TO SCREEN

OR

NOT TO SCREEN

Less is more?

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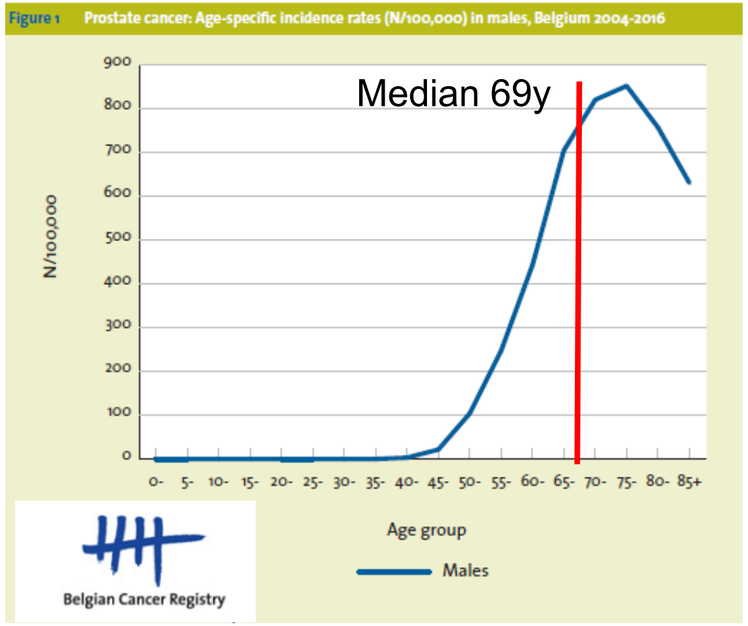
PROSTATE CANCER STATISTICS IN BELGIUM

50-69 years	16,085	
1) Prostate	4,455	28%
2) Lung	2,529	16%
3) Colon and rectum	1,884	12%
4) Head and Neck	1,275	8%
5) Oesphagus	599	4%
Other cancer types	5,343	33%
70-79 years	**10,681**	
1) Prostate	3,025	28%
2) Lung	1,773	17%
3) Colon and rectum	1,478	14%
4) Bladder	629	6%
5) Head and Neck	398	4%
Other cancer types	3,378	32%
80-89 years	**6,119**	
1) Prostate	1,364	22%
2) Colon and rectum	1,002	16%
3) Lung	926	15%
4) Bladder	499	8%
5) Non-Hodgkin lymphoma	223	4%
Other cancer types	2,105	34%



9050 new diagnoses in 2016 (25%)

1532 Pca deaths in 2015 (10%) (BUT 60% dies at age >80y)

Data from Belgian Cancer Registry

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PROSTATE CANCER SCREENING

Screening: A strategy used in a population to identify the possible presence of an as-yet-undiagnosed disease in individuals without signs or symptoms

Population or mass screening is defined as the examination of asymptomatic men (at risk)

Initiated by screener / health authorities

Early detection or opportunistic screening represents individual case findings, initiated by the patient and/or his physician

Guidelines on

Prostate Cancer

POTENTIAL BENEFITS OF PCA SCREENING

- PCa is an important public health problem: 2-5% of all deaths in European men
- Longer life expectancy in men will result in more men suffering from Pca.
- Prostate Cancer is only curable when detected in a localized stage.
- Treatment of advanced disease only marginally improves survival and is very costly
- Treatment-related side-effects increase with advancing stage.

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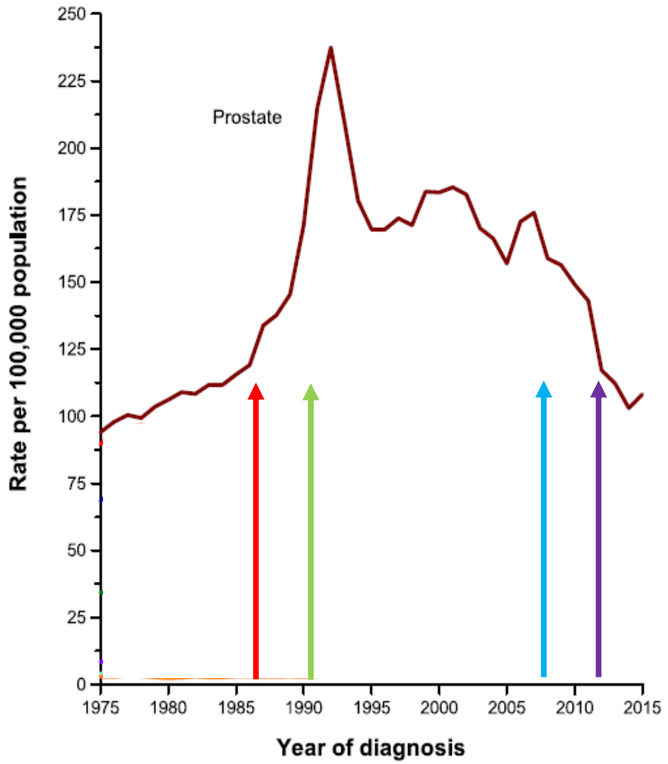
PSA SCREENING HAS A STRONG INFLUENCE ON PCA INCIDENCE



1987 Prostate-Specific Antigen as a serum marker for Adenocarcinoma of the prostate

1991 Measurement of Prostate-Specific antigen in serum as a screeni

U.S. Preventive Services TASK FORCE

2008 Grade I (Insufficient evidence)
Grade D 75+

2012 Grade D for all

2018 Grade C (screen some)
Grade D 70+

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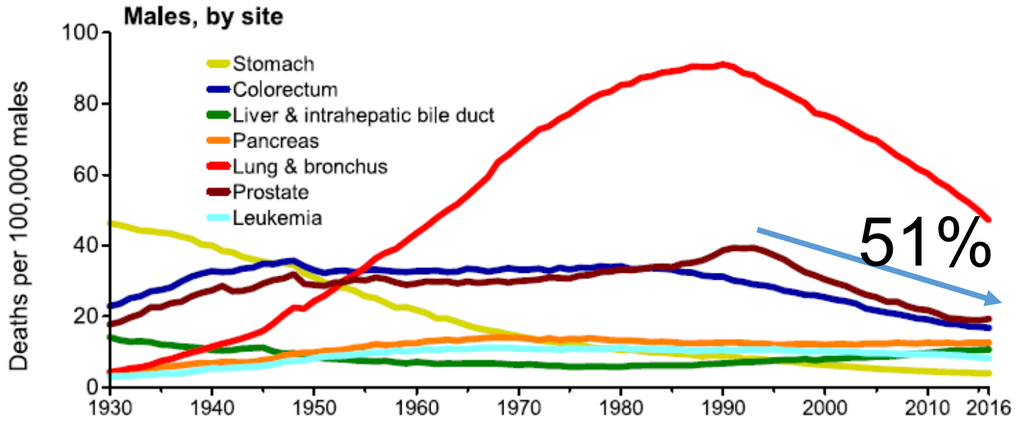
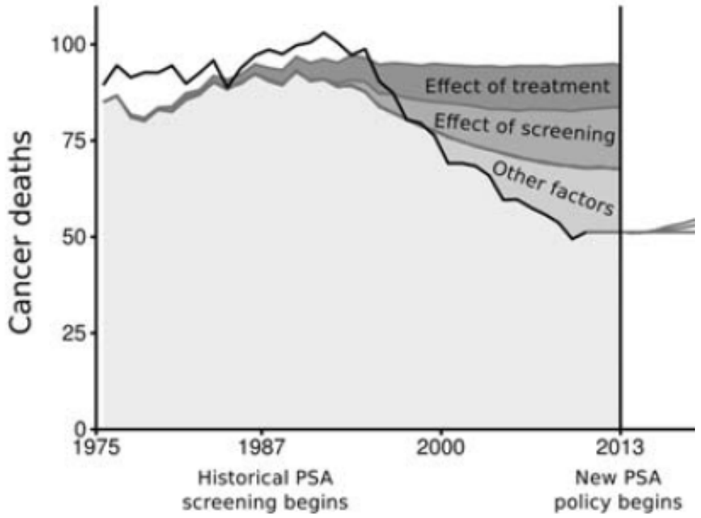
Siegel R. CA Cancer J Clin 2019, Stamey T. NEJM 1987, Catalona W. NEJM 1991

PROSTATE CANCER MORTALITY





- Pca mortality stabilized since 2013 after 2 decades of constant reduction

- Improvements in PCa are explained by PSA screening as well as treatment improvements

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CAN PROSTATE CANCER SCREENING REDUCE PROSTATE CANCER-RELATED MORTALITY?

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	CAP	PLCO	ERSPC
Population	8 centres in UK	10 centres in USA	8 European countries
Recruitment	2001-2009	1993-2001	1991-2003
Sample size	419,582	76,685	162,388
Age	50-69	55-74	55-69 Sweden 50-70
Screening interval	Single PSA test	Annual PSA for 6 yrs DRE for 4 yrs	4 yrs Sweden: 2 yrs Belgium: 7 yrs
Indication for Bx	PSA ≥ 3 ng/dl	PSA ≥ 4 ng/ml Suspicious DRE	PSA ≥ 3 – 4 ng/dl Sweden ≥2,5 ng/ml
Biopsy	Per protocol (10 core)	At discretion of physician/patient	Per Protocol (6 cores, later 10-12 cores)
Participation rate	36%	85%	83%
Biopsy compliance	85%	30-40%	86%
Contamination	10-15%	75-85%	25-40%

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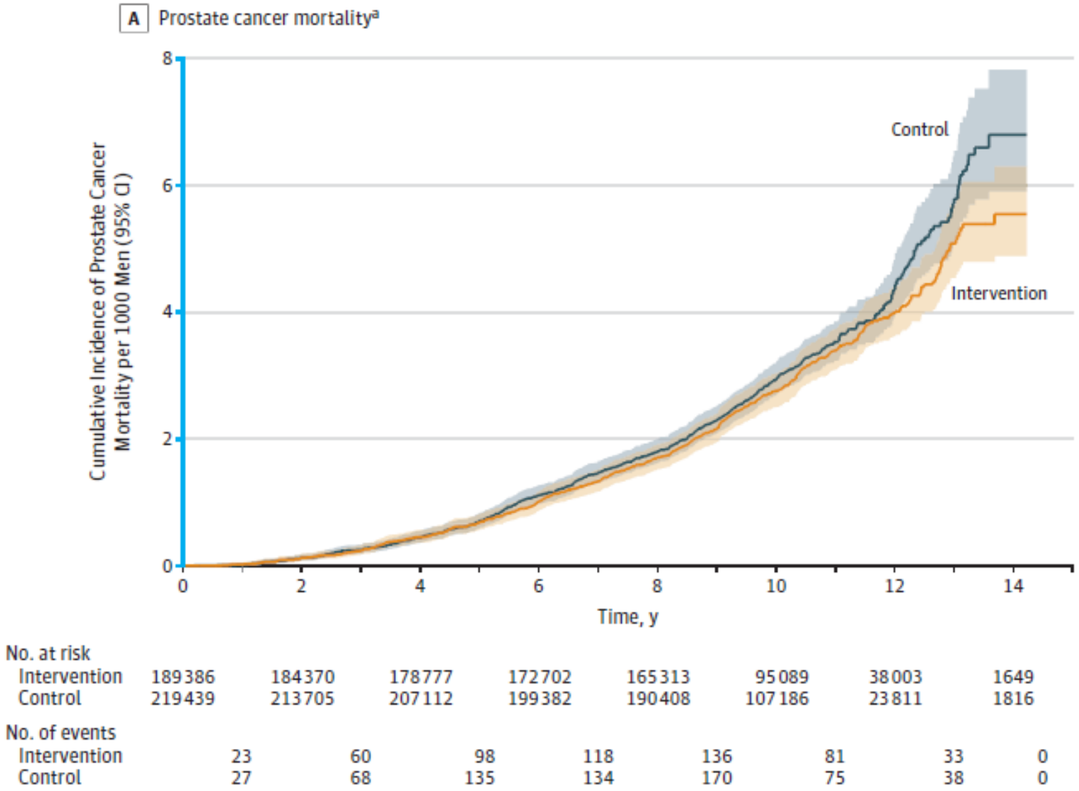
Martin M. JAMA 2018,Andriole GL. NEJM 2009, Schröder FH. NEJM 2009/2012,

CAP TRIAL: A SINGLE PSA TEST AT AGE 50-69 DOES NOT REDUCE PCA MORTALITY AT 10 YEARS



JAMA | Original Investigation

Effect of a Low-Intensity PSA-Based Screening on Prostate Cancer Mortality
The CAP Randomized Clinical Trial

Rate/1000 person years:

Intervention: 0,30 (0,27-0,32)
Control: 0,31 (0,29-0,33)

RR 0,96 (0,85-1,08)

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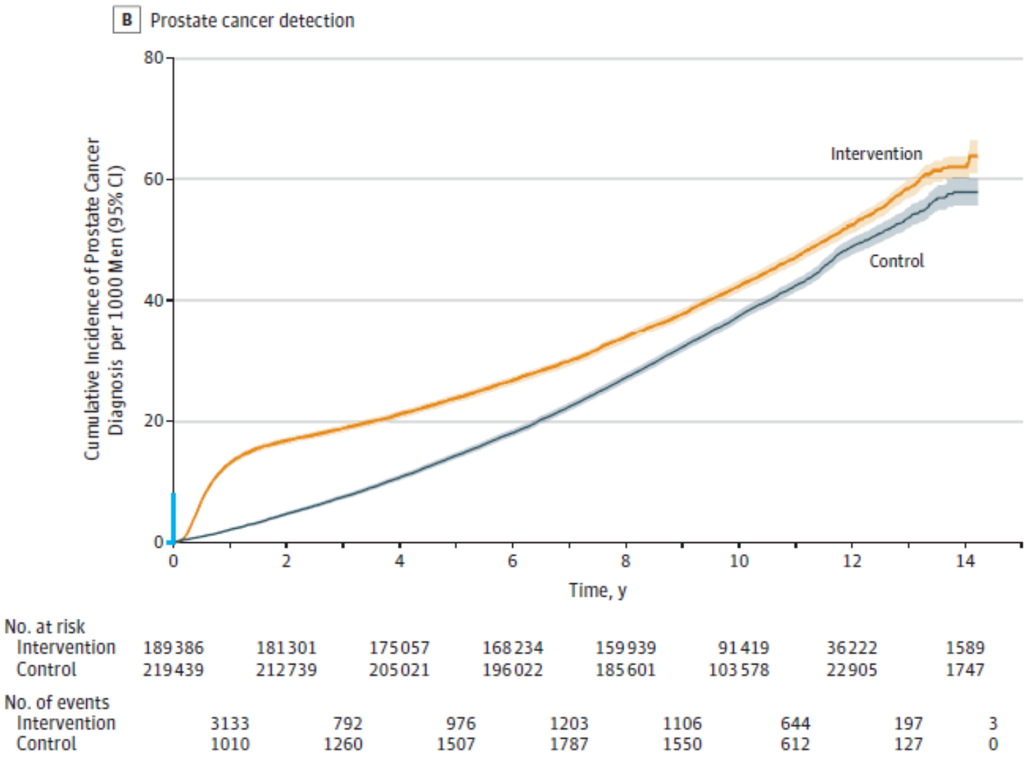
CAP TRIAL: A SINGLE PSA TEST INCREASES THE RISK OF BEING (OVER) DIAGNOSED WITH (LOW RISK) PCA



JAMA | Original Investigation

Effect of a Low-Intensity PSA-Based Screening on Prostate Cancer Mortality
The CAP Randomized Clinical Trial

Rate/1000 person years:

Intervention: 4,45 (4,36-4,55)
Control: 3,80 (3,72-3,89)

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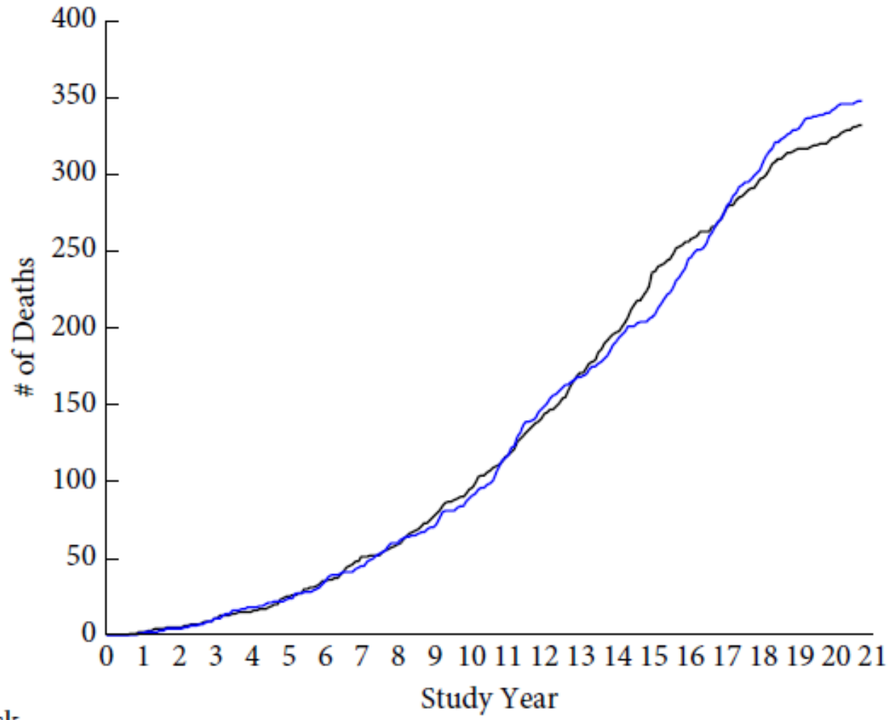
THE PLCO TRIAL DID NOT DEMONSTRATE AN IMPROVEMENT IN PCA MORTALITY AFTER MEDIAN 17Y

Fig. 1 Cumulative prostate cancer deaths by trial arm. Black line: intervention arm; blue line: usual care arm.



# at Risk								
Intervention	38340	36873	35863	33941	31206	26572	14643	5268
Usual Care	38343	37276	35760	33825	30891	25798	13878	4934

Rate/1000 person years:

Intervention: 0,55
Control: 0,59

RR: 0,93 (0,81 – 1,08)

No reduction of Pca mortality in organized versus opportunistic screening

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Pinsky PF. BJU int 2019

RATES OF PSA TESTING IN PLCO WERE VERY SIMILAR IN BOTH ARMS

Time Period	Trial Arm	Total Surveyed, No.[a]	PSA Test Within Past Year for Screening, %	PSA Test Within Past Year for Any Purpose, %	PSA Test Within Past 3 y for Any Purpose, %[b]	PSA Test Ever for Any Purpose, %[b]
Study years 0-5[c]	Control	2214	46.0	52.5	67.9	78.9
Study years 6-9	Intervention	861	47.6	54.4	88.9	98.8
	Control	1068	45.6	54.6	78.4	83.6
Study years 10-13	Intervention	702	43.7	53.1	73.7	98.9
	Control	807	47.5	56.4	80.2	88.1
Study years 14-17	Intervention	294	40.5	45.6	71.1	99.3
	Control	339	43.1	50.2	76.4	87.9
All postscreening study years (6-17)	Intervention	1857	45.0	52.5	80.3	98.9
	Control	2214	45.9	54.6	78.7	85.9

A trial comparing organized versus opportunistic screening rather than screening versus no screening

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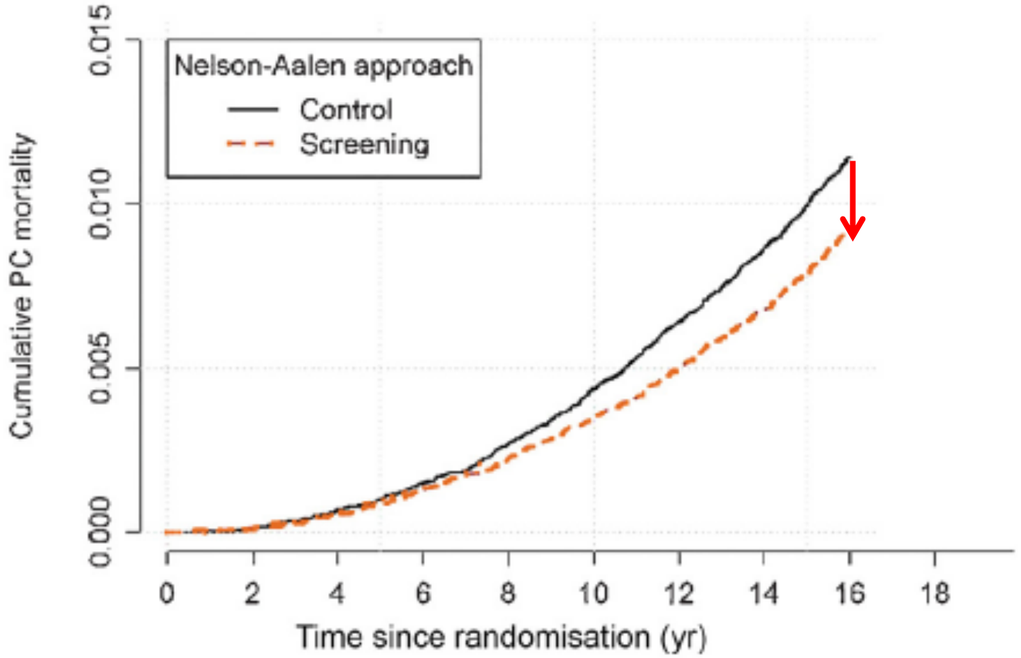
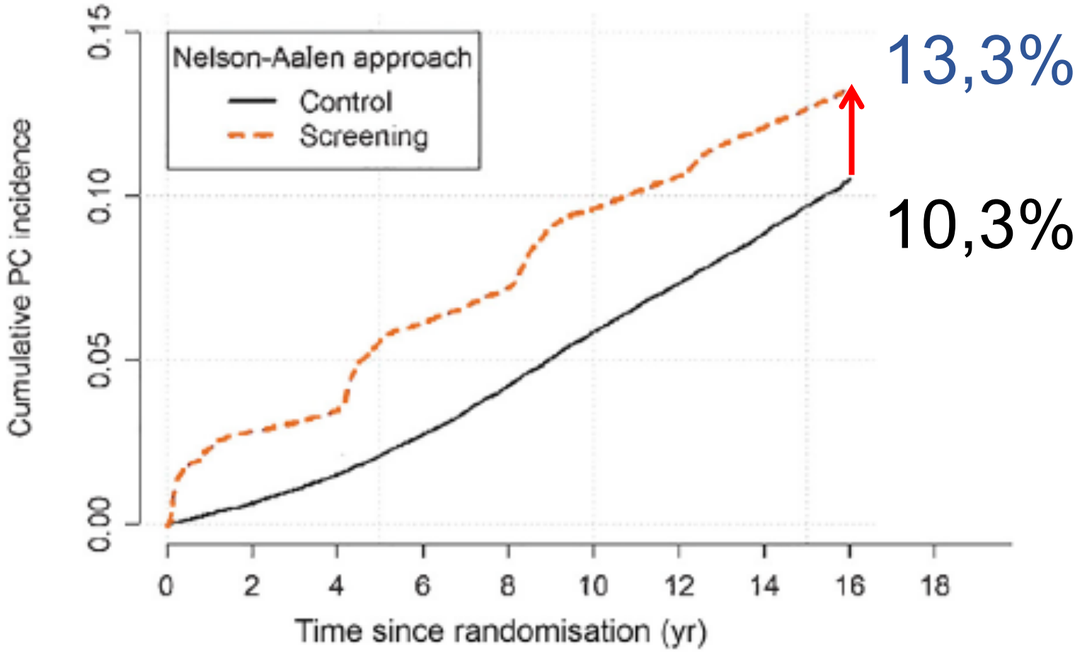
Shoag JE, et al. N Engl J Med, 2016, Pinsky PF. Cancer 2016

THE ERSPC STUDY DEMONSTRATES A 20% REDUCTION IN PCA MORTALITY AT 16 YEARS





Follow up (yrs)	NNI	NND	RR Reduction
9	1410	48	15%
11	979	35	22%
13	781	27	21%
16	570	18	20%

NNI=Number needed to invite to screening to prevent one prostate cancer death
NND=Number needed to invite to diagnose to prevent one prostate cancer death

Hugosson J. et al., Eur Urol 2019

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CAN PROSTATE CANCER SCREENING MAINTAIN THE QUALITY OF LIFE (QALYS)?

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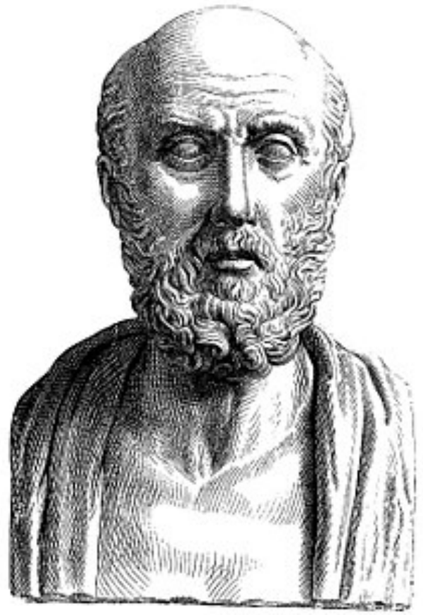
HARMS OF PSA SCREENING

- High risk over **overdiagnosis**: about half of the men with screen-detected cancers would not have developed symptoms during their life-time
- The time between screen-diagnosis and clinical symptoms (lead time) is strong: mean 5-10years
- Psychological harm
- Potential side effects of treatments and active surveillance



‘Primum non nocere’

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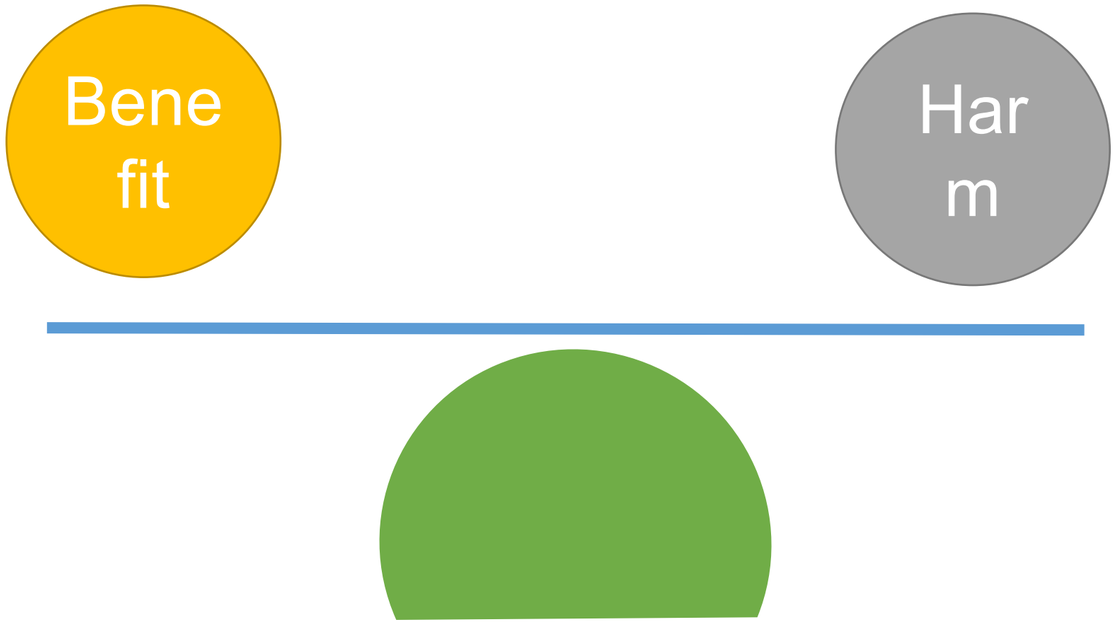
WILL I LIVE LONGER AND/OR BETTER AFTER SCREENING?

Reassurance
↓ Pca mortality
↓ Pca metastasis

False positives, anxiety
Overdiagnosis
Overtreatment



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IN THE ERSPC STUDY SCREENING REDUCES PCA MORTALITY BUT IS OFFSET BY A REDUCTION IN QALYS.

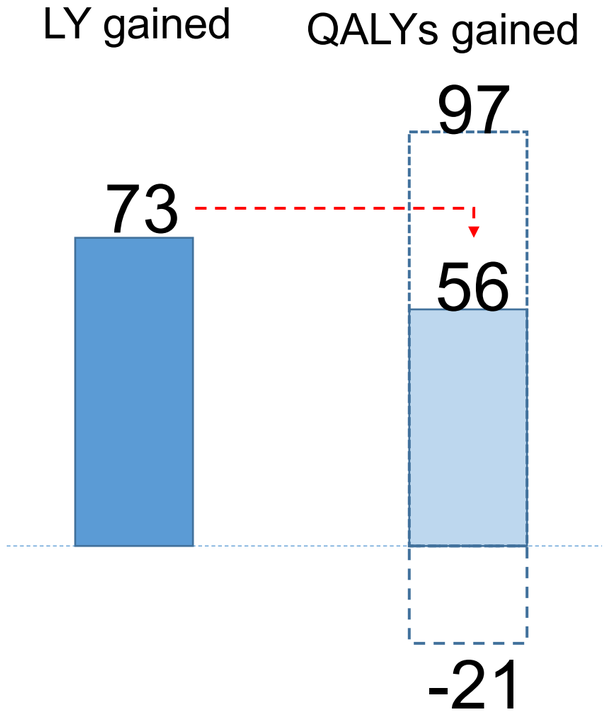

Table 3. Effect of Various Health States with and without Annual Screening for Prostate Cancer over the Lifetime of 1000 Men between the Ages of 55 and 69 Years.*

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 net effect of PCa screening can be a loss or a gain, depending on patients' utilities for their potential future health states.

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SOX HC. NEJM 2012 , Heijnsdijk EAM. NEJM 2012

QALY: Quality-adjusted life years

CURRENT HEATH POLICY GUIDELINES?

The UK NSC recommendation on Prostate cancer screening/PSA testing in men over the age of 50

Recommendation	Systematic population screening programme not recommended
Last review completed	January 2016
Next review due in	2019/20

U.S. Preventive Services TASK FORCE

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men aged 55 to 69 years	For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening.	C
Men 70 years and older	The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older.	D

KCE
FEDERAAL KENNISCENTRUM VOOR DE GEZONDHEIDSZORG

A decision aid for an informed choice when patient asks for PSA screening

KCE Reports 224

2

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It Ain't What You Do, It's the Way You Do It: Five Golden Rules for Transforming Prostate-Specific Antigen Screening

Andrew Vickers [a,*], *Sigrid Carlsson* [b,c], *Vincent Laudone* [b], *Hans Lilja* [b,d,e]

WHAT CAN WE DO TO REDUCE THE HARMS OF PSA SCREENING?

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Vickers A. Eur Urol 2014

SHARED-DECISION MAKING

- Up to 1 in 4 primary care providers prescribe a PSA test without discussing it with the patients

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A decision aid for an informed choice when patient asks for PSA screening

KCE Reports 224

EAU – EANM – ESTRO – ESUR – SIOG Guidelines on

Prostate Cancer

Recommendations	LE	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	3	Strong

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Volk RJ. ANN FAM. Med 2013, EAU guidelines 2019

DON'T SCREEN MEN WHO WON'T BENEFIT

- Autopsy studies demonstrate that most men will develop Pca if they live long enough
- There is still excessive PSA screening in old and comorbid patients (about 50% op PSA tests are performed at age >70y)
- EAU guidelines 2019

Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status (PS) and a life-expectancy of at least ten to fifteen years.	3	Strong
Offer early PSA testing in well-informed men at elevated risk of having PCa: • men > 50 years of age; • men > 45 years of age and a family history of PCa; • African-Americans > 45 years of age.	2b	Strong

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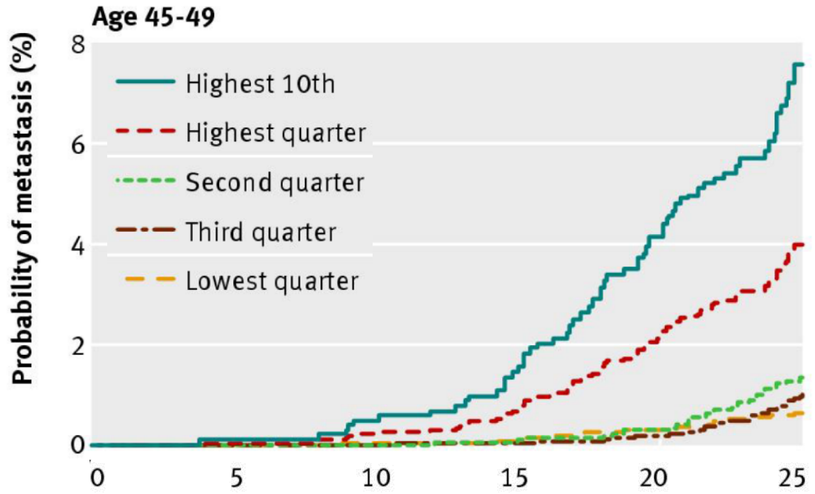
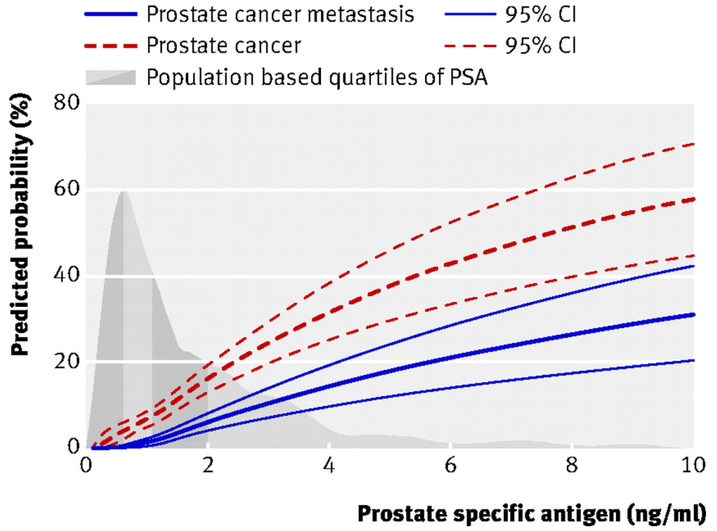
Drazer MW. JCO 2015, Bell KJL. Int J Canc 2015

RISK ADAPTED SCREENING

Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study



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



Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to eight years in those not at risk.	3	Weak

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Vickers A. BMJ 2013, Vickers A J. BMJ 2010

AVOID UNNECESSARY BIOPSIES

- **Confirm an isolated PSA rise** before proceeding with further testing

- Rule out other reasons of PSA rise (infection, BPH)
- Use risk calculators (eg ERSPC), PSA density
- mp MRI pre-biopsy can reduce unnecessary biopsies by 25%
- Other tests like PCA3, SelectMDX, PHI

Recommendation	LE	Strength rating
To avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: • risk-calculator; • imaging; • an additional serum or urine-based test.	3	Strong

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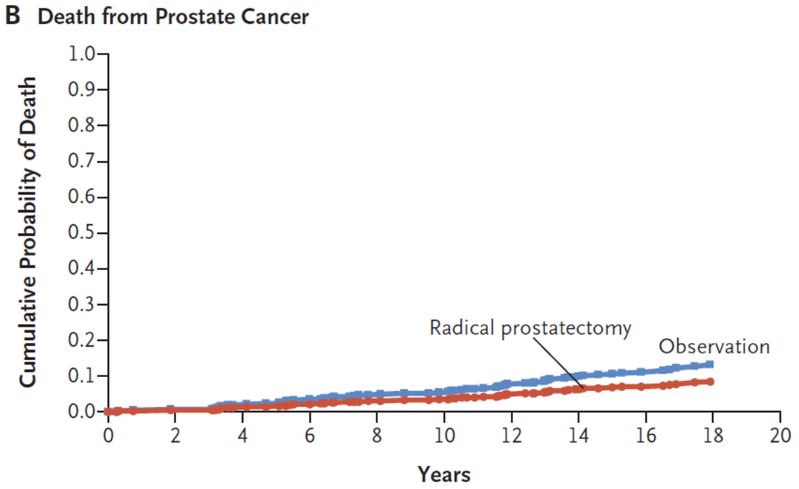
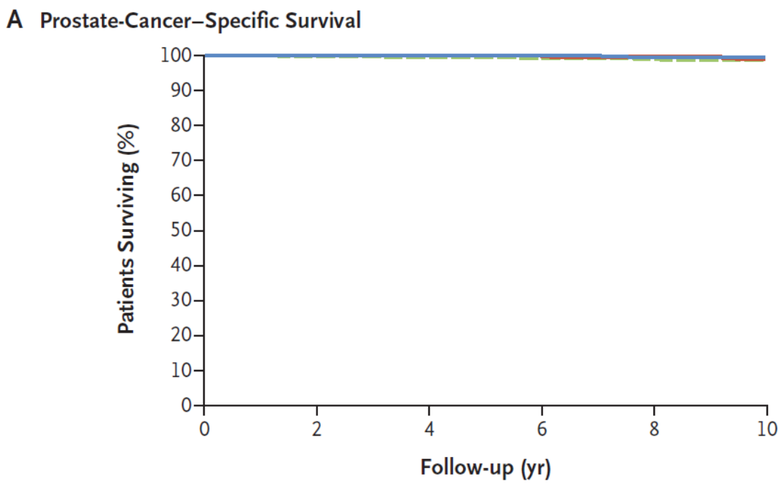
DON’T TREAT MEN WITH LOW RISK DISEASE

PIVOT



ProtecT



Active surveillance (AS)	
Offer AS to patients suitable for curative treatment but with low-risk PCa.	Strong

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CONCLUSIONS

- Insufficient data to support population-based screening:
  - *(Limited) Reduction in PCa mortality at the high cost of anxiety, overdiagnosis and overtreatment*
  - Opportunistic screening should be offered if the patient is well-informed and consents (shared-decision making)

- As uro-oncology specialists we have to do better to reduce harms of PCa screening in order to maximize the net benefits:
  - Optimize/restrict indications for screening
  - Optimize/restrict indications for biopsies (role of MRI, genomic tests,…)
  - Optimize/restrict indications for treatment

DETECTION OF PROSTATE CANCER IS LIKE PICKING YOUR NOSE IN PUBLIC… IF YOU FIND SOMETHING YOU NEED TO KNOW EXACTLY WHAT TO DO WITH IT…

Ian Tannock, MD, PhD

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