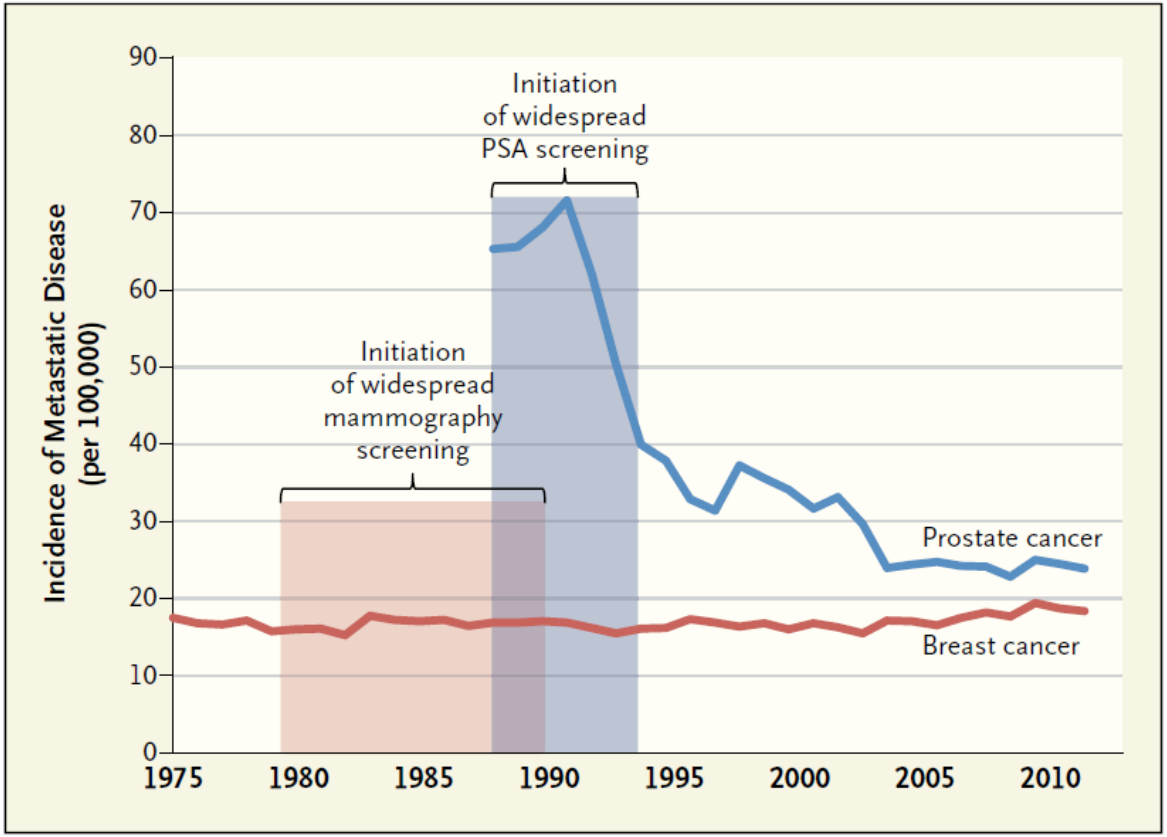
Breast Cancer Screening, Incidence, and Mortality Across US Counties



JAMA Intern Med. Published online July 06, 2015. doi:10.1001/jamainternmed.2015.3043

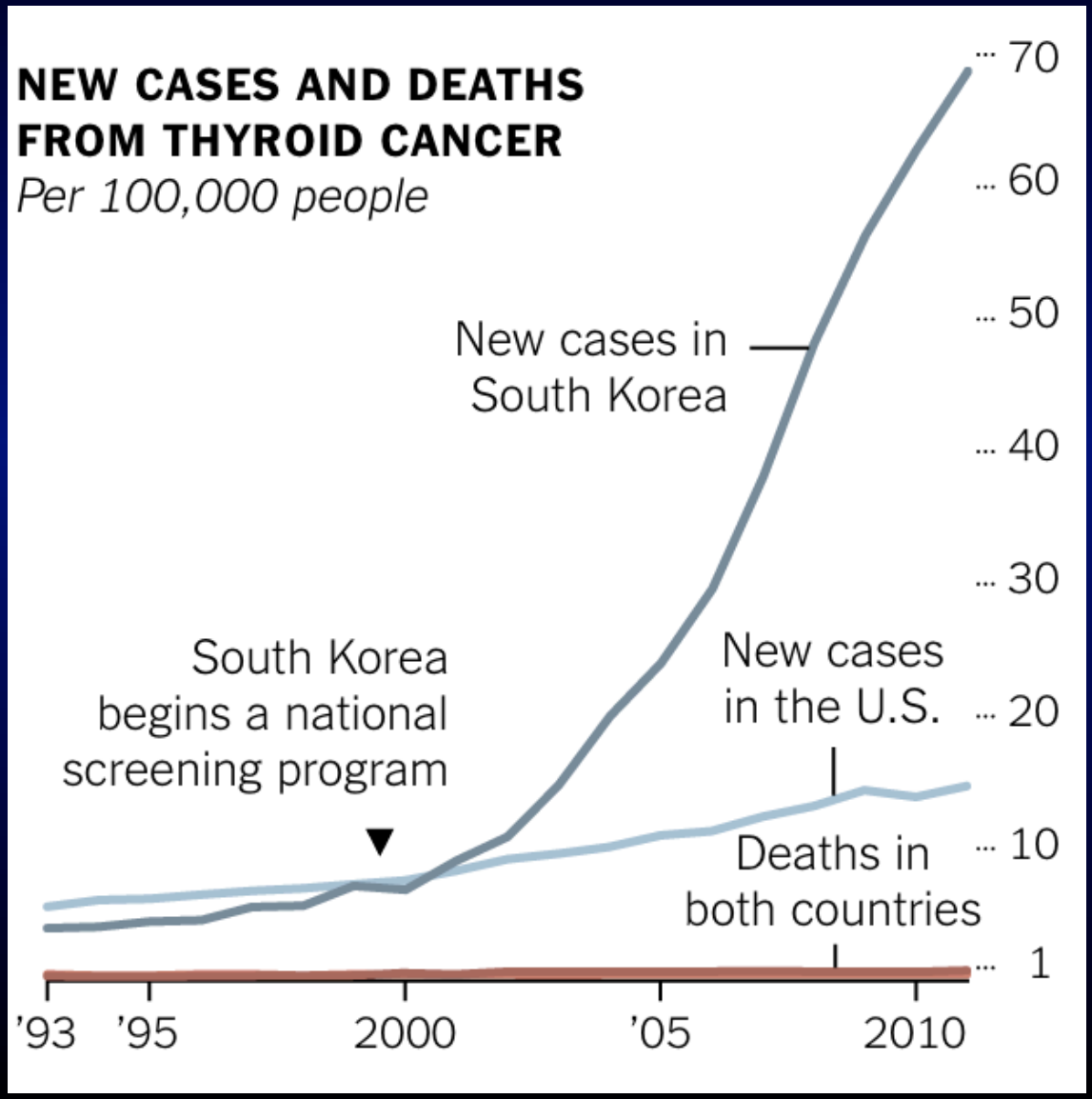
Trends in Metastatic Breast and Prostate Cancer — Lessons in Cancer Dynamics

H. Gilbert Welch M.D., M.P.H., David H. Gorski, M.D., Ph.D., and Peter C. Albertsen, M.D.



N ENGL J MED 373;18 NEJM.ORG OCTOBER 29, 2015

Overdiagnosis by Screening
Ahn et al: NEJM 2014, 371: 1765-67



OPEN ACCESS Freely available online PLoS MEDICINE

Immediate Risk for Cardiovascular Events and Suicide Following a Prostate Cancer Diagnosis: Prospective Cohort Study

Katja Fall[1,2]*, Fang Fang[1,3], Lorelei A. Mucci[2,3], Weimin Ye[1], Ove Andrén[4], Jan-Erik Johansson[4], Swen-Olof Andersson[4], Bär Sparén[1], Georg Klein[5], Meir Stampfer[2,3], Hans Olov Adami[1,2], Unnur Valdimarsdóttir[1,6]

December 2009 | Volume 6 | Issue 12 | e1000197

Table 3. RRs of death from specific cardiovascular events during the first week and the first 4 wk after the diagnosis of prostate cancer by history of cardiovascular disease in Sweden, 1990–2004.

Category	All Cardiovascular Events		Myocardial Infarction	Embolism/Thrombosis	Other Heart Disease	Acute Cerebro-Vascular Events
	n	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Men without a history of cardiovascular events						
Cancer-free	51,378	1.0	1.0	1.0	1.0	1.0
PCa, 1 wk after diagnosis	38	4.8 (3.2–6.9)	4.8 (2.8–7.5)	18.3 (7.1–37.5)	5.9 (1.9–14.9)	—
PCa, 4 wk after diagnosis	84	2.9 (2.2–3.7)	2.9 (2.0–3.9)	10.1 (4.3–19.9)	2.7 (1.2–5.7)	3.5 (1.3–7.1)
Men with a history of cardiovascular events						
Cancer-free	204,627	1.0	1.0	1.0	1.0	1.0
PCa, 1 wk after diagnosis	116	2.8 (2.0–3.8)	3.9 (2.9–5.1)	7.9 (3.6–14.7)	4.8 (2.4–8.3)	1.3 (0.4–3.3)
PCa, 4 wk after diagnosis	265	1.8 (1.4–2.2)	2.1 (1.4–2.2)	4.0 (2.0–7.0)	2.4 (1.4–3.8)	1.1 (0.6–1.9)

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December 2009 | Volume 6 | Issue 12 | e1000197

Table 4. Incidence rates and RRs of suicide during the first year after the diagnosis of prostate cancer in Sweden, 1961–2004.

Category		Suicide	IR per 1,000 person-years	RR[a] (95% CI)
Totals	Cancer-free	31,822	0.3	1.0
	PCa	136	0.9	2.6 (2.1–3.0)

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

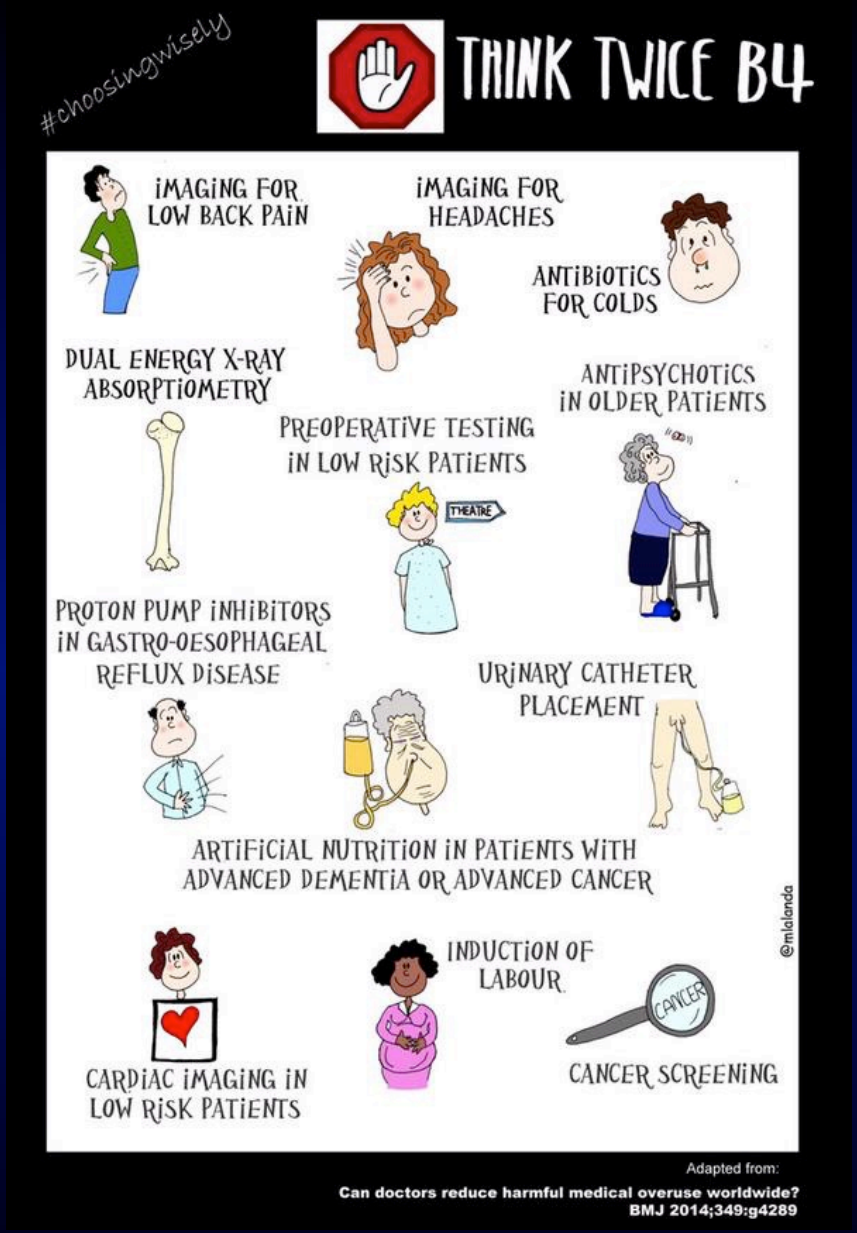
Eveline A.M. Heijnsdijk, Ph.D., Elisabeth M. Wever, M.Sc., Anssi Auvinen, M.D., Jonas Hugosson, M.D., Stefano Ciatto, M.D.,* Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Arnauld Villers, M.D., Alvaro Páez, M.D., Sue M. Moss, Ph.D., Marco Zappa, M.D., Teuvo L.J. Tammela, M.D., Tuukka Mäkinen, M.D., Sigrid 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.

Table 3. Effect of Various Health States with and without Annual Screening for Prostate Cancer over the Lifetime of 1000 Men between the Ages of 55 and 69 Years.*

Health State	Utility Loss	No Screening	Screening	Difference between Screening and No Screening	Quality Adjustment
		no. of men		*no. of life-yr†*	*no. of life-yr (range)‡*
Screening attendance	−0.01	0	8242	8242	158	−1.6 (−1.9 to −0.3)
Biopsy	−0.10	313	605	292	17	−1.7 (−2.2 to −1.0)
Cancer diagnosis	−0.20	112	157	45	4	−0.7 (−0.9 to −0.6)
Radiation therapy						
At 2 mo after procedure	−0.27	43	48	5	1	−0.2 (−0.2 to −0.1)
At >2 mo to 1 yr after procedure	−0.22	43	48	5	4	−0.9 (−1.6 to −0.5)
Radical prostatectomy						
At 2 mo after procedure	−0.33	32	68	35	6	−2.0 (−2.7 to −0.6)
At >2 mo to 1 yr after procedure	−0.23	32	68	35	30	−6.9 (−9.1 to −2.7)
Active surveillance	−0.03	28	48	20	106	−3.2 (−15.8 to 0)
Postrecovery period						
No overdiagnosis	−0.05	75	71	−4	109	−5.5 (−36.4 to 0)
Overdiagnosis	−0.05	0	45	45	215	−10.8 (−30.3 to 0)
Palliative therapy	−0.40	40	26	−14	−35	14.1 (5.1 to 26.9)
Terminal illness	−0.60	31	22	−9	−4	2.6 (2.6 to 3.3)

* The rate of attendance at screenings was assumed to be 80%. The total adjustment in the number of life-years owing to all health effects was −16.7 (range, −93.8 to 24.4).
† The difference in the number of men who underwent screening and those who did not undergo screening has been multiplied by the duration of the health states (as shown in Table 1).
‡ The difference in life-years for each health state has been multiplied by the utility loss to calculate the adjustment for quality of life.

N ENGL J MED 367;7 NEJM.ORG AUGUST 16, 2012



Endorsed By WHO And other European societies

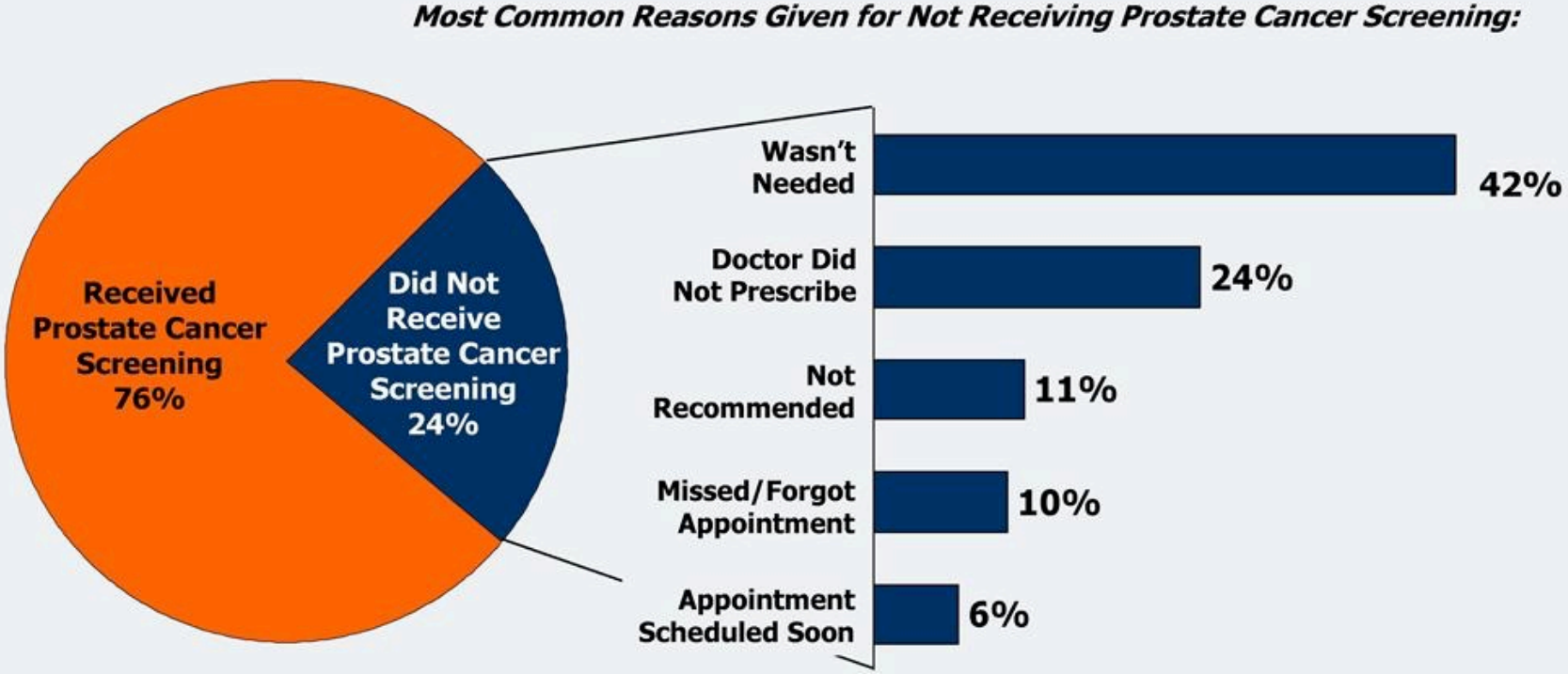
Factors promoting overdiagnosis of cancer

- Existence of a silent disease reservoir
- Activities leading to its detection (particularly screening)

G. Welch and W. Black, JNCI, 2010

Preventive Service Utilization by Male Medicare Beneficiaries, 2008

Prostate Cancer Screening



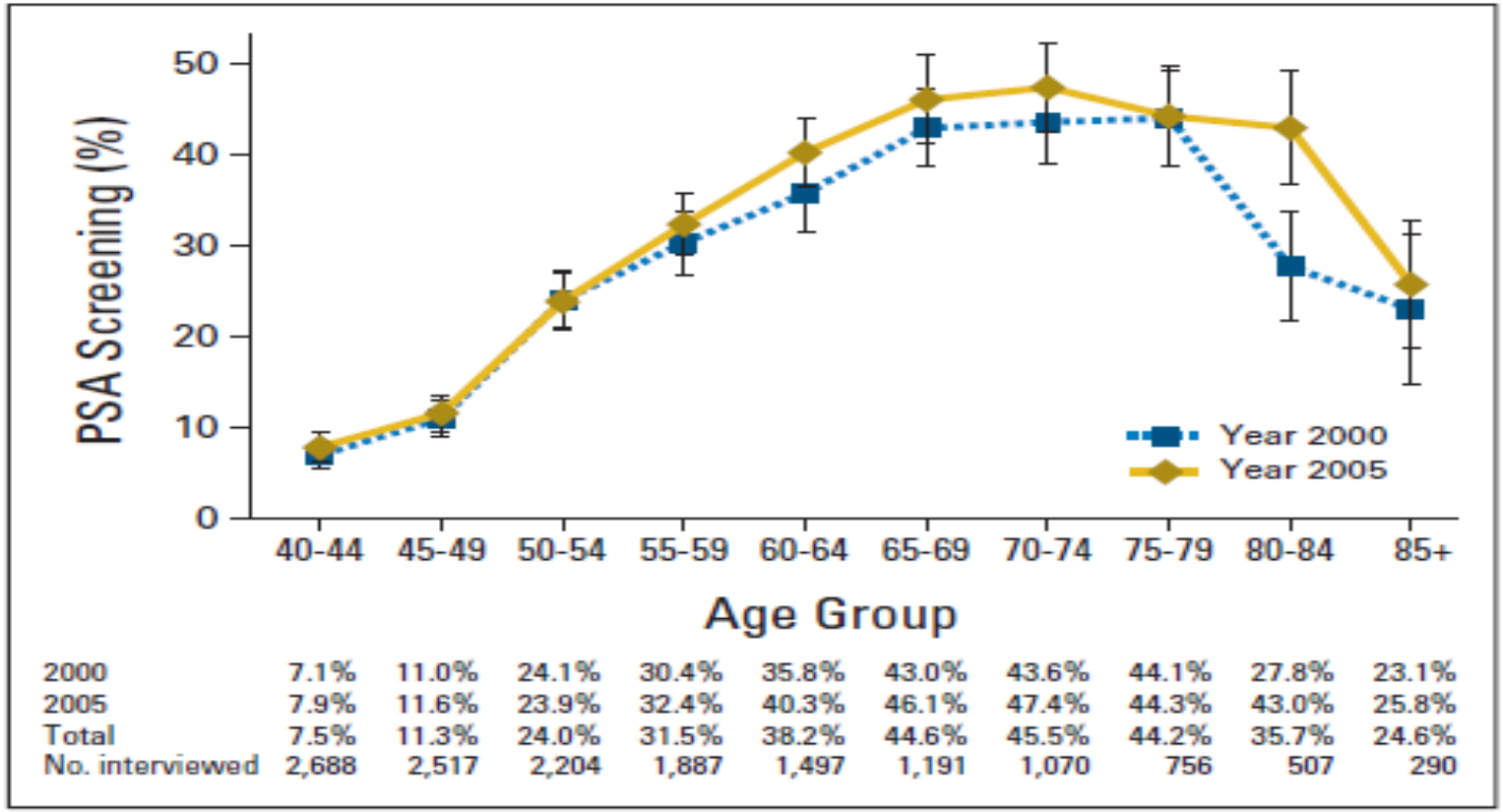
VOLUME 29 · NUMBER 13 · MAY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Population-Based Patterns and Predictors of Prostate-Specific Antigen Screening Among Older Men in the United States

Michael W. Drazer, Dezheng Huo, Mara A. Schonberg, Aria Razmaria, and Scott E. Eggener



	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2000	7.1%	11.0%	24.1%	30.4%	35.8%	43.0%	43.6%	44.1%	27.8%	23.1%
2005	7.9%	11.6%	23.9%	32.4%	40.3%	46.1%	47.4%	44.3%	43.0%	25.8%
Total	7.5%	11.3%	24.0%	31.5%	38.2%	44.6%	45.5%	44.2%	35.7%	24.6%
No. interviewed	2,688	2,517	2,204	1,887	1,497	1,191	1,070	756	507	290

Fig 1. Estimated prevalence of prostate-specific antigen (PSA) screening (with 95% CIs) within the past year by year and age, National Health Interview Survey 2000 and 2005.

National Trends in Prostate Cancer Screening Among Older American Men With Limited 9-Year Life Expectancies

Evidence of an Increased Need for Shared Decision Making

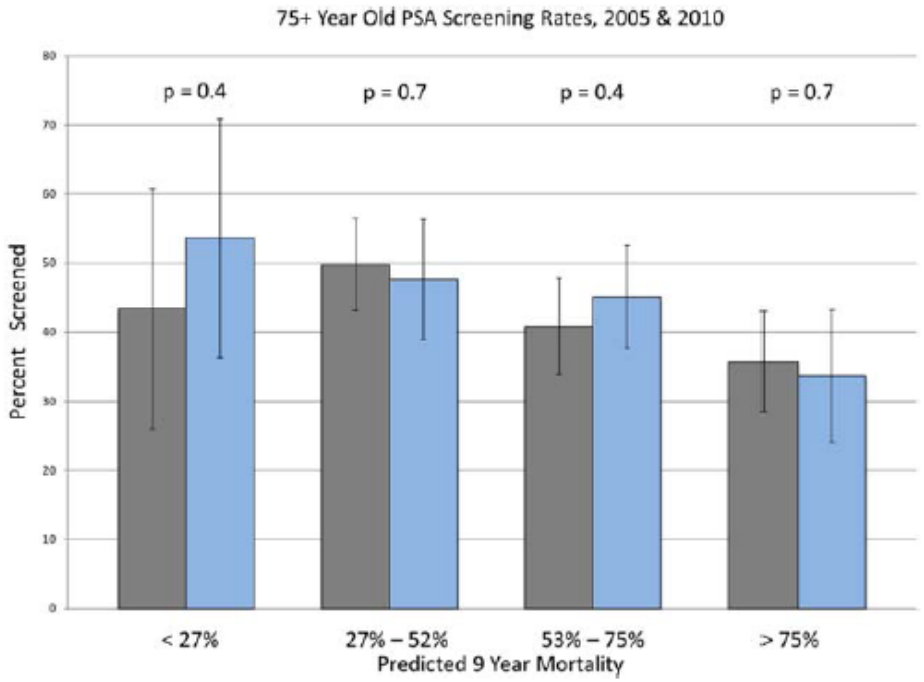
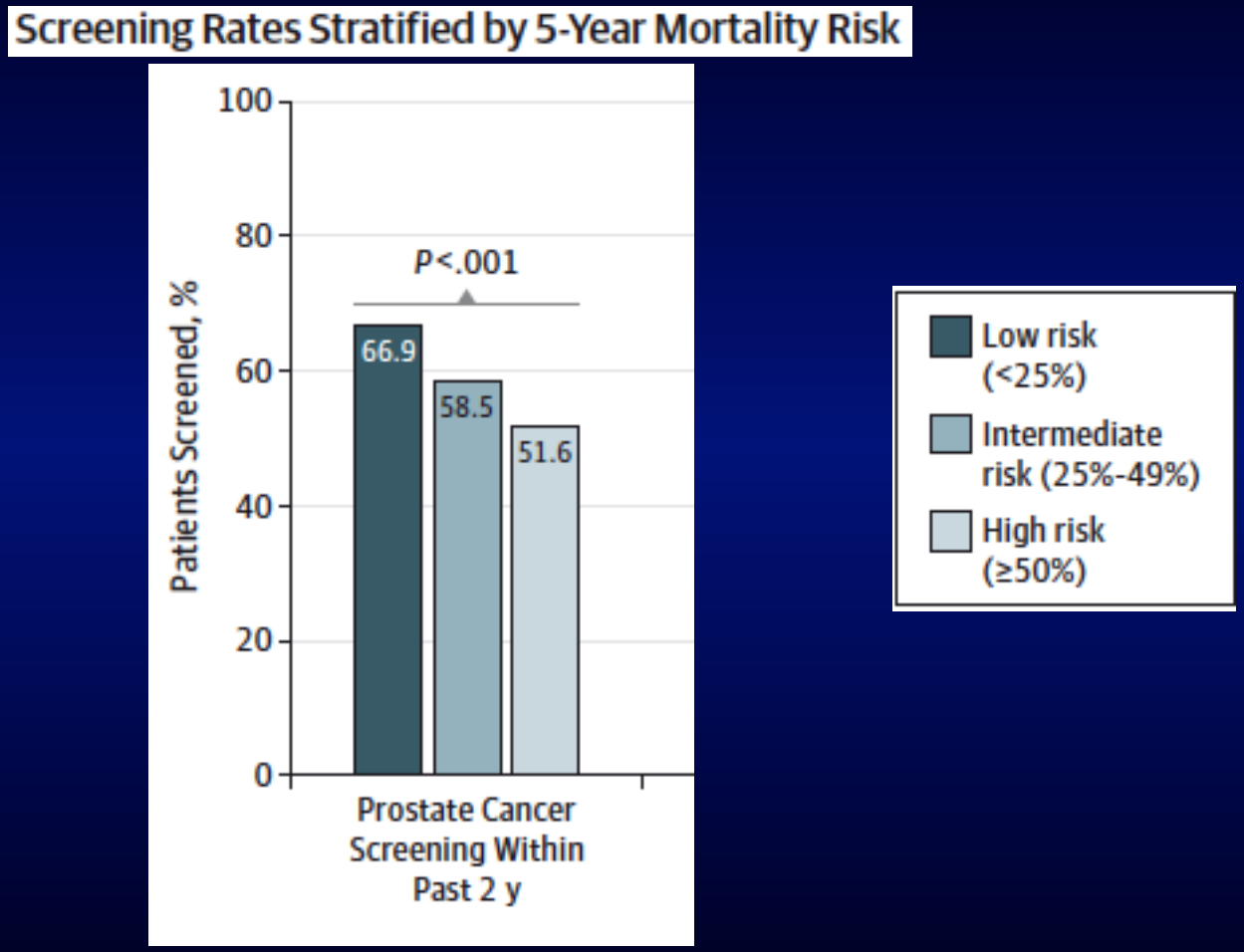


Figure 2. Prostate-specific antigen (PSA) screening rates are illustrated in men aged ≥75 years by predicted 9-year mortality in 2005 (gray) and 2010 (blue). Error bars represent 95% confidence intervals.

DOI: 10.1002/cncr.28600,

Cancer Month 00, 2014

Cancer Screening Rates in Individuals With Different Life Expectancies



JAMA Intern Med. doi:10.1001/jamainternmed.2014.3895
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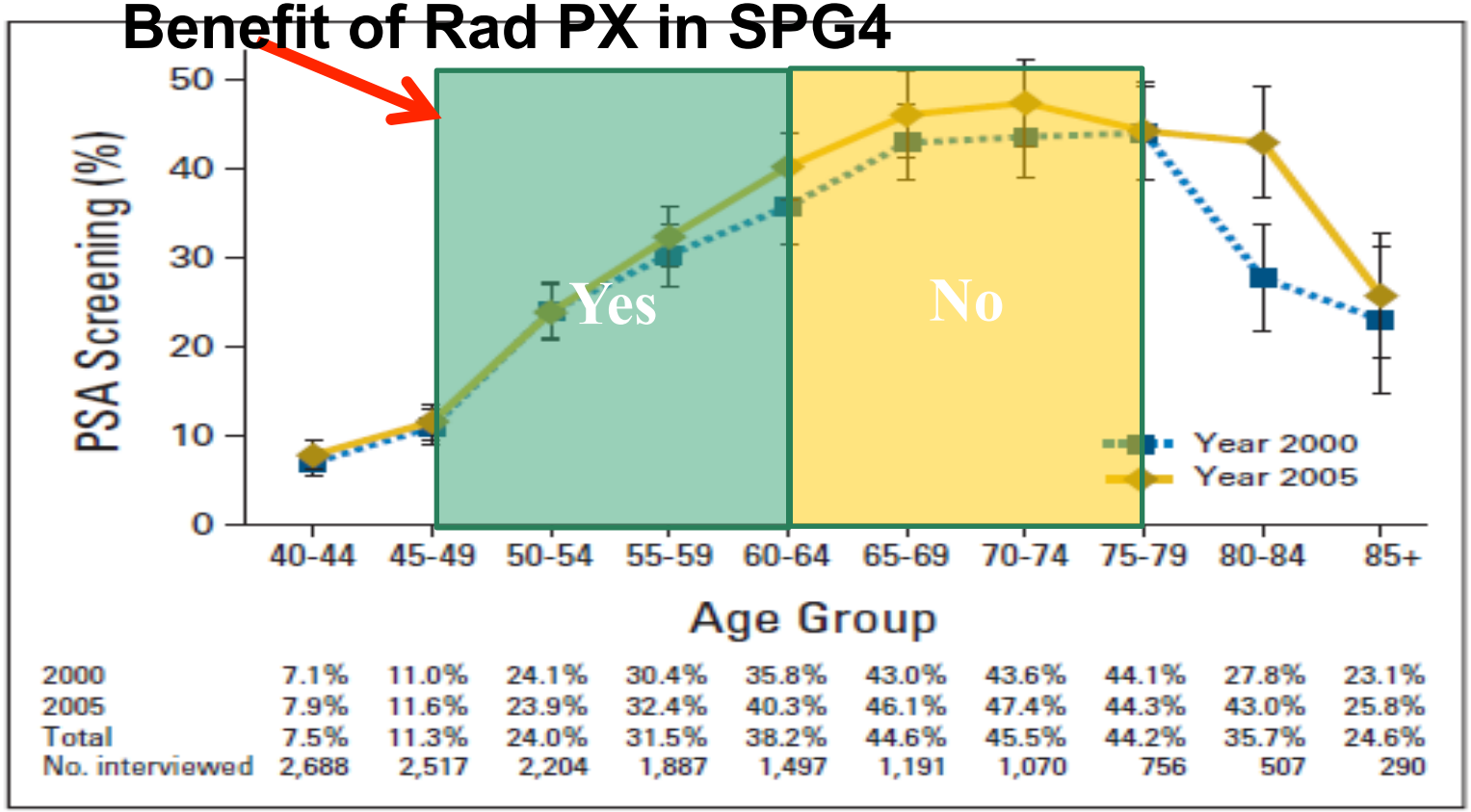
Benefit of Rad PX in SPG4



	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2000	7.1%	11.0%	24.1%	30.4%	35.8%	43.0%	43.6%	44.1%	27.8%	23.1%
2005	7.9%	11.6%	23.9%	32.4%	40.3%	46.1%	47.4%	44.3%	43.0%	25.8%
Total	7.5%	11.3%	24.0%	31.5%	38.2%	44.6%	45.5%	44.2%	35.7%	24.6%
No. interviewed	2,688	2,517	2,204	1,887	1,497	1,191	1,070	756	507	290

Fig 1. Estimated prevalence of prostate-specific antigen (PSA) screening (with 95% CIs) within the past year by year and age, National Health Interview Survey 2000 and 2005.

Current PSA Screening Practice

- We have been screening too late in life
  - The clinically detected cancers in the 45-64 yo men for which RadPx was effective would likely have been screen detectable by PSA at least 5 years prior.
  - In the US randomised trial of RadPx (PIVOT) for screen-detected cancers, the mean age was 66.8 yrs. and no overall mortality benefit observed.
    - Men with PSA>10 or aggressive dx benefit

Original Investigation | LESS IS MORE

Measuring Low-Value Care in Medicare

Aaron L. Schwartz, BA; Bruce E. Landon, MD, MBA; Adam G. Elshaug, PhD, MPH; Michael E. Chernew, PhD; J. Michael McWilliams, MD, PhD

JAMA Intern Med. doi:10.1001/jamainternmed.2014.1541
Published online May 12, 2014.

Financial Importance and Cost-Effectiveness

The cost of a PSA test can range from $70–$400 (Kale, 2013; Korenstein, 2012). Approximately 30 million men undergo PSA testing in the U.S. annually, translating to an estimated $3 billion in associated direct costs (Kale, 2013; Korenstein, 2012). This figure does not account for downstream costs or additional subsequent services such as biopsies, ultrasounds, treatment of irregular screening results or specialist consultation. The Medicare fee-for-service program spent $447 million annually on PSA-based screenings, approximately one-third of which was spent on men older than 75 (Ma, 2013).

Proposals to measure the quality of a physician

Proposed New Measures for HEDIS®[1] 2015:
Colorectal and Prostate Cancer Appropriateness/Overuse Measures

NCQA seeks comments on the following proposed new measures for inclusion in the HEDIS 2015 measurement set:

1. *Non-Recommended Colorectal Cancer Screening in Older Adults.*
   The percentage of members 86 years and older who were screened unnecessarily for colorectal cancer.
2. *Non-Recommended PSA-Based Screening in Older Men.*
   The percentage of men 70 years and older who were screened unnecessarily for prostate cancer using prostate-specific antigen (PSA)-based screening.

Note: *For both measures, a lower rate indicates better performance.*

CMS Quality Measures

- Project Title: Electronic Clinical Quality Measures for (1) Functional Status Assessment and Target Setting for Patients with Congestive Heart Failure and (2) Non-Recommended Prostate-Specific Antigen (PSA)-Based Screening
- Dates:
- The public comment period begins at 9:00 a.m. (EST) on October 26, 2015, and ends at 11:59 p.m. (EST) on November 20, 2015.
- https://jira.oncprojectracking.org/browse/PCQM

Factors promoting overdiagnosis of cancer

- Existence of a silent disease reservoir
- Activities leading to its detection (particularly screening)
- Long natural history and hence limited cancer-specific mortality

G. Welch and W. Black, JNCI, 2010

Mortality of men in Observation Arms of Contemporary Randomized Trials

	Follow-up (Yrs)	No. Men	No. Deaths	No. CaP Death	Ratio Death/ CaP Death
Goteborg	14	19,904	3,841	122	31.2
PLCO	13	38,654	5,982	145	41.2
ERSPC	13	89,352	16,749	462	36.3
PIVOT (Men with localized CaP "fit" for RP)	10	367	152	31	4.9

VOLUME 29 · NUMBER 4 · FEBRUARY 1 2011
JOURNAL OF CLINICAL ONCOLOGY
EDITORIALS

Serum Prostate-Specific Antigen for the Early Detection of Prostate Cancer: Always, Never, or Only Sometimes?

Peter R. Carroll, Jared M. Whitson, and Matthew R. Cooperberg, *University of California at San Francisco, San Francisco, CA*

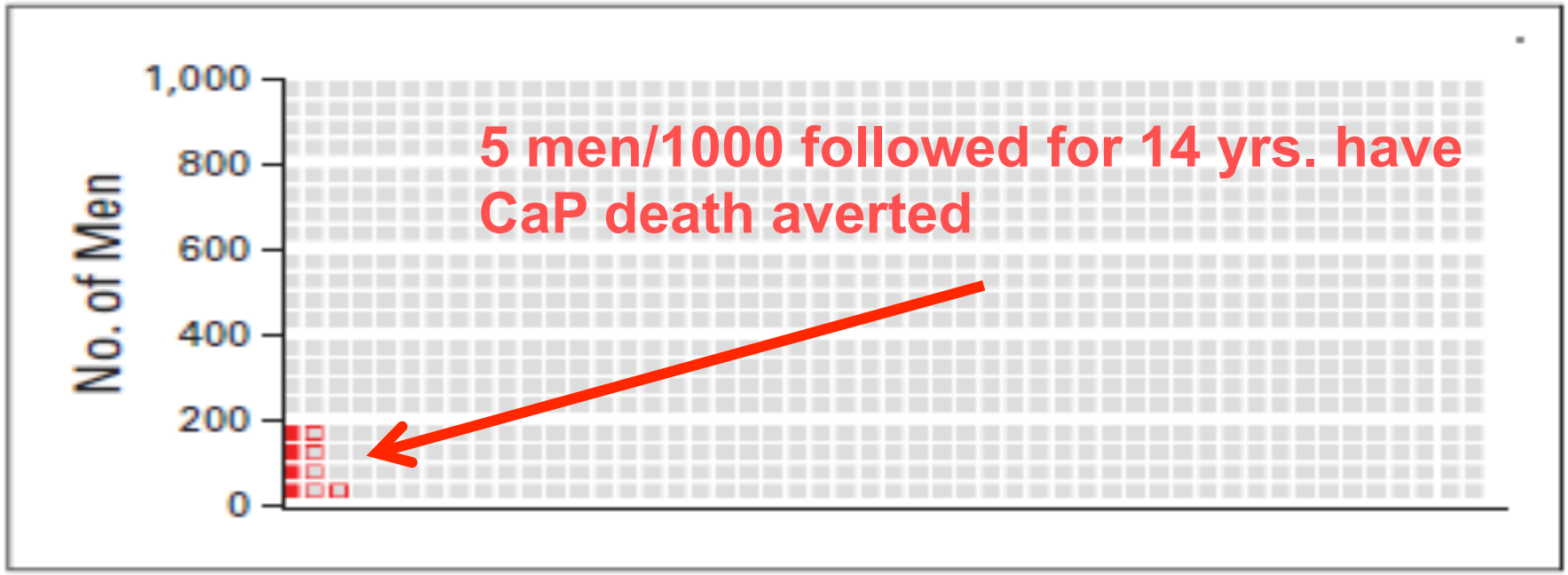


Fig 1. Absolute reduction in prostate cancer mortality. According to data from the Göteborg trial,[10] screening would reduce prostate cancer mortality from nine to four men per 1,000 at 14-year follow-up. Gray boxes indicate men who would not die as a result of prostate cancer in this time period, regardless of screening. Solid red boxes indicate men dying as a result of prostate cancer despite screening. Open red boxes indicate those among whom prostate cancer–specific mortality would be prevented by screening.

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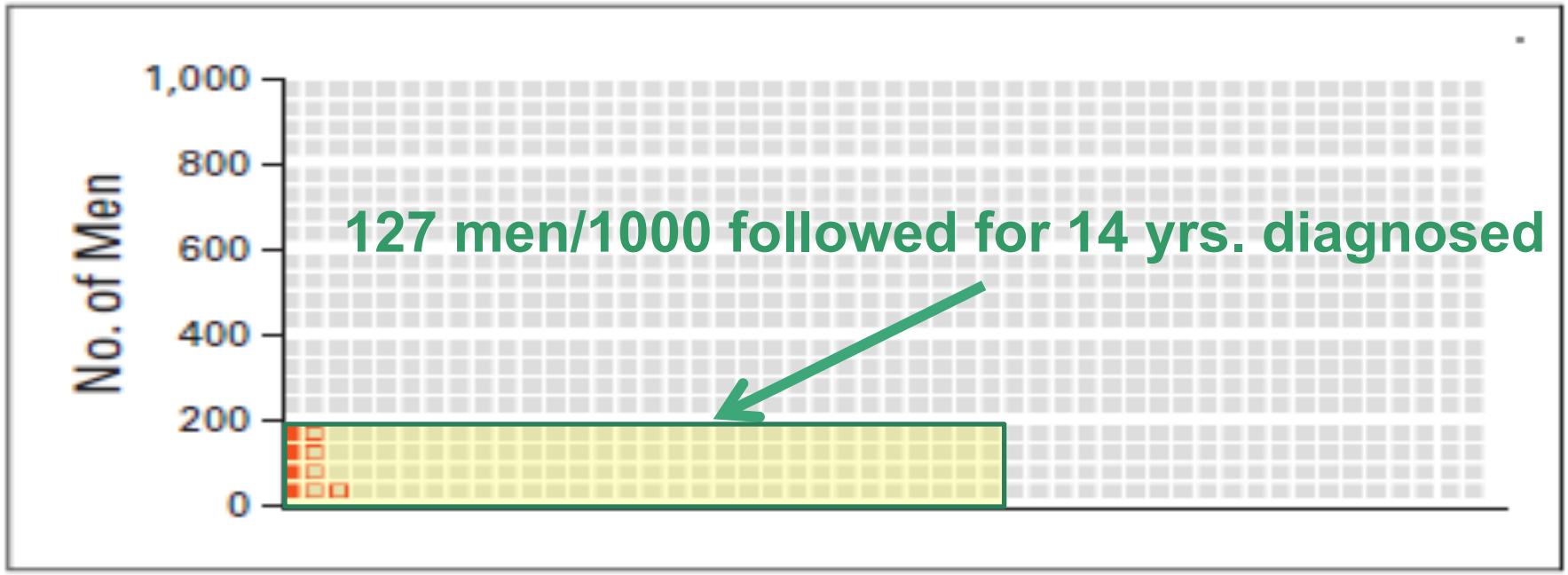

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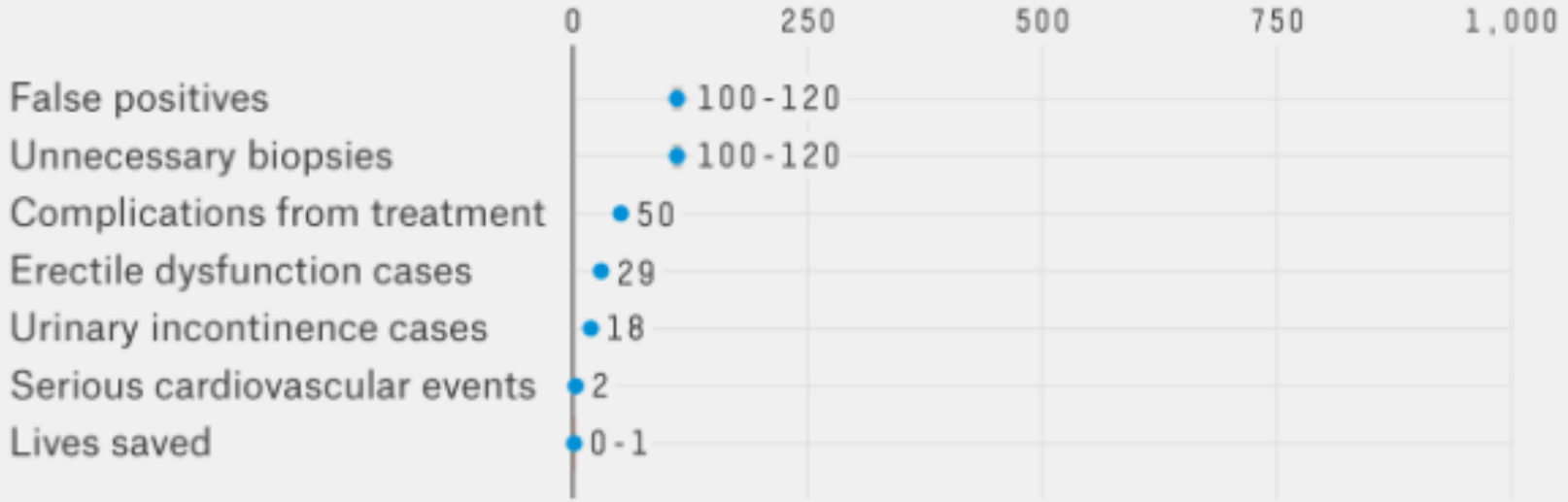
Prostate Cancer Detection

Medical outcomes if 1,000 men ages 55-69 are screened every 1-4 years for a decade; estimate range comes from multiple studies



SOURCE: NATIONAL CANCER INSTITUTE

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

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D.,
Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,

Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up

J Natl Cancer Inst 2012;104:125–132

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Manuscript received March 17, 2011; revised November 8, 2011; accepted November 9, 2011.

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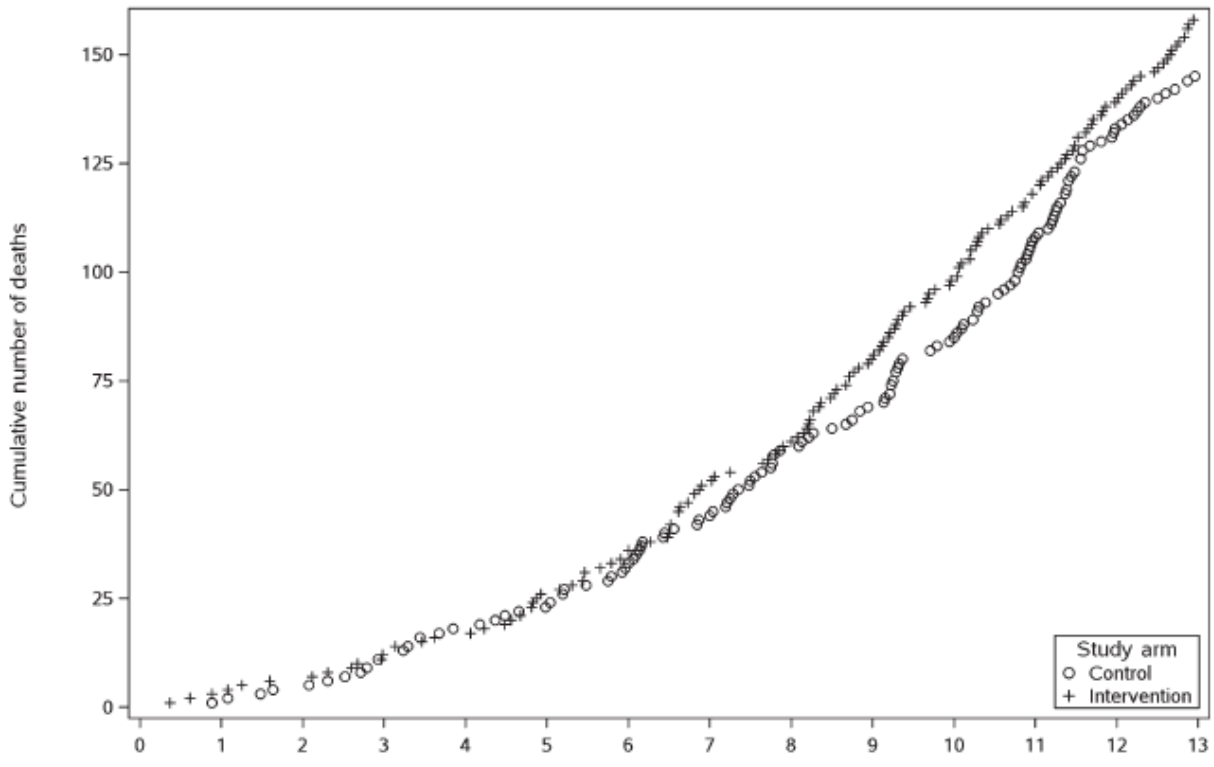

Cumulative deaths - I	3	6	12	16	26	36	51	61	80	98	118	140	158
Cumulative PY - I	38217	76112	113629	150725	187382	223541	259118	294052	328048	359768	387164	409535	426977
Cumulative deaths - C	1	4	11	18	23	33	44	59	69	85	108	133	145
Cumulative PY - C	38223	76132	113635	150689	187278	223329	258811	293631	327455	358904	386109	408262	425439

Figure 3. Cumulative deaths from prostate cancer in the intervention and control arms from year 1 to year 13. C = control arm; I = intervention arm; PY = person-years.

PLCO: Special Considerations

- Pre-screening
  - One-third had prior PSA/DRE
- Contamination in control arm
  - 85% compliance v. 42% contamination
- Overall Survival of PLCO cohort
  - Overall mortality 0.46 (v. anticipated)
- CaP Treatment

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Table 2. Primary treatment of prostate cancers diagnosed through 13 years by clinical stage and trial arm in the PLCO trial

			All prostate cancers						
			Primary treatment*						
Clinical stage†	Trial arm	No.	Prostatectomy No. (%)	Radiation No. (%)	Radiation and hormone No. (%)	Hormone No. (%)	Other ablative with curative intent No. (%)	No known curative intent No. (%)	Not available No. (%)
Stage I	Intervention	19	3 (15.8)	3 (15.8)	—	—	—	13 (68.4)	—
	Control	17	2 (11.8)	3 (17.6)	—	—	—	12 (70.6)	—
Stage II (T1 or T1A)	Intervention	49	7 (14.3)	2 (4.1)	3 (6.1)	1 (2.0)	—	35 (71.4)	1 (2.0)
	Control	50	10 (20.0)	4 (8.0)	1 (2.0)	1 (2.0)	—	34 (68.0)	—
Stage II (T1B or T1C)	Intervention	2530	1022 (40.4)	584 (23.1)	461 (18.2)	134 (5.3)	28 (1.1)	282 (11.1)	19 (0.8)
	Control	2265	859 (37.9)	519 (22.9)	454 (20.0)	133 (5.9)	36 (1.6)	249 (11.0)	15 (0.7)
Stage II (T2, T2A, T2B, or T2C)	Intervention	1477	646 (43.7)	296 (20.0)	275 (18.6)	86 (5.8)	23 (1.6)	149 (10.1)	2 (0.1)
	Control	1269	484 (38.1)	257 (20.3)	301 (23.7)	108 (8.5)	24 (1.9)	92 (7.2)	3 (0.2)
Stage III	Intervention	58	5 (8.6)	13 (22.4)	28 (48.3)	8 (13.8)	2 (3.4)	2 (3.4)	—
	Control	65	14 (21.5)	10 (15.4)	34 (52.3)	7 (10.8)	—	—	—
Stage IV	Intervention	96	1 (1.0)	5 (5.2)	14 (14.6)	71 (74.0)	—	4 (4.2)	1 (1.0)
	Control	111	1 (0.9)	1 (0.9)	24 (21.6)	77 (69.4)	—	8 (7.2)	—
Not available	Intervention	21	16 (76.2)	—	—	2 (9.5)	—	2 (9.5)	1 (4.8)
	Control	38	26 (68.4)	1 (2.6)	—	3 (7.9)	—	8 (21.1)	—
Total	Intervention	4250	1700 (40.0)	903 (21.2)	781 (18.4)	302 (7.1)	53 (1.2)	487 (11.5)	24 (0.6)
	Control	3815	1396 (36.6)	795 (20.8)	814 (21.3)	329 (8.6)	60 (1.6)	403 (10.6)	18 (0.5)
	Total	8065	3096 (38.4)	1698 (21.1)	1595 (19.8)	631 (7.8)	113 (1.4)	890 (11.0)	42 (0.5)

Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

Paul F. Pinsky[a,*], Amanda Black[b], Howard L. Parnes[a], Robert Grubb[c], E. David Crawford[d], Anthony Miller[e], Douglas Reding[f], Gerald Andriole[c]

Observed versus expected prostate cancer specific survival.

Group	Hazard ratio (95% CI)[a]	Ratio of 10 year case fatality rates (95% CI)[b]
All cases	0.54 (0.47–0.60)	0.59 (0.51–0.68)
Intervention arm	0.50 (0.43–0.59)	0.54 (0.42–0.67)
Control arm	0.57 (0.48–0.67)	0.66 (0.53–0.78)
Intervention (year 0–5, 1+ screen)	0.46 (0.38–0.56)	0.47 (0.37–0.57)
Intervention, no PLCO screens	1.44 (0.89–2.3)	1.79 (0.98–2.6)
All Gleason 5–7	0.62 (0.52–0.75)	0.66 (0.51–0.81)
All Gleason 8–10	1.08 (0.88–1.30)	1.07 (0.87–1.27)

Cancer Epidemiology 36 (2012) e401–e406

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Innappropriate Criticisms of PLCO

- "Low biopsy rate"
- "Delayed biopsy missed the chance for cure"
- These were the results of the "real world" design of PLCO—results reported to pt and primary MD; they decided whether further evaluation was necessary.
- In ERSPC, screened men saw Urologists for biopsy and treatment decisions.

Prostate Cancer Incidence

	PLCO		ERSPC*	
	Screened Arm	Usual Care Arm	Screened Arm	Usual Care Arm
Cancers	**3452**	**2974**	**5990**	**4307**
Rate** (per 10,000 person years)	**103**	**88**	**93**	**55**

- **Core age group**

Prostate Cancer Mortality

	PLCO		ERSPC*	
	Screened Arm	Usual Care Arm	Screened Arm	Usual Care Arm
Deaths	**92**	**82**	**214**	**326**
Rate* (per 10,000 person years)	**2.7**	**2.4**	**3.5**	**4.1**
Rate Ratio (95% CI)	**1.11 (0.83 to 1.50)**		**0.80 (0.65 to 0.98)**	

***Core age group**

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After 13 years of follow-up, there was no evidence of a mortality benefit for organized annual screening in the PLCO trial compared with opportunistic screening, which forms part of usual care, and there was no apparent interaction with age, baseline comorbidity, or pretrial PSA testing.

J Natl Cancer Inst 2012;104:125–132

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.,

Prostate-Cancer Mortality at 11 Years of Follow-up
NEJM 366:981, 2012

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up
Lancet 384:2027, 2014

	PLCO	ERSPC
Age Group	**55-74**	**50-74; 55-69 (Core)**
Enrolled	**77,000 1993-2001**	**162,000 1991-2001**
Locations	**10 U.S. Centers**	**7 Eur. Countries**
Randomization	**Individual**	**Variable: Generally @ Population level**
PSA Cutoff	**4 ng/ml; "community standard"**	**3 ng/ml except Scandanavia (2.5)**
DRE	**All men**	**Some men**
Testing Frequency	**Annual (PSA 6X; DRE 4X)**	**Year 0 & 4 (usual)** **Year 0, 2 and 4 (1 center)**
Biopsy	**"Community Standard" both arms**	**Center v. Community**
Treatment	**"Community Standard" both arms**	**Center v. Community**

Special Considerations: ERSPC

- Variable screening protocols
  - "It may be more appropriate to analyze as a meta-analysis than as a single trial" (Boyle and Brawley; Cancer, 2009)

NCCN Briefing

- After 13 years of follow-up, the rate ratio of prostate cancer mortality in the screened arm was 21% (95% CI 0.69 to 0.91), equivalent to 1 prostate cancer death averted per 781 men screened or 1 per 27 additional prostate cancers detected.[10] Potential shortcomings of the ERSPC include lack of a significant effect of screening on all-cause mortality; overreliance on secondary analyses adjusting for non-compliance; and unbalanced treatment differences between study arms.[11,12]

Special Considerations: ERSPC

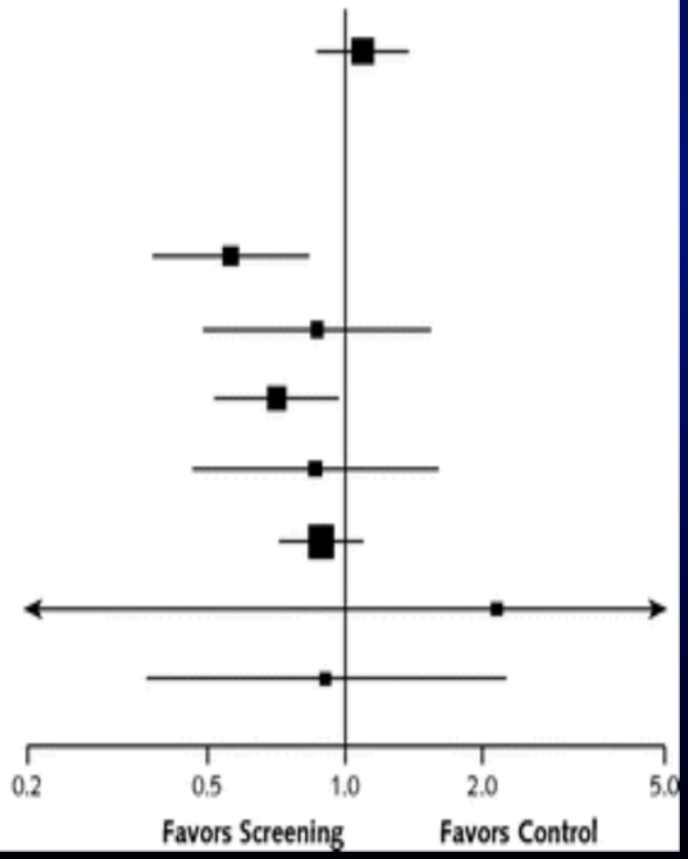
- Variable screening protocols
  - "It may be more appropriate to analyze as a meta-analysis than as a single trial" (Boyle and Brawley, Cancer, 2009)
- >20% mortality reduction seen only in "core group"
  - Not men of all ages
  - All sites not included
- Significant Mortality reduction in only 2 of 7 sites

  Removal of either site eliminates benefit

USPSTF

Moyer et al Ann Int Med 2012

Country	Screened		Control		Risk Ratio (95% CI)
	Deaths	Total	Deaths	Total	
PLCO trial					
United States	158	38 340	145	38 345	1.09 (0.87–1.36)
ERSPC trial					
Sweden	39	5901	70	5951	0.56 (0.38–0.83)
Belgium	22	4307	25	4255	0.86 (0.48–1.52)
Netherlands	69	17 443	97	17 390	0.71 (0.52–0.96)
Italy	19	7266	22	7251	0.86 (0.46–1.58)
Finland	139	31 970	237	48 409	0.89 (0.72–1.09)
Spain	2	1056	1	1141	2.15 (0.20–23.77)
Switzerland	9	4948	10	4955	0.89 (0.36–2.20)



Prostate Cancer Mortality in the Finnish Randomized Screening Trial

J Natl Cancer Inst;2013;105:719–725

Tuomas P. Kilpeläinen, Teuvo L. Tammela, Nea Malila, Matti Hakama, Henrikki Santti, Liisa Määttänen, Ulf-Håkan Stenman, Paula Kujala, Anssi Auvinen

One must also bear in mind that the statistical power in a single ERSPC center was insufficient for conclusive evidence on screening, which is why the trial was based on international collaboration (12). Nevertheless, the Finnish trial was the largest component of the ERSPC trial, with more than 80 000 men and 415 PC deaths, which is more than in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (76 693 and 174, respectively) (3) or the Swedish component of the ERSPC trial (19 904 and 122, respectively) (5).

Age-Adjusted CaP Mortality per 100,000 men

Sweden	20.4
Finland	17.2
Netherlands	15.1
Switzerland	14.9
USA	10.8
Spain	10.8
Italy	10.5

Special Considerations: ERSPC

- Treatment differences between arms

UICC global cancer control

Int. J. Cancer: 126, 2387–2393 (2010)

IJC International Journal of Cancer

The effect of study arm on prostate cancer treatment in the large screening trial ERSPC

Tineke Wolters[1], Monique J. Roobol[1], Ewout W. Steyerberg[2], Roderick C.N. van den Bergh[1], Chris H. Bangma[1], Jonas Hugosson[3], Stefano Ciatto[4], Maciej Kwiatkowski[5], Arnauld Villers[6], Marcos Luján[7], Vera Nelen[8], Teuvo L.J. Tammela[9] and Fritz H. Schröder[1]

Table 3. Treatment modalities in the cohort and per study arm, excluding men with distant metastases ($n = 379$)

Treatment	Total group, no. (%)	Screen, no. (%)	Control, no. (%)	Low-risk PC, no. (%)		Intermediate-risk PC, no. (%)		High-risk PC, no. (%)	
				Screen	Control	Screen	Control	Screen	Control
Radical prostatectomy	3,064 (38.3)	2,113 (41.3)	951 (32.8)	1,099 (39.7)	342 (39.2)	663 (50.3)	403 (41.3)	351 (34.2)	206 (19.6)
Radiotherapy	2,689 (33.6)	1,597 (31.2)	1,092 (37.7)	695 (25.1)	246 (28.2)	419 (31.8)	365 (37.4)	483 (47.0)	481 (45.9)
Active Surveillance	1,545 (19.3)	1,111 (21.7)	434 (15.0)	916 (33.1)	251 (28.8)	153 (11.6)	130 (13.3)	42 (4.1)	53 (5.1)
Hormonal therapy	712 (8.9)	291 (5.7)	421 (14.5)	56 (2.0)	34 (3.9)	84 (6.4)	78 (8.0)	151 (14.7)	309 (29.5)
Total	8,010	5,112	2,898	2,766	873	1,319	976	1,027	1,049

Additionally, treatment per arm is described stratified by risk group according to the criteria by d'Amico *et al.*[4] Differences in treatment distribution were statistically significant in all risk groups at the $p < 0.05$ level.

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UICC
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- Treatment location also differed between screen and control men
  - Screened patients were 6x more likely to be treated at large academic centers
  - Screened men likely received better XRT and more aggressive treatment for hormone relapsing disease

Why concern about treatment effects in ERSPC?

- It is now clear that most of the decline in US CaP mortality that began in early 1990s had to be due to treatment (not screening)
  - Too early for screening per ERSPC
    - Need at least 10 years to observe benefit
  - Radical Prostatectomy rates increased more than 10x between 1980 and 1990 (Lu-Yao, J Urol 1997)
  - XRT improved by 3D conformal therapy

PLCO and ERSPC: Keep an Eye out

- Combined analysis completed
- "two micro-simulation models to individual-level incidence and mortality data from 238,936 men participating in the trials. A cure parameter for the efficacy of screening was estimated separately for each trial. We changed step-by-step major known differences in trial settings, including enrollment and attendance patterns, screening intervals, PSA thresholds, receipt of biopsies, control arm contamination and primary treatment patterns, to ultimately reflect a more ideal protocol situation and differences between the trials"

The USPSTF Prostate Screening Statement

The USPSTF recommends against routine PSA-based screening for prostate cancer (grade D recommendation).

A grade D recommendation means that the USPSTF has concluded that there is at least moderate certainty that the harms of performing the intervention equal or outweigh the benefits in the target population

Early Detection of Prostate Cancer: European Association of Urology Recommendation

EUROPEAN UROLOGY 64 (2013) 347–354

- Statement 1: Early detection of prostate cancer reduces prostate cancer–related mortality
- Statement 2: Early detection of prostate cancer reduces the risk of being diagnosed and developing advanced and metastatic prostate cancer
- Statement 3: A baseline serum prostate-specific antigen level should be obtained at 40–45 yr of age
- Statement 4: Intervals for early detection of prostate cancer should be adapted to the baseline prostate-specific antigen serum concentration
- Statement 5: Prostate-specific antigen screening should be offered to men with a life expectancy of ≥10 yr

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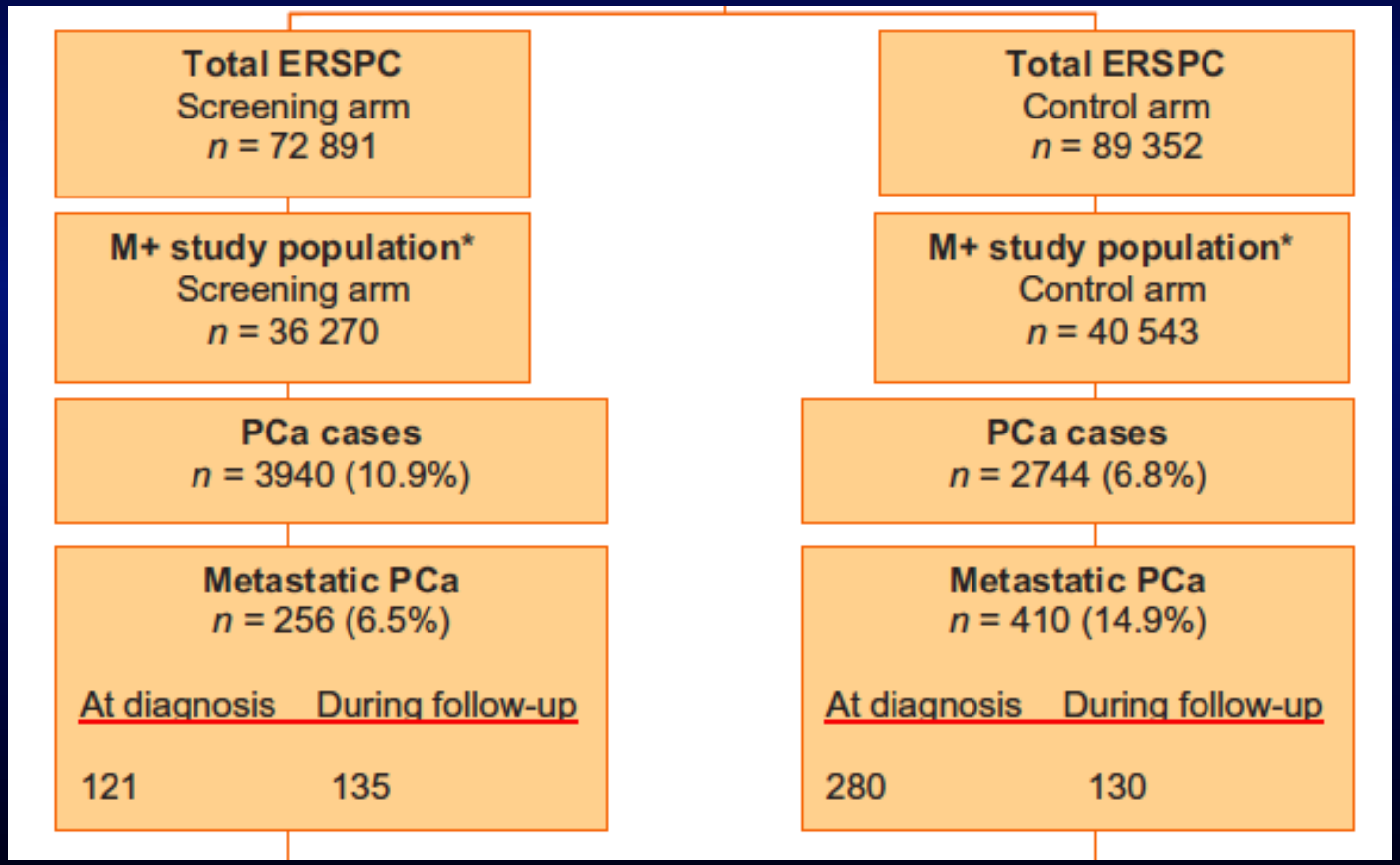
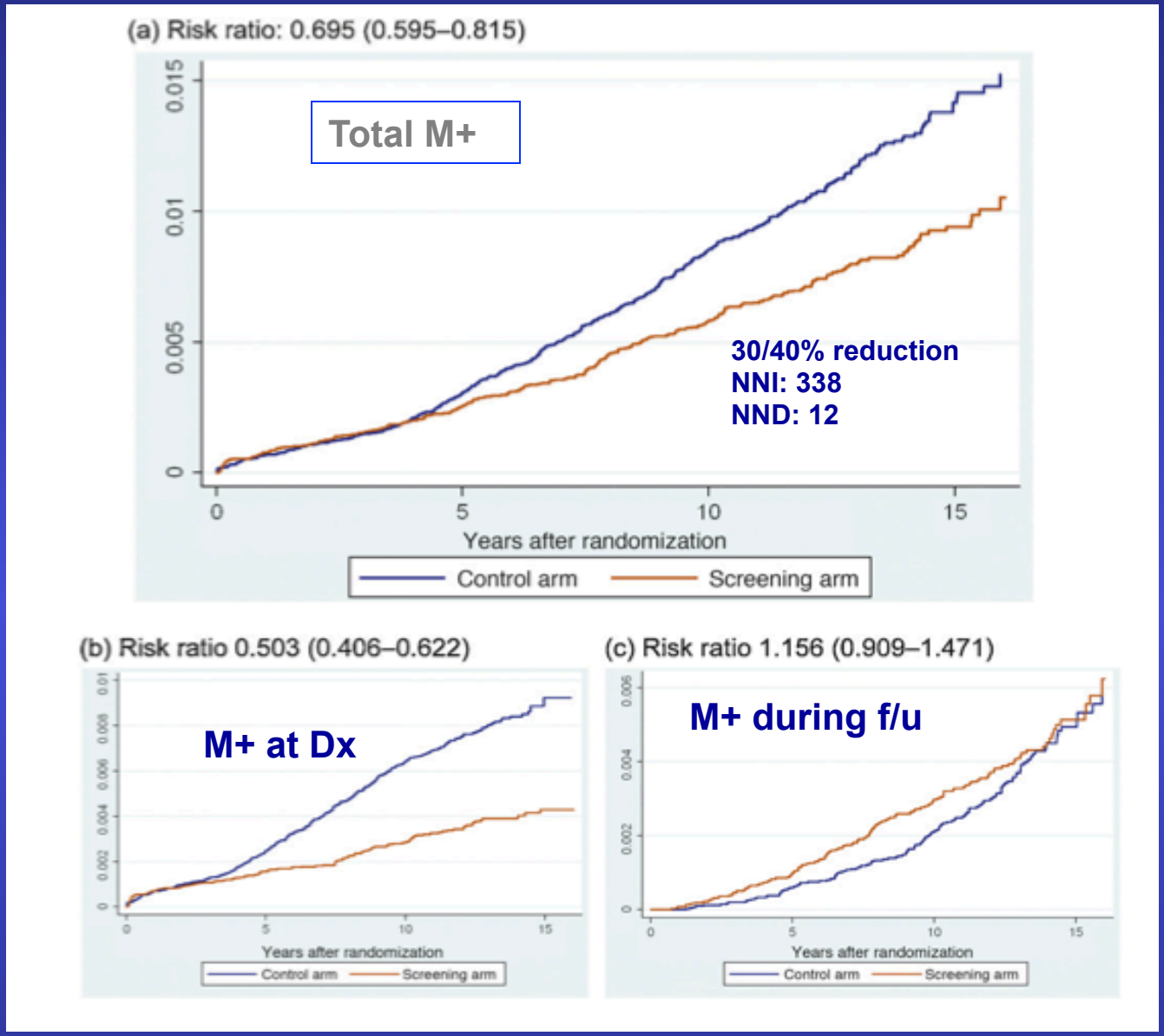
EUROPEAN UROLOGY 62 (2012) 745–752





Schroder Eur. Urol 2012

Metastatic CaP in pre- and post PSA Era

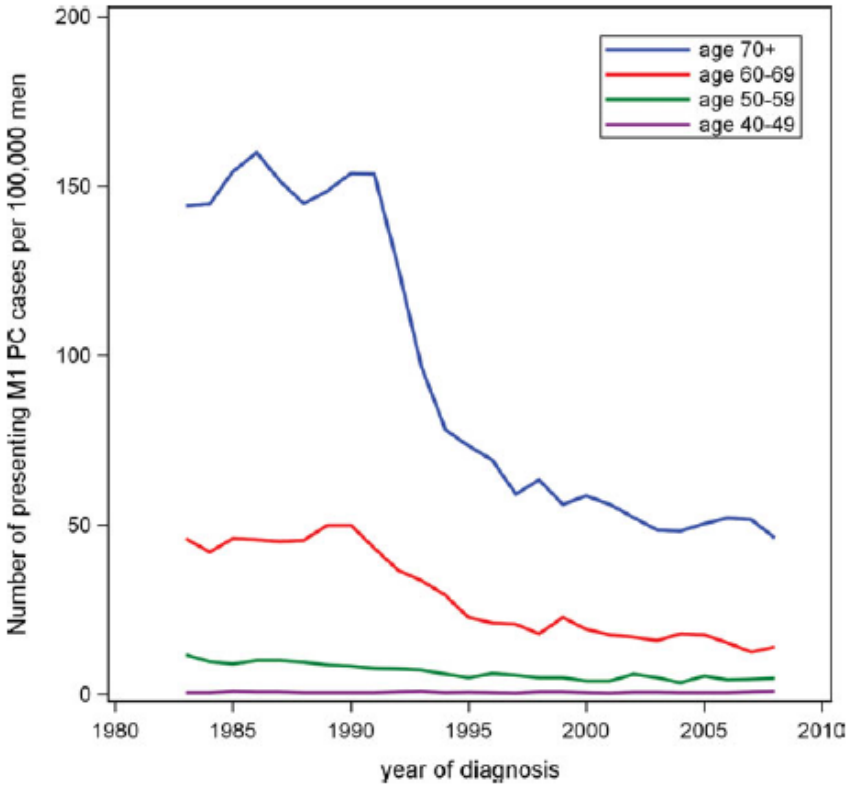


Figure 1. Annual incidence rates of presenting with metastatic prostate cancer (M1 PC) are illustrated according to age among white men.

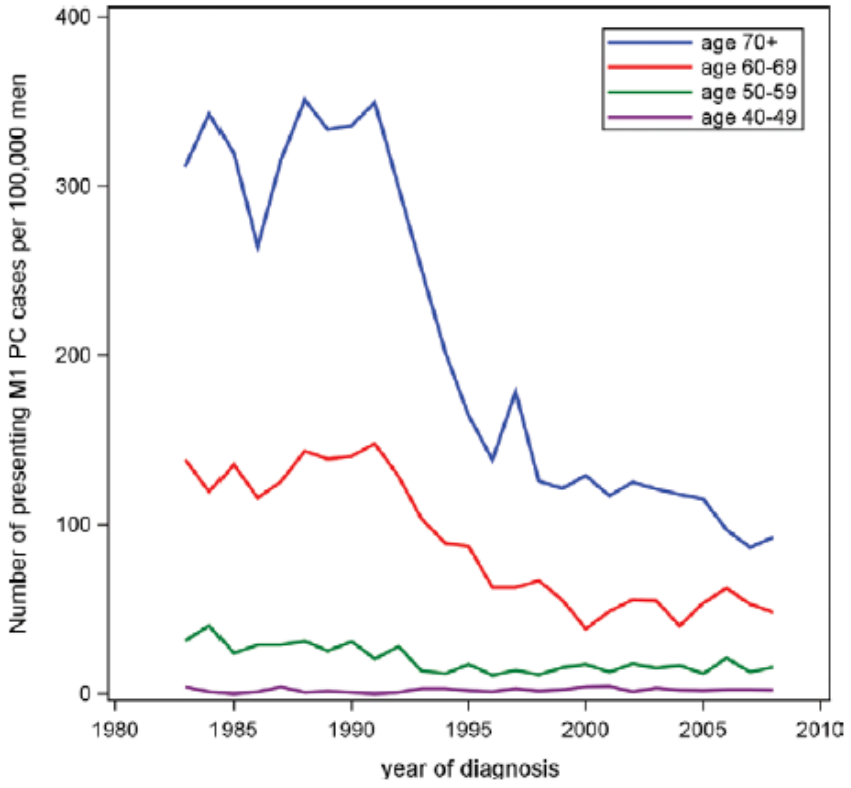


Figure 2. Annual incidence rates of presenting with metastatic prostate cancer (M1 PC) are illustrated according to age among black men.

Scosyrev et al: Cancer 2012;118:5768-76

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Initial PSA Below 1 in PLCO and ERSPC

- PLCO (BJUI 102:1524, 2008)
  - < 0.6% risk of aggressive CaP over 7-10 years
- ERSPC (Van Leewen et al Cancer, 2010)
  - NNS 24,642 and NNT 724 to prevent 1 death.

Malmo
(Lilja et al; Cancer 2011; 117:1210)

- Top PSA decile in early 40's
  - First test: >1.3
    - 1.5% 15 year met/death
  - Second test (PSA> 1.6)
    - 5.2% 15 yr met/death
- Overall, ~ half of all met/ CaP deaths came from top PSA decile

Malmo
(Lilja et al; Cancer 2011; 117:1210)

- ~75% had PSA below 1 @ age 40-45
  - <1% 15 year met/ CaP death
  - If second PSA <1, 15 year met/death <0.2%
  - If third PSA below 1 up to age 50, ? exempt from screening
  - If three PSA <2 up to age 60, ? exempt from screening

US Physician's Health Study

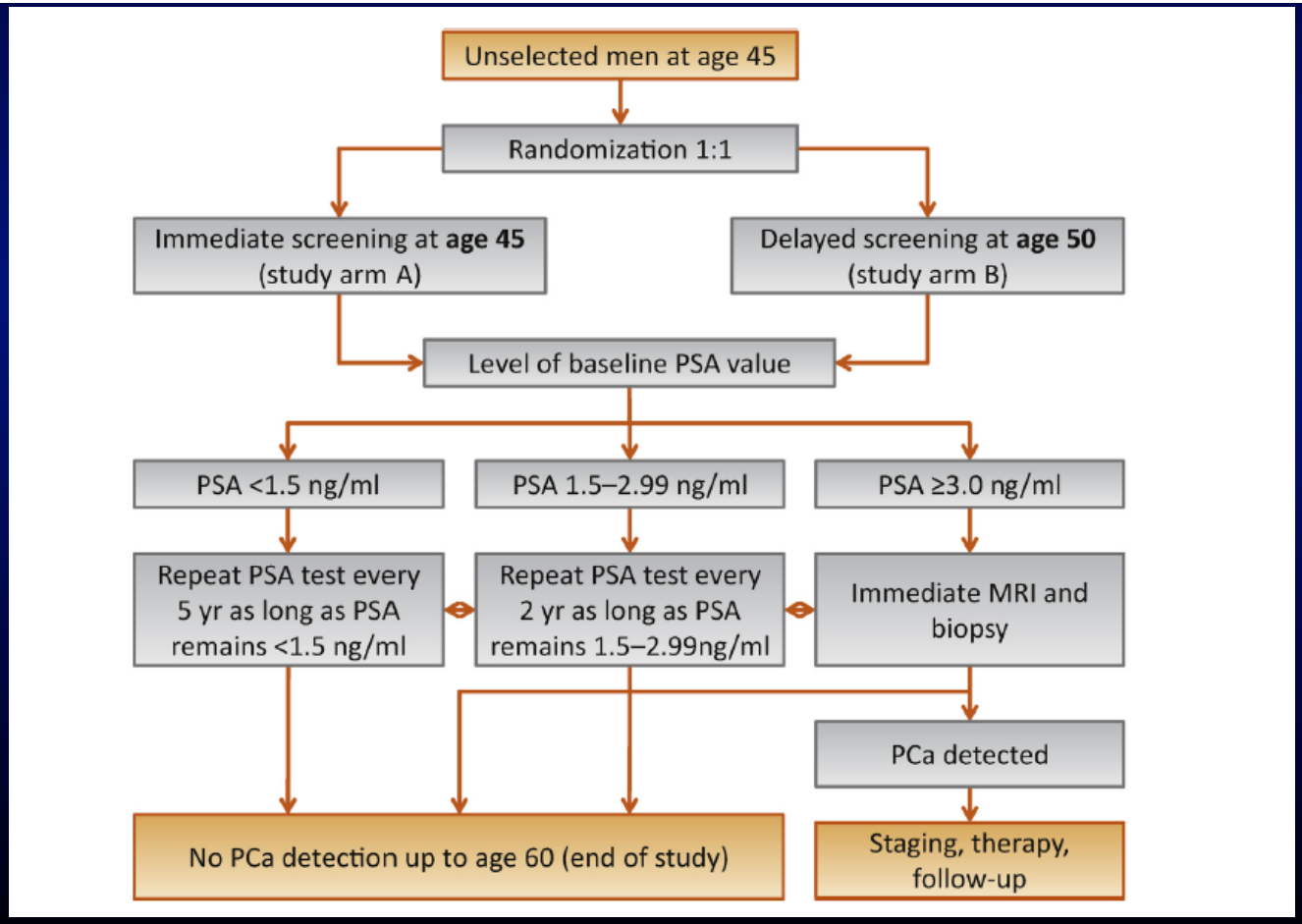
- PSA in men <60 (median PSA <1)
- Followed from 1982-2012
- Men in top PSA decile had ~30x OR for CaP
- Men in top PSA quartile had ~6x OR for lethal CaP (v. lowest quartile)

Preston et al.: J. Urol 2015

Prospective Randomized Evaluation of Risk-adapted Prostate-specific Antigen Screening in Young Men: The PROBASE Trial

EUROPEAN UROLOGY 64 (2013) 873–875

Christian Arsov[a,*], *Nikolaus Becker*[b], *Boris A. Hadaschik*[c], *Markus Hohenfellner*[c], *Kathleen Herkommer*[d], *Jürgen E. Gschwend*[d], *Florian Imkamp*[e], *Markus A. Kuczyk*[e], *Gerald Antoch*[f], *Glen Kristiansen*[g], *Roswitha Siener*[h], *Axel Semjonow*[i], *Freddie C. Hamdy*[j], *Hans Lilja*[j,k], *Andrew J. Vickers*[l], *Fritz H. Schröder*[m], *Peter Albers*[a]



EARLY DETECTION OF PROSTATE CANCER: AUA GUIDELINE

1. The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C)

   In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.

2. The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C)

   For men younger than age 55 years at higher risk (e.g. positive family history or African American race), decisions regarding prostate cancer screening should be individualized.

3. For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B)

   The greatest benefit of screening appears to be in men ages 55 to 69 years.

EARLY DETECTION OF PROSTATE CANCER: AUA GUIDELINE

4. To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of the benefits and reduce overdiagnosis and false positives. (Option; Evidence Strength Grade C)

   Additionally, intervals for rescreening can be individualized by a baseline PSA level.

5. The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C)

   Some men age 70+ years who are in excellent health may benefit from prostate cancer screening.

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NCCN Guidelines Version 2.2015
Prostate Cancer Early Detection

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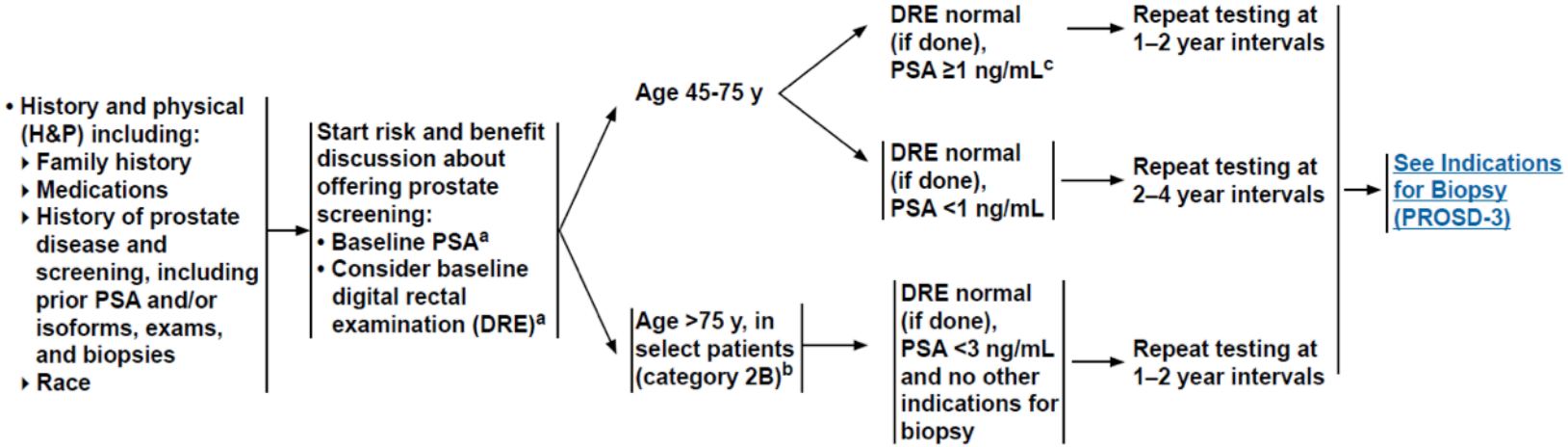

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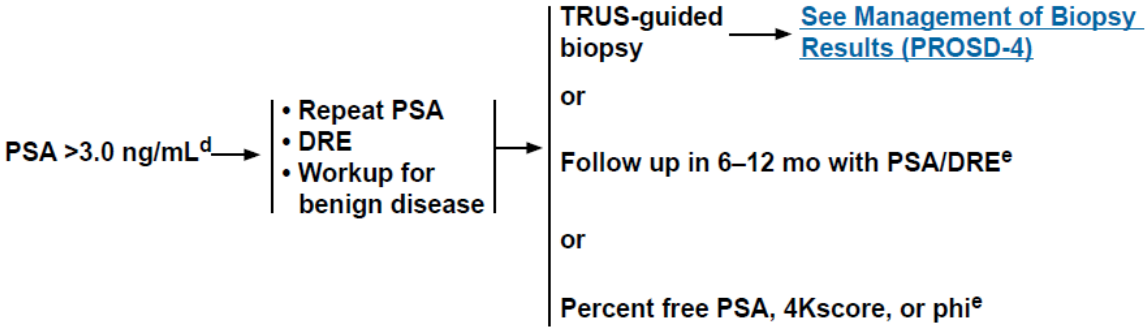
INDICATIONS FOR BIOPSY



TRUS-GUIDED BIOPSY
Initial and Repeat
Extended-pattern biopsy (12 cores)

- Number of cores:
  - Sextant (6),
  - Lateral peripheral zone (6), and
  - Lesion-directed at palpable nodule or suspicious image
- Anteriorly directed biopsy is not supported in routine biopsy. However, the addition of a transition zone biopsy to an extended biopsy protocol may be considered in a repeat biopsy if PSA is persistently elevated.
- Multiparametric MRI may help identify regions of cancer missed on prior biopsies and should be considered in selected cases after at least 1 negative biopsy.
- For high-risk men with negative biopsies, consideration can be given to a saturation biopsy strategy (including transperineal techniques) and/or the use of multiparametric MRI followed by an appropriate biopsy technique based on the results.
- Local anesthesia can decrease pain/discomfort associated with prostate biopsy and should be offered to all patients.

4K: Future risk of Metastatic CaP

- 15 to 20 year future risk of mets correlated w PSA levels at age 40 to 60. Men w PSA > 2 considered at “high risk” for mets.
- If 4K score known, about half men with PSA >2 would be reclassified as low risk (<1% mets at 15 year)

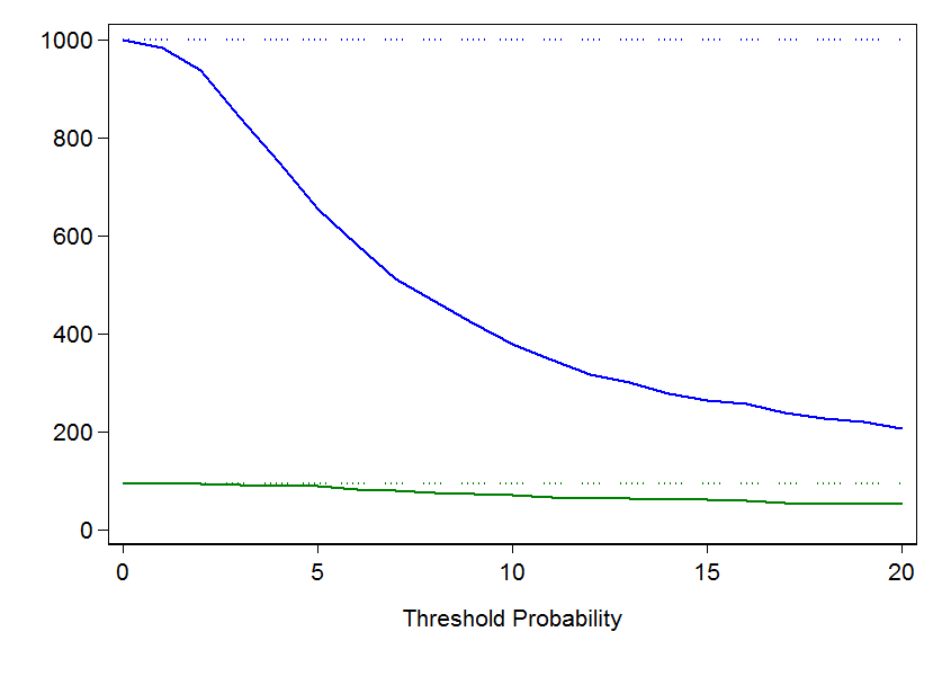
- Stattin et al: Eur Urol 2015

Use of 4K and MSP in PLCO Participants

	AUC	95% CI
Age + PSA	0.691	0.641, 0.735
Age + Four kallikrein panel	0.786	0.748, 0.816
Age + PSA + DRE	0.706	0.660, 0.746
Age + Four kallikrein panel + DRE	0.786	0.748, 0.815
Age + Four kallikrein panel + MSP	0.809	0.774, 0.838
Age + Four kallikrein panel + MSP + DRE	0.810	0.775, 0.840

	African American	Other Races	Difference	95% CI
Age + PSA	0.671	0.694	-0.023	-0.19, 0.14
Age + Four kallikrein panel	0.803	0.781	0.022	-0.10, 0.13
Age + PSA + DRE	0.691	0.710	-0.019	-0.18, 0.14
Age + Four kallikrein panel + DRE	0.790	0.783	0.007	-0.12, 0.12

Biopsies Avoided using 4K in PLCO



CaP Early Detection: 2016

- PSA based screening can reduce CaP mortality
  - Mass screening based on age alone not optimal
  - Risk-adapted screening likely better to minimize overdiagnosis
    - Start in 40's
- New markers and better biopsy will likely aid diagnosis and prognosis and may increase the benefit of screening by reducing detection and treatment of low risk tumors