

Prostate Cancer Screening Anno 2019

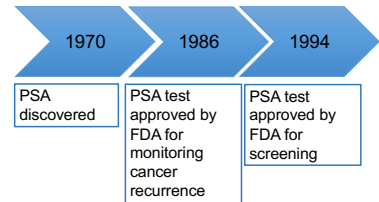
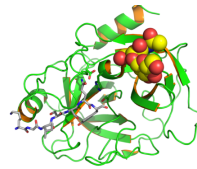
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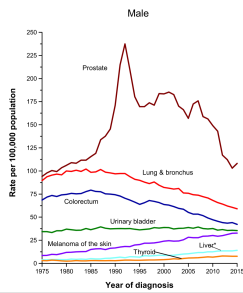
Prostate Specific Antigen

Kallikrein secreted by epithelial cells of the prostate



EAU Guidelines Prostate Cancer

Prostate Cancer: Epidemiology

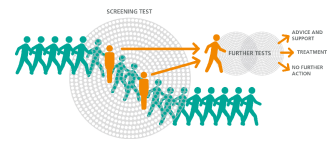


Estimated Deaths			Males	
Lung & bronchus	76,650	24%		
Prostate	31,620	10%		
Colon & rectum	27,640	9%		
Pancreas	23,800	7%		
Liver & intrahepatic bile duct	21,600	7%		
Leukemia	13,150	4%		
Esophagus	13,020	4%		
Urinary bladder	12,870	4%		
Non-Hodgkin lymphoma	11,510	4%		
Brain & other nervous system	9,910	3%		
All Sites	321,670	100%		

Siegel et al. CA Cancer Clin 2019;69:7-34

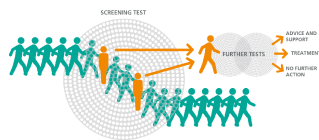
Screening vs. Early Detection

- **Screening:** the systematic examination of asymptomatic men (at risk); usually initiated by health authorities
- **Early detection:** An individualised risk-adapted strategy



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Why Are We Still Talking About PSA Screening in 2019!?!

- PSA screening is one of the most controversial topics in the urological literature
- **Conflicting results** from prospective trials
- **Conflicting interpretation** of prospective trials
- **Conflicting recommendations** from scientific societies



Screening: EAU Position Paper

Structured Population-based Prostate-specific Antigen Screening for Prostate Cancer: The European Association of Urology Position in 2019

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PSA Screening – Is There a Benefit?

Study	Setting	Enrolment criteria	N. Of men (intervention/c ontrol)	Trigger for biopsy	Screening frequency
CAP	Cluster RCT	Men aged 50-69	195912/219445	PSA ≥3 ng/ml	One-time screening
ERSPC	RCT	Men aged 55-69	72891/89352	PSA ≥3 ng/ml	2-4 years
Labrie (Quebec)	RCT	Men aged 45-80	31133/15353	PSA ≥3 ng/ml	Annual screening
Lundgren (Stockholm)	RCT	Men aged 55-70	2400/25081	PSA >10 ng/ml	One-time screening
PLCO	RCT	Men aged 55-74	38340/38343	PSA ≥4 ng/ml	Annual screening

Ilic et al. *BMJ* 2018;362

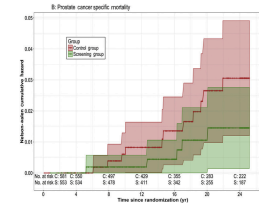
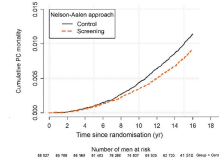
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Screening based on multiple PSA testing rounds reduces PCa-specific mortality in asymptomatic men aged between 55 and 69 years

- 162,388 men randomized to PSA testing
- 1100 men randomized to screening every 2-year vs. control (Rotterdam pilot 1 cohort)
- Median follow-up: **16 years**
- The rate ratio of mortality was 0.80 at 16 yr
- Median follow-up: **19 years**
- Relative risk of CSM: 0.46%
- At 16-year follow-up:
 - NNS: 570
 - NND: 18



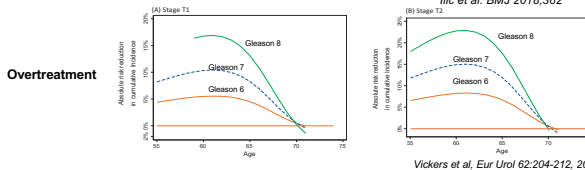
Hugusson et al. *Eur Urol* 2019;76:43-51

Osses et al. *Eur Urol* 2019;75:374-7

PSA Screening – Harms

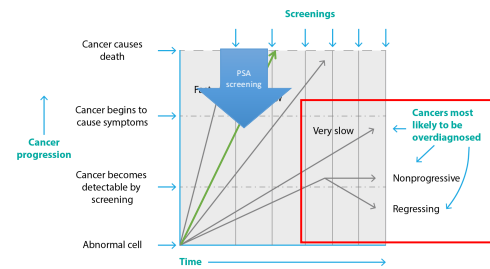
Study	PSA screening	Control	Relative risk (95% CI)	Relative risk (95% CI)
PLCO 2017	4075/38 340	3601/38 343	1.13 (1.08 to 1.18)	
CAP 2018	4938/189 386	4192/219 439	1.36 (1.31 to 1.42)	
ERSPC (cont) 2014	6067/772 891	4254/89 352	1.75 (1.68 to 1.82)	
Random effect: P<0.001 for heterogeneity, I ² =99%			1.39 (1.09 to 1.79)	

Ilic et al. *BMJ* 2018;362



Vickers et al. *Eur Urol* 62:204-212, 2012

PSA Screening: Finding the Balance Between Early Diagnosis and Overdiagnosis



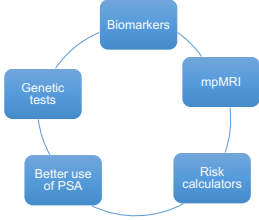
How Can We Optimize PSA Screening?

Improved detection of csPCa:

- PSA alone has a low positive predictive value for csPCa

Reduced risk of overdiagnosis and overtreatment:

- Prostate biopsy in all pts with elevated PSA levels are associated with the risk of overdiagnosis
- Additional tools are needed to identify men with elevated PSA levels who should be considered for a prostate biopsy

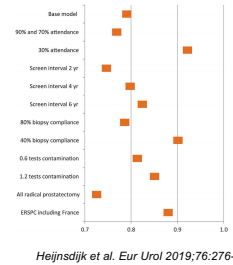


Improving the Efficacy of PSA Screening Increasing Compliance and Screening Intensity

- Simulation model to predict the influence of study features on the results of the ERSPC

- The benefits of screening would have been larger with:

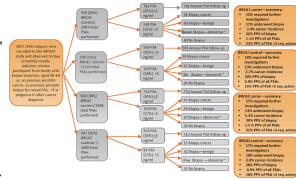
- Increased attendance
- A 2-year screening interval
- An 80% biopsy compliance



Heijnsdijk et al. Eur Urol 2019;76:276-9

Improving the Efficacy of Screening: Genetic Tests to Identify Men at Risk

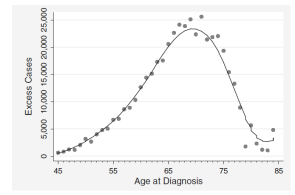
- Mutations in BRCA2 cause a higher risk of early-onset aggressive PCa
- Participants underwent PSA screening for 3 yr, and if PSA > 3.0 ng/ml, men were offered biopsy
- Cancer incidence rate per 1000 person years was higher in BRCA2 carriers than in noncarriers
- BRCA2 carriers were diagnosed at a younger age (61 vs 64 yr) and were more likely to have csPCa than non-carriers (77% vs 40%)



Page et al. Eur Urol 2019; in press

Reducing the Risk of Overdiagnosis: Consider Life Expectancy

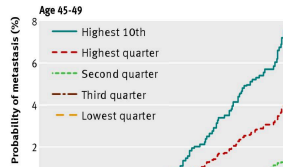
- 50% of excess prostate cancer diagnosed through PSA screening occur in men > 70 yr of age
- Any decrease in mortality associated with PSA screening in men > 70 yr might be offset by the risk of overdiagnosis
- Screening should be considered only in selected men > 70 yr with above average PSA levels and long life expectancy to minimize the risk of overdiagnosis



Vickers et al. BMC Medicine 2014

Reducing the Risk of Overdiagnosis: Baseline PSA Levels

- Patients with a baseline PSA of 1.6 ng/ml have a 20-yr risk of metastasis and cancer-specific mortality higher than 4% and 2%, respectively
- A baseline PSA value at the age of 45 yr should be obtained to identify men more likely to experience metastases and CSM
- Screening intervals should be adjusted according to baseline PSA levels



Vickers et al. BMJ 2013;15:346;f2023

Reducing the Risk of Overdiagnosis: Risk Calculators

- Update of the ERSPC Rotterdam risk calculator 3
- At 1% risk threshold, the updated calculator would spare 34% biopsies with the risk of missing only 2% high-risk cases

Model and predictor	OR (95% CI)	
	Low-risk PCa	High-risk PCa
DRE model	2.29 (2.06-2.55)	0.66 (0.47-0.94)
PSA	1.60 (0.99-2.61)	1.83 (1.03-3.26)
Age	1.51 (1.16-2.07)	0.38 (0.26-0.56)
Abnormal DRE	0.26 (0.20-0.32)	0.11 (0.07-0.16)
Area under the curve (95% CI)	0.70 (0.68-0.72)	0.68 (0.66-0.70)
TRUS model	2.60 (2.33-2.91)	0.58 (0.40-0.84)
PSA	1.62 (1.00-2.61)	1.83 (1.03-3.26)
Age	1.51 (1.16-2.07)	0.38 (0.26-0.56)
Abnormal DRE	0.26 (0.20-0.32)	0.11 (0.07-0.16)
Area under the curve (95% CI)	0.73 (0.70-0.75)	0.69 (0.67-0.71)

Risk	(A) No. of men biopsied	(B) No. of biopsies saved (% of total A)	(C) No. of PCs detected (% PPV)	(D) No. of LR PCs detected (% of A)	(E) No. of LR PCs missed (% of total D)	(F) No. of HR PCs detected (% of A)	(G) No. of HR PCs missed (% of total F)
Total	3580	0	849 (23.7)	607 (17.0)	0	242 (6.8)	0
1%	2373	1207 (33.7)	736 (31.0)	498 (21.0)	168 (7.8)	227 (10.0)	5 (2.1)
1.5%	2017	1563 (43.7)	675 (33.5)	443 (22.0)	164 (7.7)	232 (11.5)	10 (4.1)
2%	1749	1831 (51.3)	625 (36.3)	408 (23.3)	150 (8.8)	227 (13.0)	15 (6.2)
3%	1412	2168 (60.6)	581 (41.1)	357 (25.3)	250 (41.2)	224 (15.9)	18 (7.4)
5%	1024	2556 (71.4)	493 (48.1)	284 (27.7)	323 (53.2)	209 (20.4)	33 (13.6)

Roobol M et al. Eur Urol 2017;72:45-51

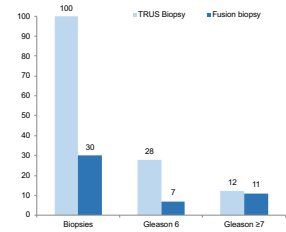
Reducing the Risk of Overdiagnosis: mpMRI as a Triage test

	PROMIS	PRECISION	MRI-FIRST	4M
N. Of biopsies	-27%	-28%	-21%	-49%
Detection of clinically significant PCa	-1%	+12%	+2.4%	+2%
Detection of clinically insignificant PCa	-5%	-13%	-16%	-11%

- Multiparametric MRI can improve selection of men for prostate biopsy
- The performance of mpMRI for PCa detection and risk estimation is improved by using it in men at risk of clinically significant disease before prostate biopsy

Reducing the Risk of Overdiagnosis: mpMRI as a Triage test

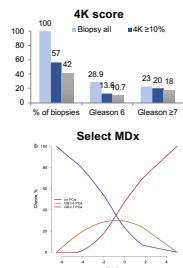
- 5th screening round ERSPC Rotterdam
- 337 men had a PSA >3 ng/ml and underwent a prebiopsy MRI
- 158 men received MRI with fusion biopsy if positive
- The use of mpMRI would have spared 2/3 of prostate biopsies and low-grade disease without increasing the risk of missing high-grade disease



Alberts et al. Eur Urol 2018;73:343-50

Reducing the Risk of Overdiagnosis: Novel Biomarkers

	SelectMDx	4Kscore	PHI
AUC	0.85	0.82	0.70-0.77
NPV (%)	95	95	67-92
Risk of missing PCa (%)	5	5	8-33
Avoided biopsies (%)	44	36	36



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Individualized PSA screening

Baseline PSA values and risk calculators should guide the use of PSA-based screening to reduce overdiagnosis

- Obtain a baseline PSA at the age of 45 for risk stratification
 - <1 ng/ml: PSA-testing intervals up to 8 yr
 - ≥1 ng/ml: PSA testing every 2-4 yr
- Stop PSA testing in men with a life expectancy <10 yr (consider PSA testing only in selected men with above average PSA levels and long life expectancy)
- In men at risk of significant PCa according to PSA levels consider the following tests to select biopsy candidates:
 - Risk calculators
 - mpMRI
 - Tests based on biomarkers and genetic polymorphisms
- Consider MRI targeted with concomitant systematic biopsy if the mpMRI is suggestive of PCa

The role of multiparametric MRI

mpMRI could reduce over-diagnosis without increasing the risk of missing high-grade disease and might be considered as a triage test in elevated PSA levels

Molecular biomarkers

Molecular biomarkers might assist physicians in the identification of men with elevated PSA levels who should be considered for a prostate biopsy

Gandaglia, Van Poppel et al. Eur Urol 2019;76:142-50