

Risk-adapted Screening for Prostate Cancer

Peter Albers, MD
Professor of Urology

Division Head, C130 Personalized Prevention and Early Detection of Prostate Cancer
German Cancer Research Center (DKFZ) Heidelberg, Germany
Chair, Department of Urology, Düsseldorf University Hospital
Heinrich-Heine-University, Düsseldorf, Germany

no conflicts of interest

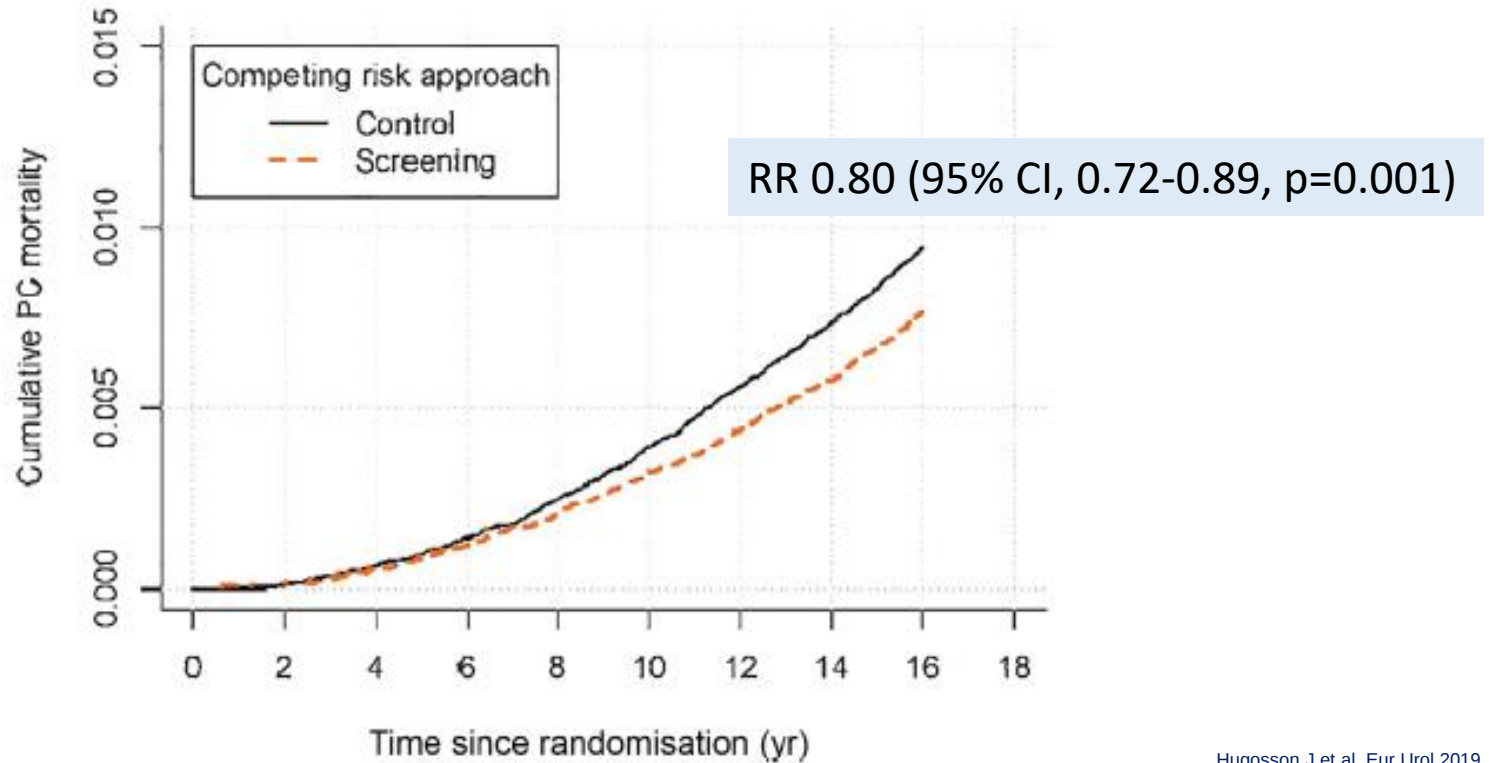
Cancer Mortality US

Estimated Deaths

			Males	Females			
Lung & bronchus	72,500	23%			Lung & bronchus	63,220	22%
Prostate	33,330	10%			Breast	42,170	15%
Colon & rectum	28,630	9%			Colon & rectum	24,570	9%
Pancreas	24,640	8%			Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%			Ovary	13,940	5%
Leukemia	13,420	4%			Uterine corpus	12,590	4%
Esophagus	13,100	4%			Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%			Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%			Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%			Brain & other nervous system	7,830	3%
All Sites	321,160	100%			All Sites	285,360	100%

Siegel RL et al CA Cancer J Clin 2020

Prostate cancer specific mortality (ERSPC)



Hugosson J et al. Eur Urol 2019



.....develops recommendations for primary care clinicians and health systems

October 2011

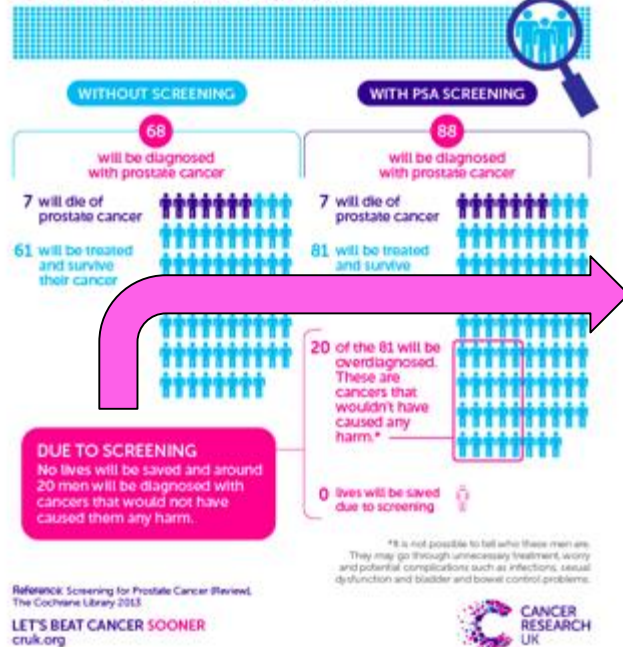


Prostate Cancer Screening Patient Information UK

PROSTATE SCREENING IN MEN

IF THERE WAS A PSA PROSTATE CANCER SCREENING PROGRAMME

Of 1,000 men aged 45–80, without any symptoms...

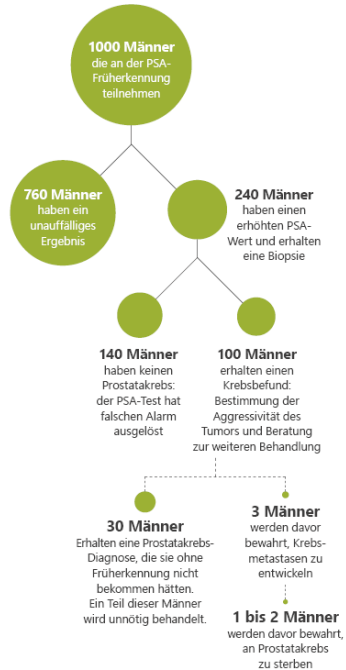


Due to screening:

- no lives will be saved
- around 20 men will be diagnosed with cancers that would not have caused any harm

<https://scienceblog.cancerresearchuk.org>

Prostate Cancer Screening Patient Information Germany



1000

men with PSA (cut-off < 4 ng/ml)

223 - 261

have an abnormal test without PCA
("false-positives")

35 - 60

get a prostate cancer diagnosis without clinical
relevance („overdiagnosis“)

3

will not get metastasis due to screening
(within in 12 years)

3

will not die from prostate cancer due to screening
(within 16 years)

www.gesundheitsinformation.de (IQWiG) and Update IQWiG Jan 06, 2020 <https://www.iqwig.de/de/projekte-ergebnisse/>

German Statutory Early Detection Program for Men

beginning at age 45 and then **yearly**:

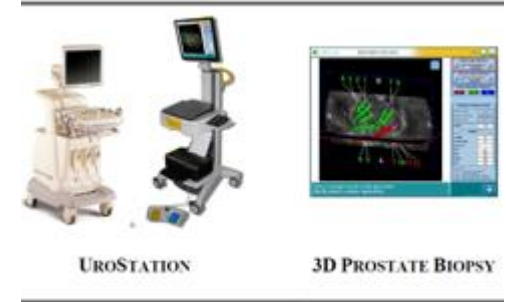
- medical history
- examination external genitalia
- examination of lymph nodes
- **digitorectal examination (DRE)**
- information

since 1971

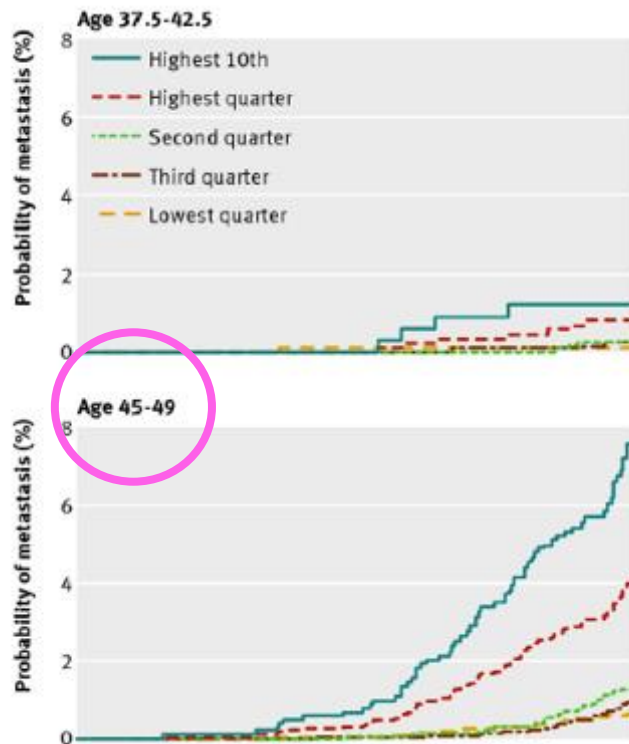
Individualised Early Detection of PCA

Potential Methods

- age-adapted risk groups
- hereditary risk
- mpMRI before biopsy
- kallikreins (4K)
- molecular serum markers (SNPs, MSI)
- urine markers (HOXC6, DLX1, T2:ERG)
- combinations
(risk calculators from ERSPC and PCPT)



Prediction of PCA metastasis by „baseline“ PSA



PSA at 45 yrs risk for metastasis after 25 yrs

PSA < 1.1 ng/ml 1.38%

PSA > 1.6 ng/ml up to 9.82%



~ 10x higher risk > 1.6 ng/ml

Vickers A et al. BMJ 2013

PROBASE

Die Deutsche Prostatakrebs Screening Studie

Risk-adapted **prostate** cancer (PCa) early detection study based on a “**baseline**” PSA value in young men – a prospective multicenter randomized trial (**PROBASE**)

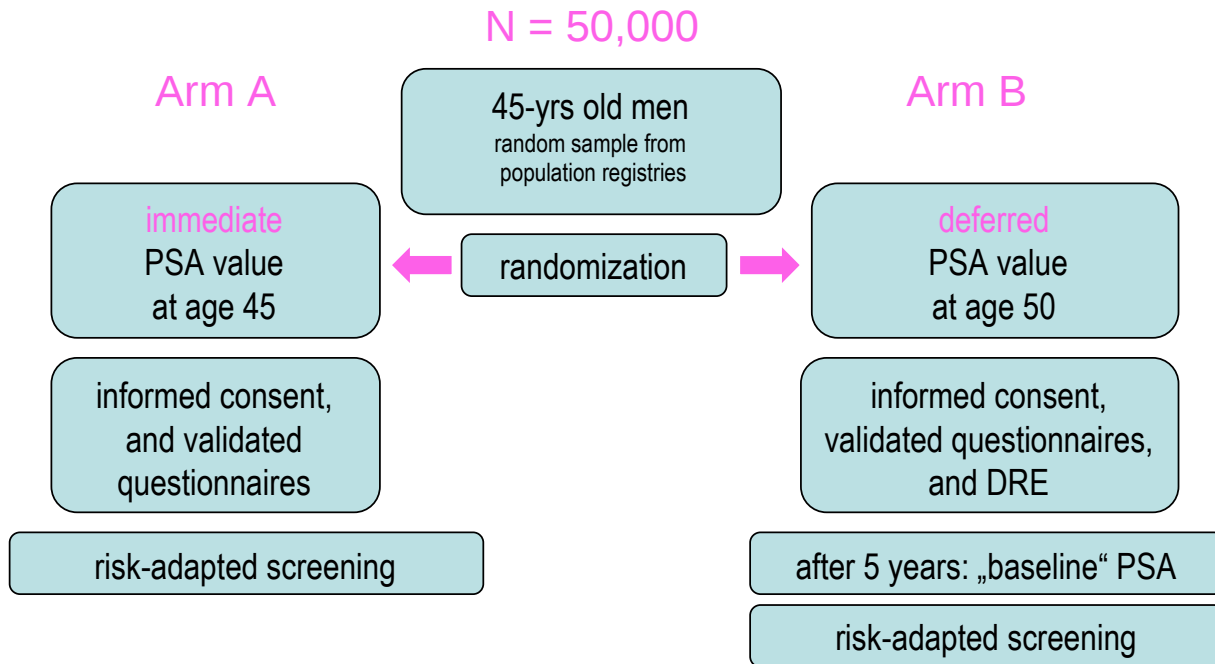


Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

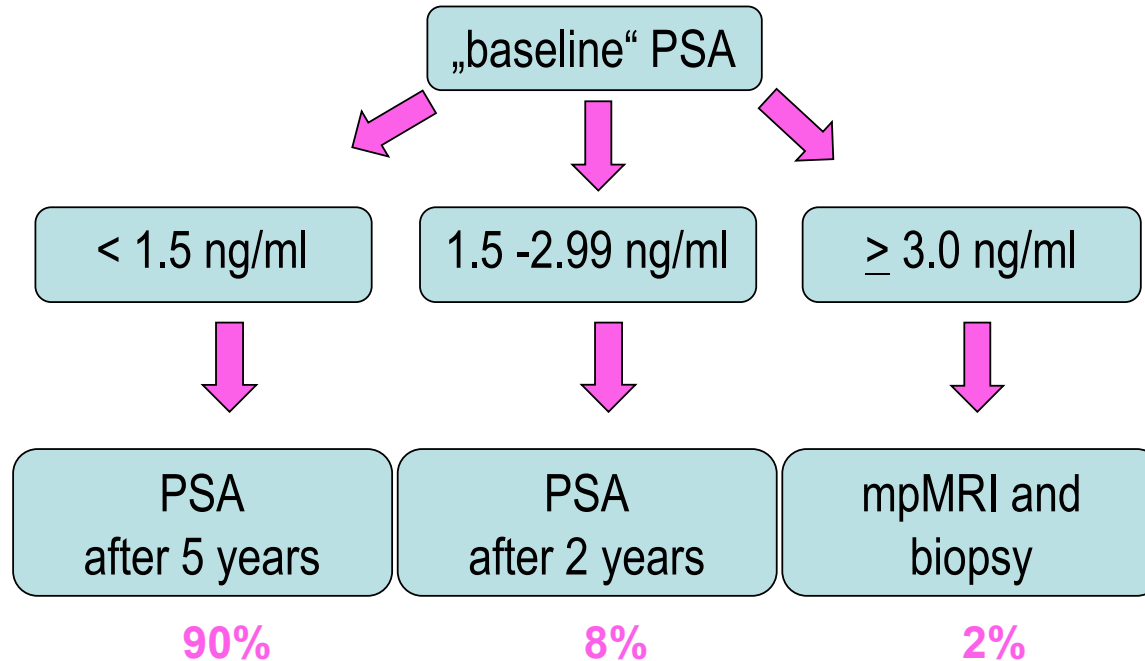
Peter Albers^{1,7}, Christian Arsov¹, Kathleen Herkommer², Jürgen Gschwend², Florian Imkamp³, Markus Kuczyk³, Boris Hadaschik^{4,5}, Glen Kristiansen⁶, Lars Schimmöller¹, Gerald Antoch¹, Ernst Rummeny², Frank Wacker³, Heinz Schlemmer⁷, Axel Benner⁷, Roswitha Siener⁶, Rudolf Kaaks⁷, Nikolaus Becker⁷

¹Düsseldorf University Hospital, ²Munich Technical University Hospital,
³Hannover University Hospital, ⁴Heidelberg University Hospital, ⁵Essen University Hospital, ⁶Bonn University Hospital,
⁷German Cancer Research Center (DKFZ) Heidelberg, Germany

Study Design



Study Design



PROBASE

Die Deutsche Prostatakrebs-„Screening“ Studie

Düsseldorf

N = 12777

Peter Albers
Christian Arsov

Heidelberg

N = 9509

Markus Hohenfellner
Viktoria Schütz
Stefan Duensing

dkfz. DEUTSCHES
KREBSFORSCHUNGSZENTRUM
IN DER HELMHOLTZ-GEMEINSCHAFT

Nikolaus Becker
Rudolf Kaaks
Axel Benner



Hannover

N = 10860

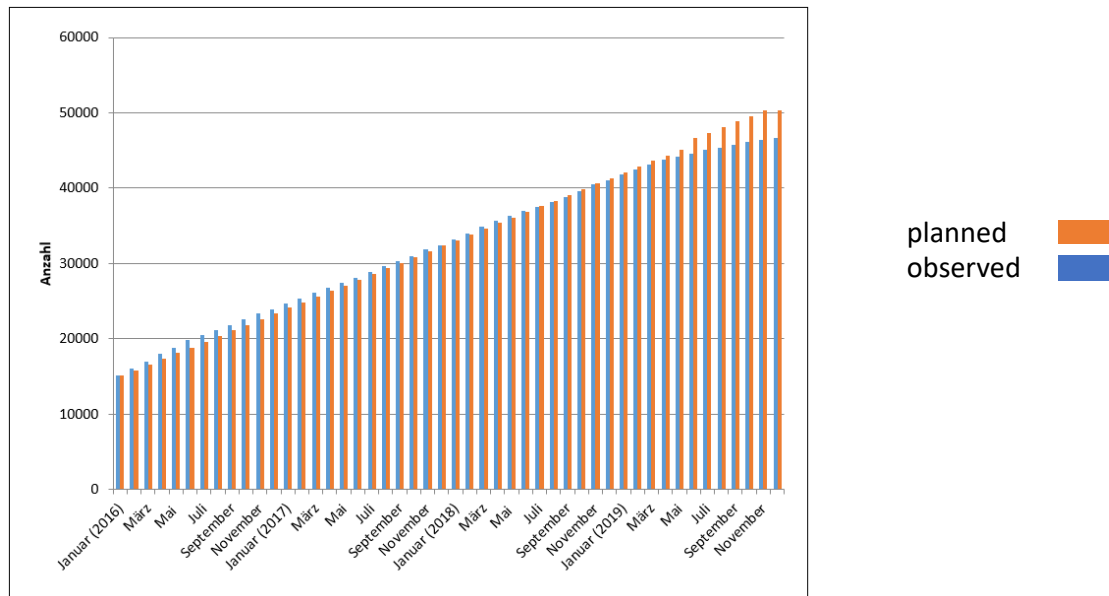
Markus Kuczyk
Florian Imkamp

Munich

N = 13496

Jürgen Gschwend
Kathleen Herkommer

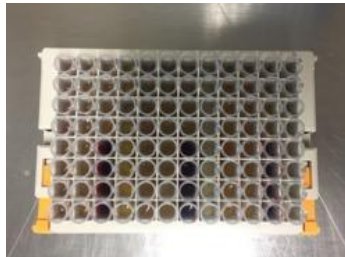
Accrual Feb 2014 – Dec 2019: 46,642 participants



data cut-off Dec 31, 2019

Establishment of a centralized PCA biobank

2023: 2.5 Mio blood samples* and 0.2 Mio urine samples



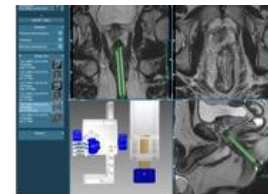
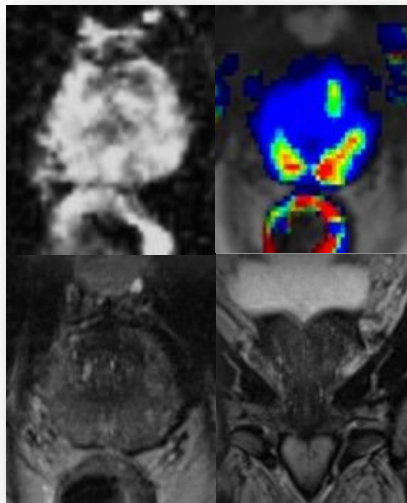
cooperation with
DKFZ - biorepository
(new building 2023)



*15 x serum, 3-4 x buffy coat, 5-6 x plasma aliquots per participant

Up-to-Date PCA Diagnostics (1)

with multiparametric MRI (reference radiology) and fusion biopsies



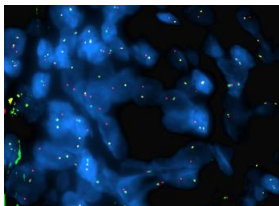
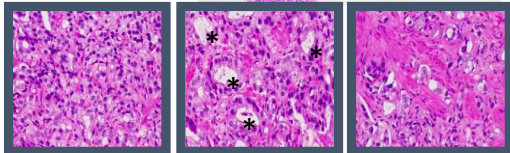
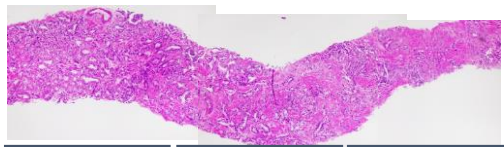
**standardization
of mpMRI diagnostics
at all study sites**

reference radiology
PD Dr. L. Schimmöller
Prof. Dr. G. Antoch
(Düsseldorf)



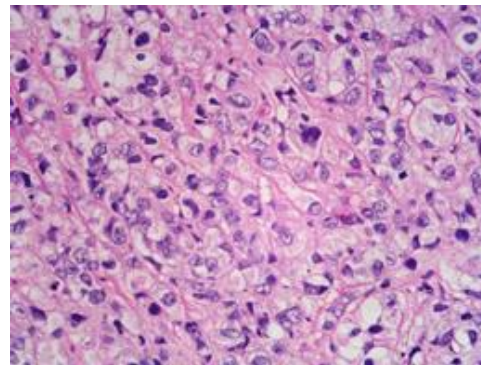
Up-to-Date PCA Diagnostics (2)

with reference pathology for biopsies and prostatectomy samples and
establishment of a tissue biobank at Bonn University, Department of Pathology



**standardization
of ISUP grading**

reference pathology
Prof. Dr. G. Kristiansen
(Bonn)



Is early-onset prostate cancer a lethal disease ?

Nat Rev Urol. 2014 June ; 11(6): 317–323. doi:10.1038/nrurol.2014.91.

Prostate Cancer in Young Men: An Important Clinical Entity

Claudia A. Salinas¹, Alex Tsodikov², Miriam Ishak-Howard¹, and Kathleen A. Cooney^{1,3}

¹Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan

²Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan

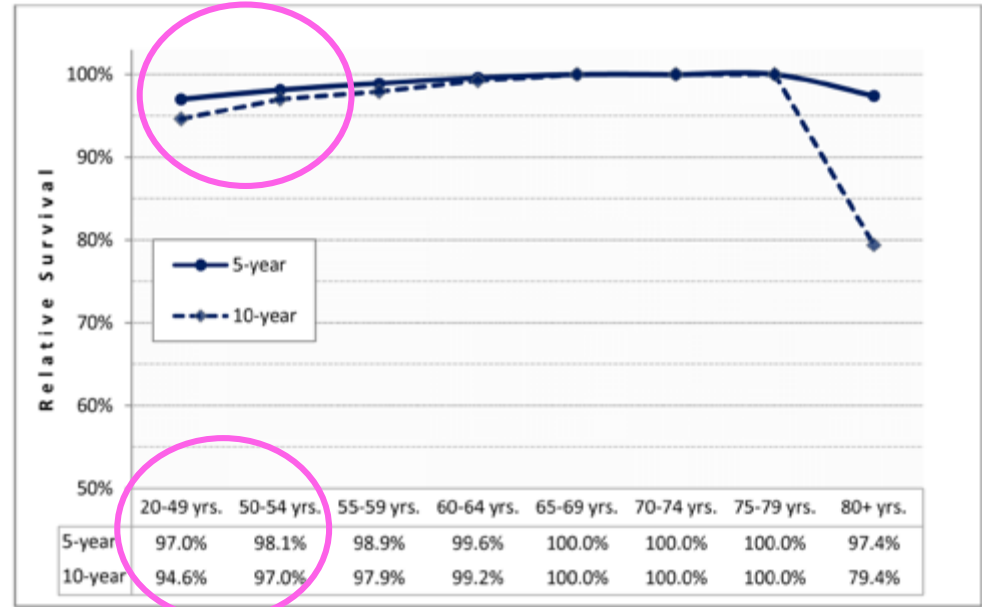
³Department of Urology, University of Michigan Medical School, Ann Arbor, Michigan

inferior 5- and 10 yrs relative survival

with prostate cancer

at age groups

20-49, 50-54 and > 80



100% = SEER relative survival data per age group

Salinas CA et al. *Nat Rev Urol* 2014

Is early-onset prostate cancer a lethal disease ?

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



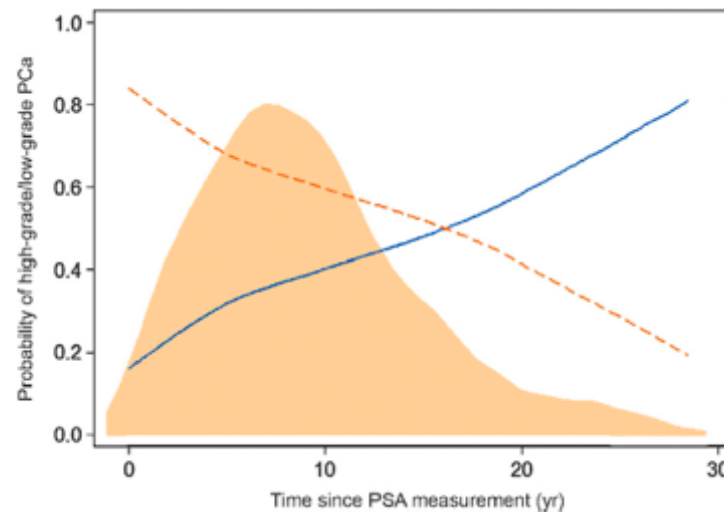
Prostate Cancer

Association Between Lead Time and Prostate Cancer Grade: Evidence of Grade Progression from Long-term Follow-up of Large Population-based Cohorts Not Subject to Prostate-specific Antigen Screening

Melissa Assel^{a,*}, Anders Dahlin^b, David Ulmert^{c,d}, Anders Bergh^e, Pär Stattin^{f,g}, Hans Lilja^{h,i,j,k,*},
Andrew J. Vickers^{a,*}

N= 1041 patients from 3 swedish cohorts with all available data

- early onset prostate cancer is usually low-grade
- grade shifts over time
- late diagnosis of PCA often reveals high-grade disease

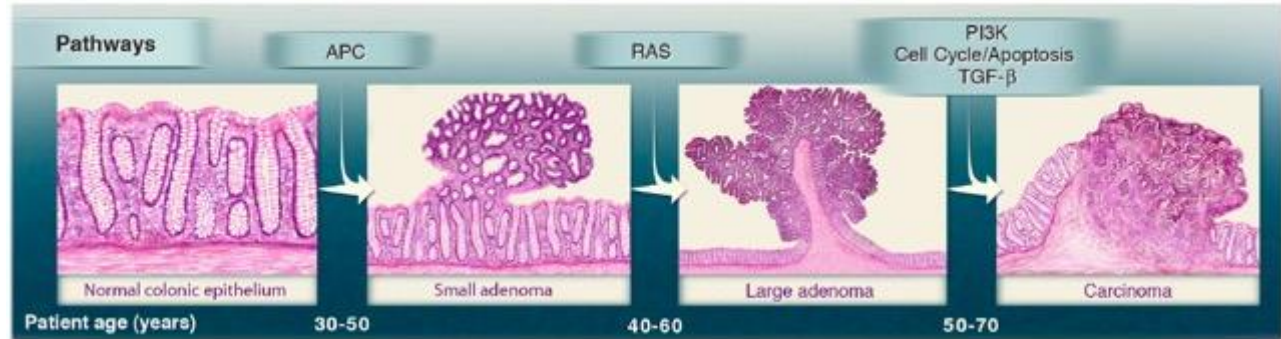


probability of low-grade (orange) and high-grade (blue) prostate cancer depending on lead time (time from elevated PSA to PCA diagnosis)

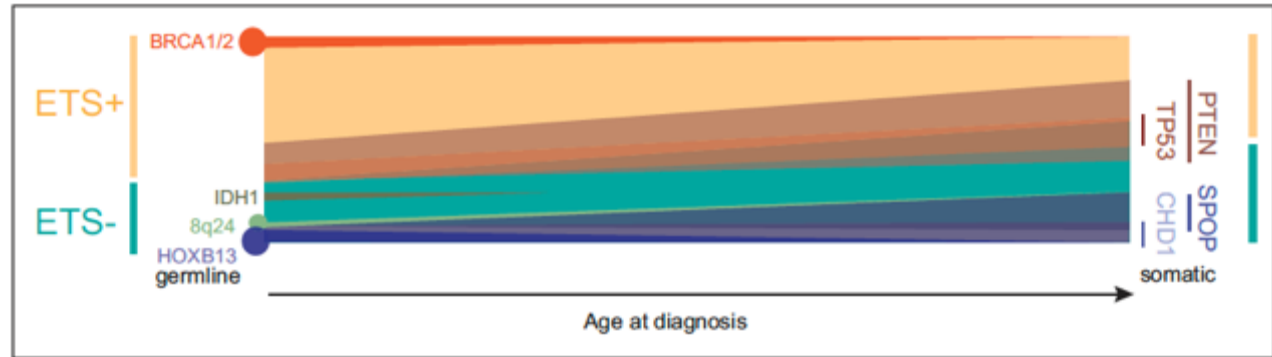
Assel M et al. Eur Urol 2017

Genetic Changes over Time

Colorectal cancer

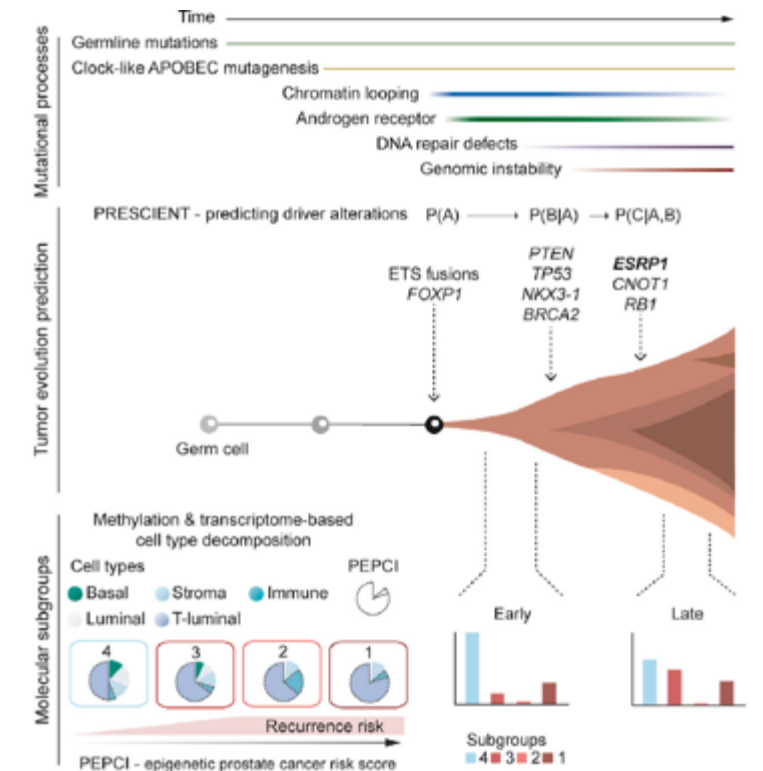


Prostate cancer



Vogelstein B et al. Science 2013, Weischenfeldt J et al. Cancer Cell 2013, Weischenfeldt J et al. Curr Op Urol 2018

Genetic Changes over Time in Early-Onset Prostate Cancer



ESRP1, CNOT1, RB1

PTEN, TP53, BRCA-2, NKX3-1

ETS fusions, FOXP1

↑
aggressiveness

Can baseline PSA predict clinically significant PCA ?



Association of Baseline Prostate-Specific Antigen Level With Long-term Diagnosis of Clinically Significant Prostate Cancer Among Patients Aged 55 to 60 Years A Secondary Analysis of a Cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

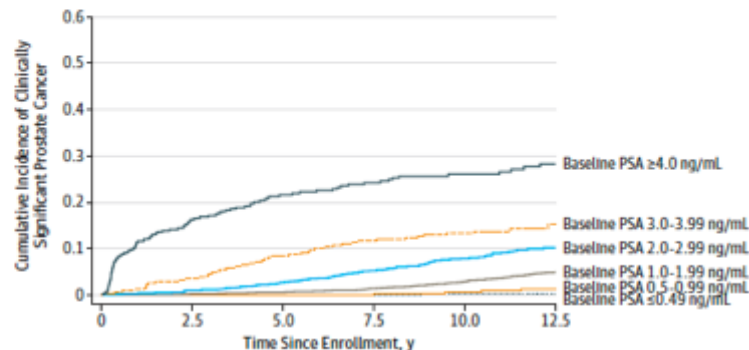
Evan Kovac, MD, CM, FRCSC; Sigrid V. Carlsson, MD, PhD, MPH; Hans Lilja, MD, PhD; Jonas Hugosson, MD, PhD; Michael W. Kattan, PhD, MBA; Erik Holmberg, PhD; Andrew J. Stephenson, MD, MBA

N= 10968 men 55-60 yrs, median age 57 (PLCO),
13 yrs f/u, **only 15 deaths from PCA**

- clinically significant (N= 425) =

biopsy with csT2b or greater, or **GS ≥ 7**
RP with pT3 or pN+ or **GS ≥ 7**
or PCA mortality

Figure 2. 13-Year Kaplan-Meier Risk of Clinically Significant Prostate Cancer Among Patients Aged 55 to 60 Years Enrolled in the Screening Arm of the PLCO Cancer Screening Trial, Stratified by Baseline Prostate-Specific Antigen (PSA) Level

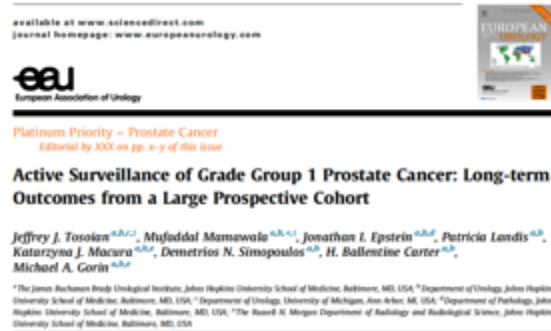


baseline PSA13 yrs probability of csPCA

< 0.49	0.4 %
< 0.99	1.5 %
< 1.99	5.4 %
< 2.99	10.6 %
< 3.99	15.3 %
> 4.0	29.5 %

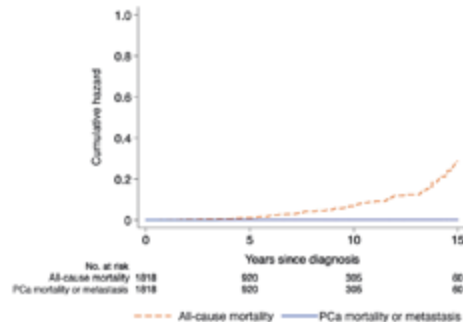
ISUP 1 (Gleason Sum Score 6) prostate cancer

Active Surveillance Cohort Johns Hopkins
(N= 1818, 1995-2018, median age 67 yrs)



N= 4 deaths from prostate cancer*

cancer-specific mortality at 15 yrs: 0.1%



Tosoian JJ et al. Eur Urol 2019

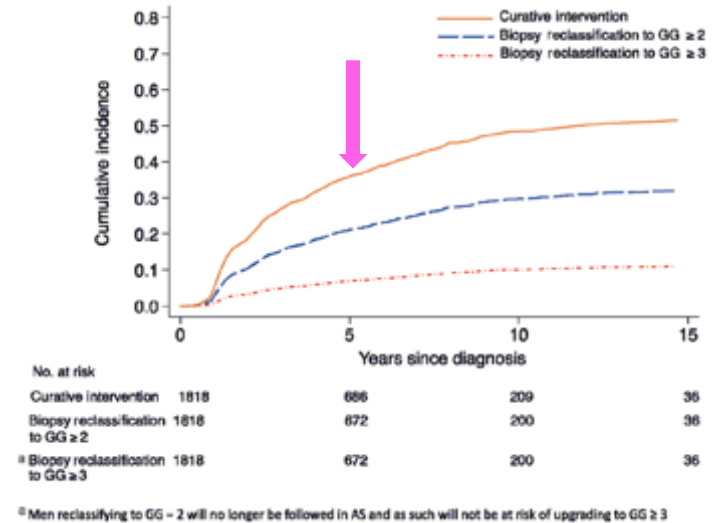
ISUP 1 (Gleason Sum Score 6) prostate cancer

Active Surveillance Cohort Johns Hopkins
(N= 1818, 1995-2018, median age 67 yrs)

15 yrs bx upgrade to ISUP 2 = 32%

ISUP 3 = 11%

15 yrs definitive treatment: 52%



Tosoian JJ et al. Eur Urol 2019

Open Questions

Is ISUP 1 (Gleason 6) „cancer“ ?

80% of patients with ISUP 1 remain without treatment for at least 10 yrs*

Do we need to detect ISUP 1 prostate cancer at all ?

If yes, at what age and how often do we then need repeat PSA ?

Is mpMRI helpful before biopsy ?

Are serum and urine markers helpful to prevent biopsies ?

*Hamdy F et al. NEJM 2017

Current Risk – Adapted Screening Trials

	participants	age	method	duration
PROBASE (Germany)	47,000*	45	age (mpMRI)	2015-2030
G2 Trial (Sweden)	40,000**	50-60	mpMRI	2015-2019
STHLM MR 2 (Sweden)	25,000***	50-74	STHLM-3	
ProScreen (Finland)	67,000****	55-67	mpMRI (**)	2018

1° Endpoints: *metastasis **overdiagnosis ***csPCA ****mortality

Summary

- **ISUP 1 PCA needs no immediate treatment**
(reduction of overtreatment)
- **grade progression to csPCA is likely to happen in 50% within 15 yrs**
- **5-yearly PSA most likely indicates grade progression**
- **mpMRI is able to improve the indication for a biopsy**
(reduction of overtreatment)
- **PROBASE will clarify whether screening can start at age 50**
(reduction of overdiagnosis)

A photograph of the German Cancer Research Center (DKFZ) building, a modern multi-story structure with a central glass tower and balconies. The building is surrounded by a courtyard with trees and benches. The sky is blue with some clouds.

Thank you for your
attention !

Further information on www.dkfz.de

dkfz.

GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION



Research for a Life without Cancer