Prostate Cancer Screening and Early Detection

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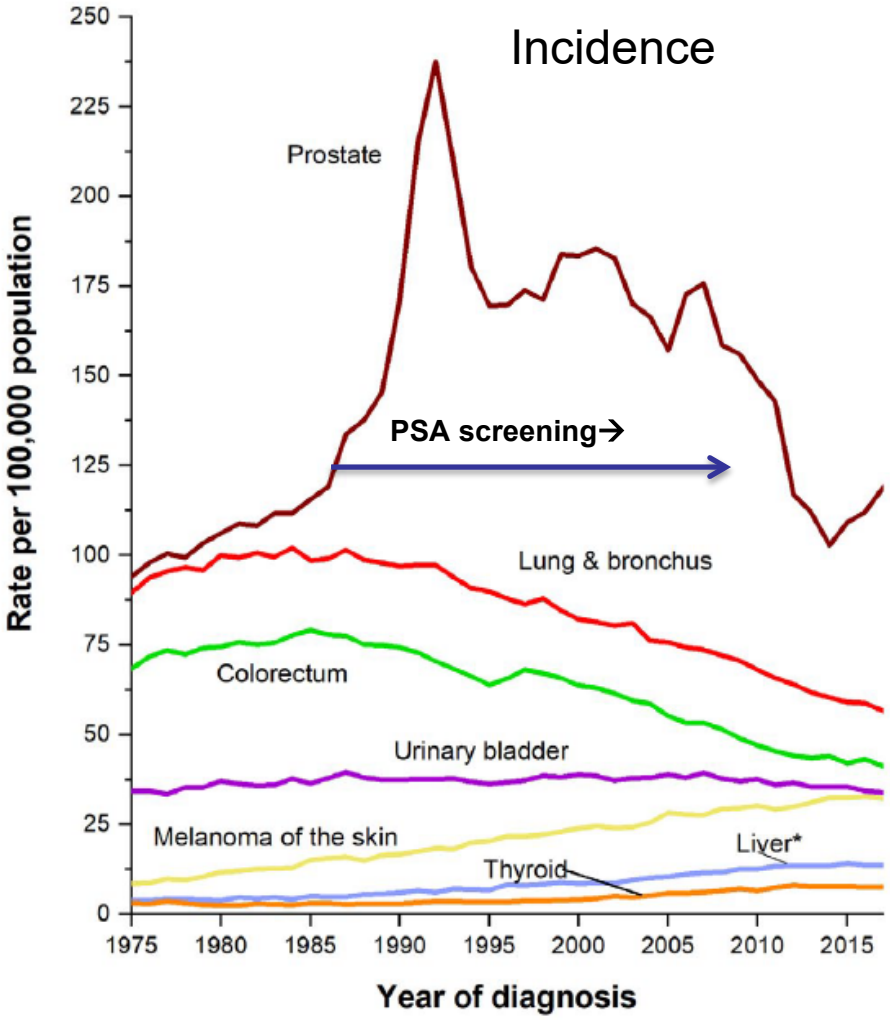
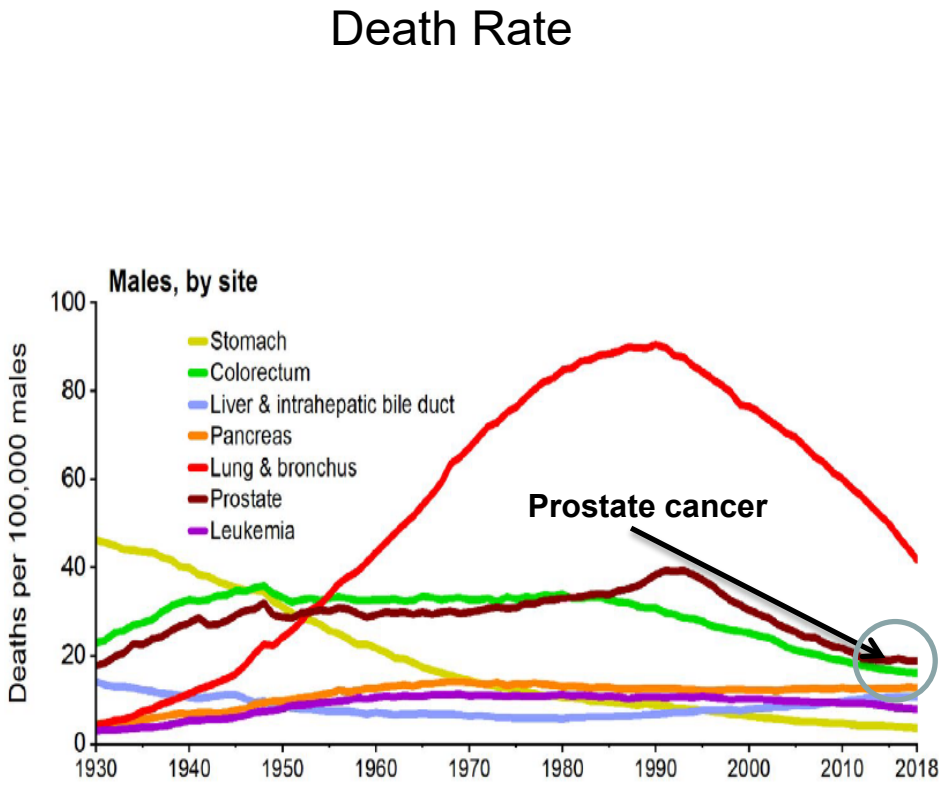
Trends in Prostate Cancer Over the Years

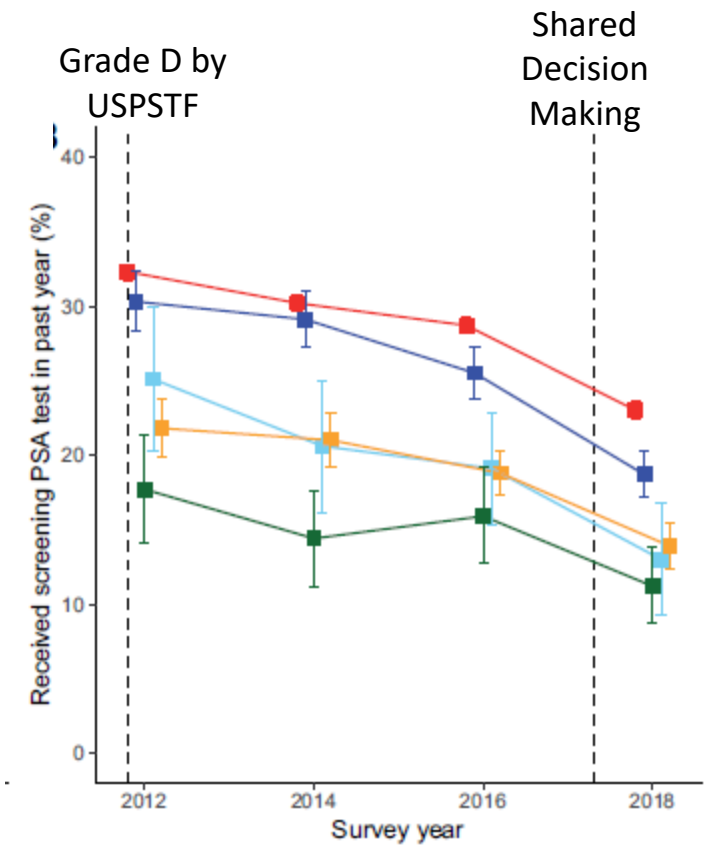




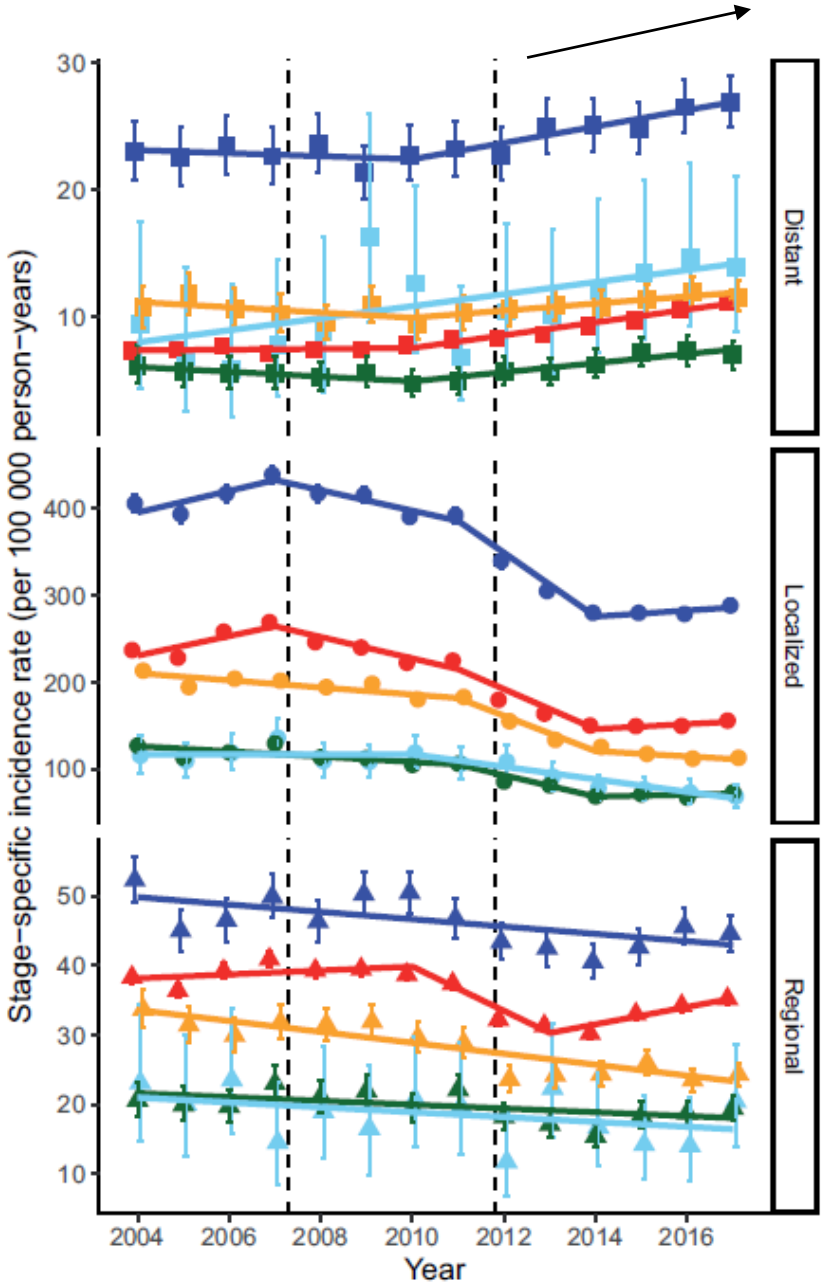
Siegal R CA Cancer J Clin 2021

Some concerning trends

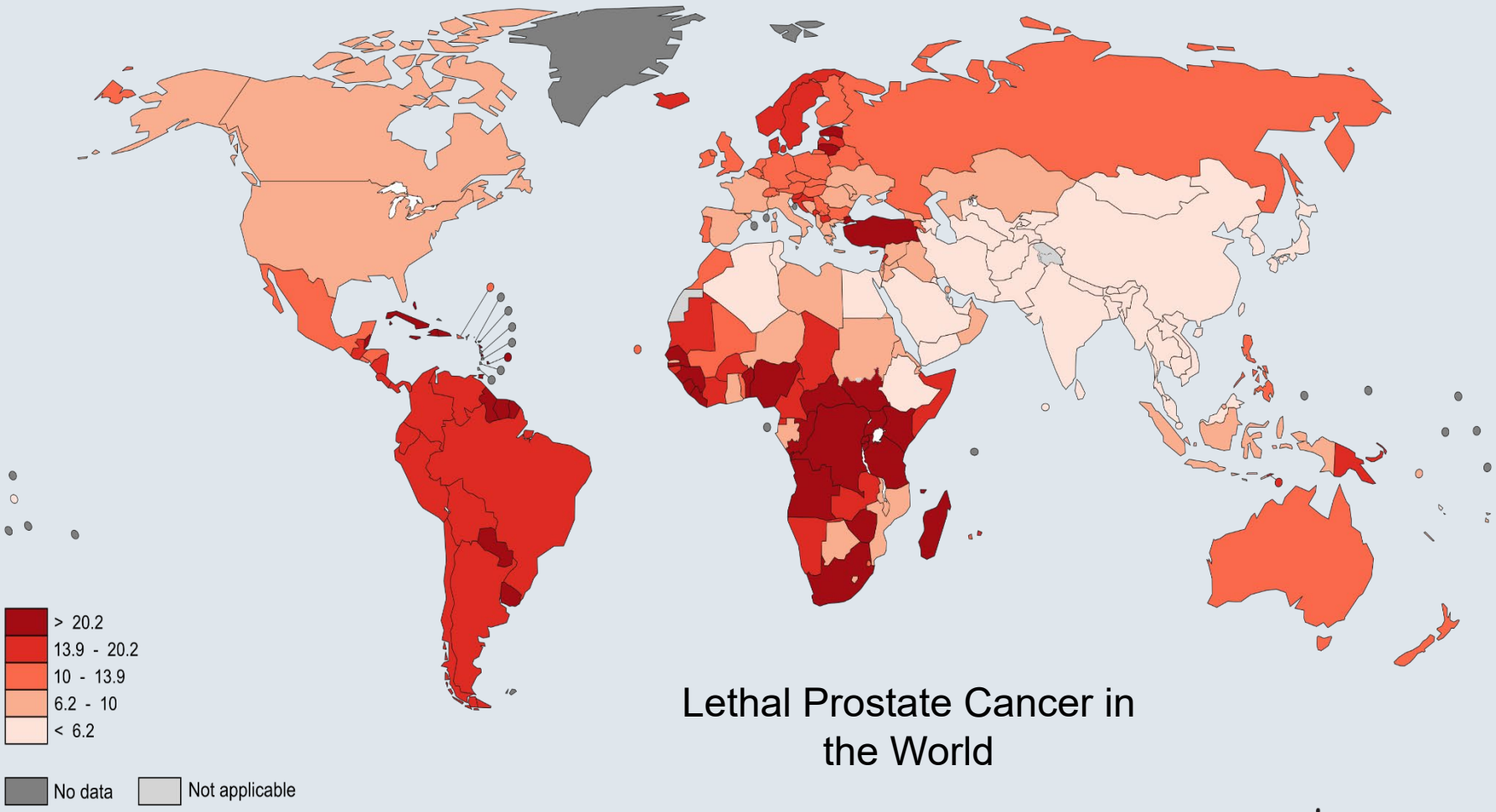
(particularly in light of ongoing COVID-19 pandemic impact)



Kensler KH et al JNCI 2021



Race and ethnicity NHW NHB NHAPI NHAIAN Hispanic



Lethal Prostate Cancer in the World

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Facts about Prostate Cancer in the US

- Most common malignancy in men other than skin cancer (globally 3rd)
- 1 in 8 men over 70 will be diagnosed with PC, **median age 67, 680 every day**
- 1 in 7 men with prostate cancer will die of their disease, **median age 78** (1 every 20 minutes)
- Second most lethal cancer in men over 80 (after lung cancer)

Estimated New Cases

	Males	
Prostate	248,530	26%
Lung & bronchus	119,100	12%
Colon & rectum	79,520	8%
Urinary bladder	64,280	7%
Melanoma of the skin	62,260	6%
Kidney & renal pelvis	48,780	5%
Non-Hodgkin lymphoma	45,630	5%
Oral cavity & pharynx	38,800	4%
Leukemia	35,530	4%
Pancreas	31,950	3%
All Sites	**970,250**	**100%**

Estimated Deaths

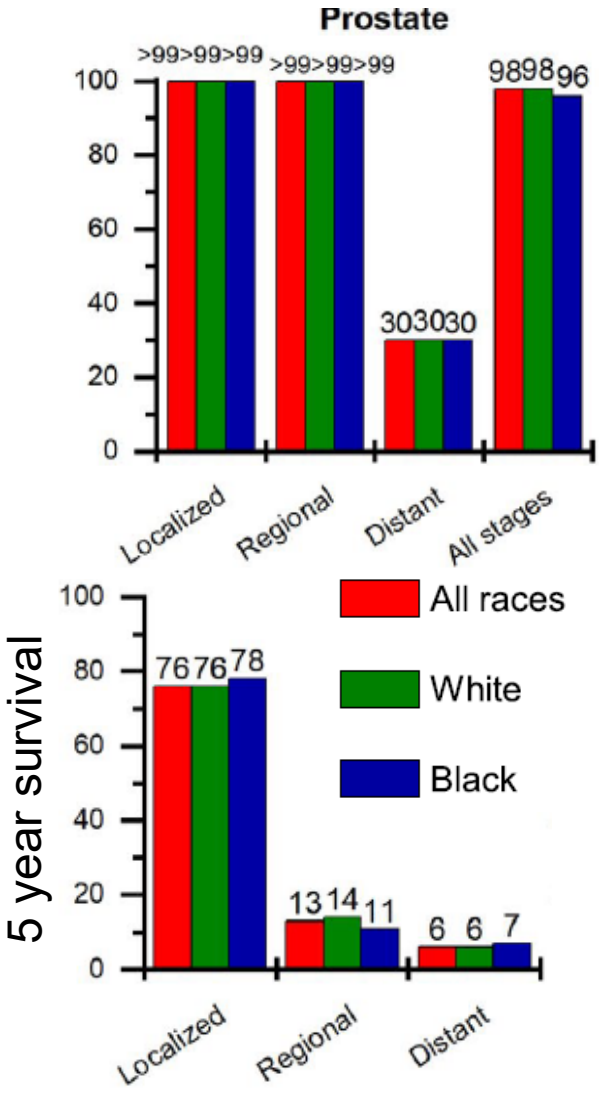
	Males	
Lung & bronchus	69,410	22%
Prostate	34,130	11%
Colon & rectum	28,520	9%
Pancreas	25,270	8%
Liver & intrahepatic bile duct	20,300	6%
Leukemia	13,900	4%
Esophagus	12,410	4%
Urinary bladder	12,260	4%
Non-Hodgkin lymphoma	12,170	4%
Brain & other nervous system	10,500	3%
All Sites	**319,420**	**100%**

Siegel R, CA Cancer J Clin 2021

Recent Favorable Trends

- Decline in death rates annually from prostate cancer of 3.4%/yr 2005-14 (until 2019, now leveling out or increasing!)
- 5 year survival remains excellent even for M1 disease
- Probability of being diagnosed with prostate cancer increases with age:
  - 1% under 40
  - 2.6% 40-59
  - 7% 60-69
  - 14.5% over 70
  - 18% (1 in 6) lifetime
- <6% present with metastatic disease

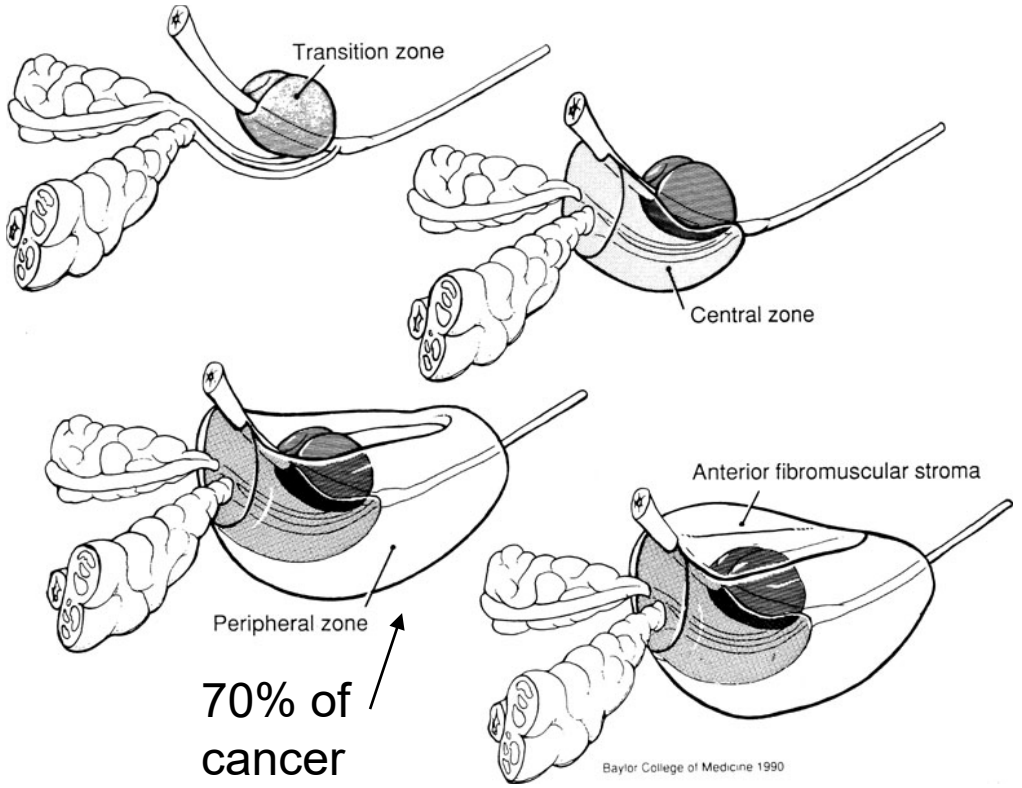
(has increased recently though!)



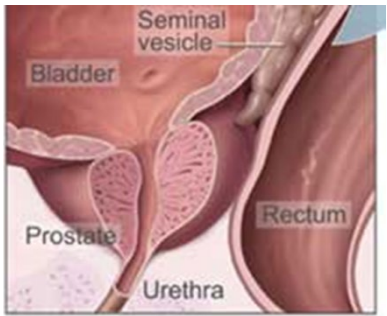
Siegel R, CA Cancer J Clin 2021

What is the prostate for anyway?

- Non-essential for life
- Walnut sized
- Helps in fertilization and carries the energy and nutrients for sperm (semen) to protect them from the harsh external environment
- Designed in a difficult location in front of the rectum and under the bladder
- Nerves for erection course on both sides of the prostate (more on this later!)



70% of cancer arises here



Risk Factors for Prostate Cancer

- Age: median age at diagnosis is 66, median age of death 78. Autopsy series demonstrate common findings of insignificant prostate cancers that increase with age.
- Race/ethnicity: African American> Caucasian >Hispanic>Asian. AA men present more with M1 disease, higher Gleason, more advanced, and have 2x higher mortality rate.
- Genetics: 9-40% contribution. RR of 2.1 if first degree relative, 5.0 if two, 11.0 if 3. Monozygotic concordance of 20-25%, dizygotic concordance of 4-7%.
  - Recent links to hereditary DNA repair defects
- Inflammation: Diet can promote prostate inflammation, aspirin and statins can reduce inflammation and risk of cancer
- Toxins: cadmium, agent orange (Vietnam), chlordecone estrogenic insecticides
- Lifestyle: obesity and sedentary lifestyle protective but increased risk of high grade disease, smoking is risk factor for aggressive disease (different epidemiologies for different diseases!)

FABLE FOR PROSTATE CANCER

There once was a pen with a turtle, a bird, and and a rabbit in it.

FABLE FOR PROSTATE CANCER

- The turtle is like slow growing PCa—it will just stay there

  The problem is that these often get diagnosed with screening and treated aggressively (or even non aggressively) when they don't require treatment

FABLE FOR PROSTATE CANCER

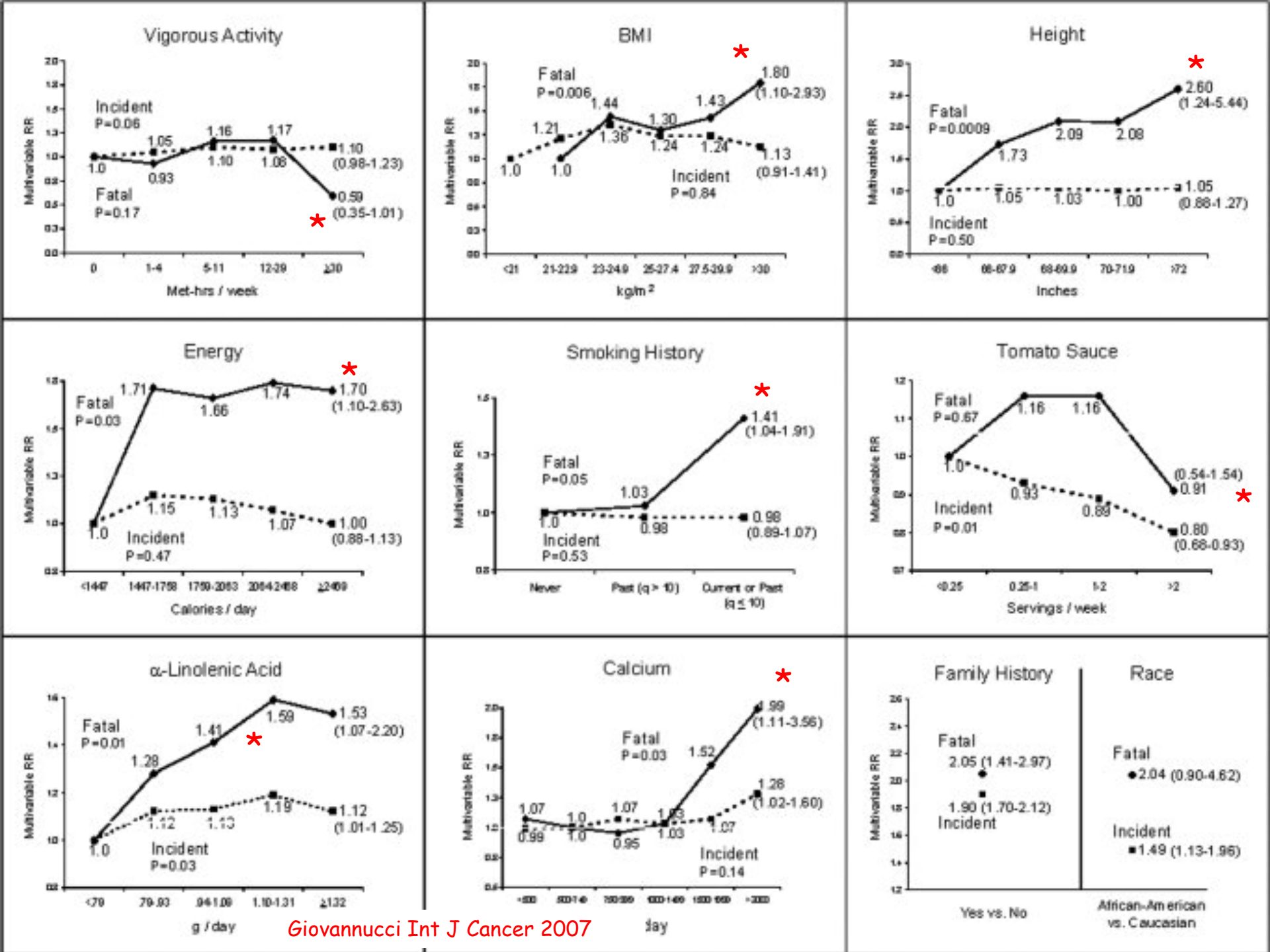
- The bird is like fast growing PCa—it flies out of the pen (spreads very quickly)

  The problem is these PCa are less likely to be detected with screening and are locally advanced or metastatic even at diagnosis and current treatments may not be aggressive or effective enough

FABLE FOR PROSTATE CANCER

- The rabbit is like moderate risk PCa which stays in the prostate for a while but eventually will jump out the prostate

  The problem with these is that even though screening and treatment may work, the side effects of the treatment are substantial and need to be diminished



Giovannucci Int J Cancer 2007

How to Avoid Aggressive Prostate Cancer

- Recent evidence supports **separate** causes for aggressive vs. non-aggressive prostate cancer supported by over 50,000 men followed for many years
- **Modifiable risk factors for aggressive prostate cancer**: reduce obesity, increase exercise, reduce tobacco use, increase tomato and cruciferous vegetable and fish intake, reduce red meat intake (especially charbroiled meats)

Giovannucci Int J Cancer 2007

Kirsh VA, JNCI 2007, 99:1200

Eat your Broccoli!

Vegetable	Intake category 1	2	3	4	P_{trend}†
Broccoli					
Servings	<1/mo	1–3/mo	1/wk	>1/wk	
Total cases, No.	501	335	235	267	
RR (95% CI)‡					
All prostate cancer	1.00 (referent)	0.99 (0.86 to 1.14)	0.94 (0.80 to 1.10)	0.91 (0.77 to 1.06)	.19
Aggressive prostate cancer	1.00 (referent)	0.93 (0.74 to 1.15)	0.80 (0.62 to 1.03)	0.76 (0.59 to 0.99)	.03
Extraprostatic cancer	1.00 (referent)	0.88 (0.61 to 1.27)	1.02 (0.69 to 1.51)	0.55 (0.34 to 0.89)	.02

- Similar trends noted for cauliflower, cole slaw (cruciferi) but NOT brussel sprouts, turnip greens, mustard greens, kale, or spinach, beans, tofu, garlic, fruits, or onions

Fruits are less preventive than vegetables!

Kirsh VA, JNCI 2007, 99:1200

Prostate Cancer Carcinogens in the Diet

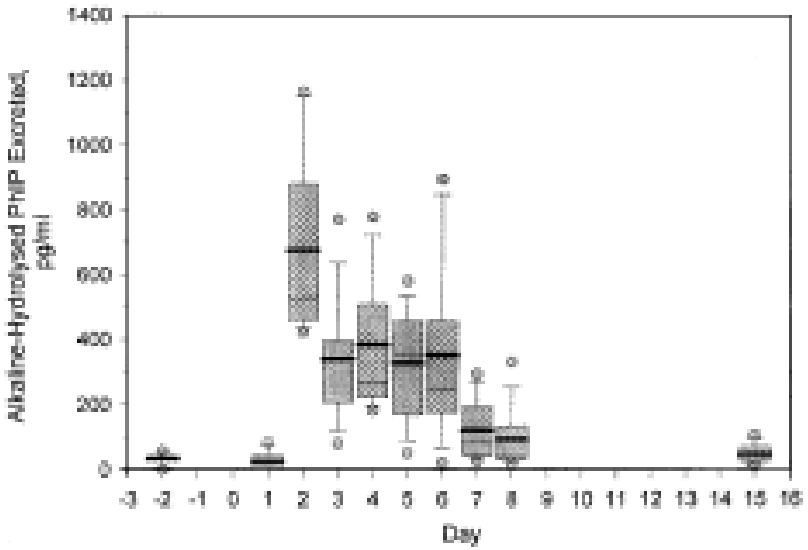
•PhIP (2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine) is the most common polycyclic aromatic hydocarbon contained in charbroiled meats cooked at high temperature (with infrequent flipping)

• PhIP is a carcinogen and may be implicated in several cancers, including colon, breast, and advanced prostate

•Can cause DNA damage

•Detoxification by compounds found in cruciferous vegetables!

•Vegans appear to have a very low incidence of many cancers (20% risk reduction)

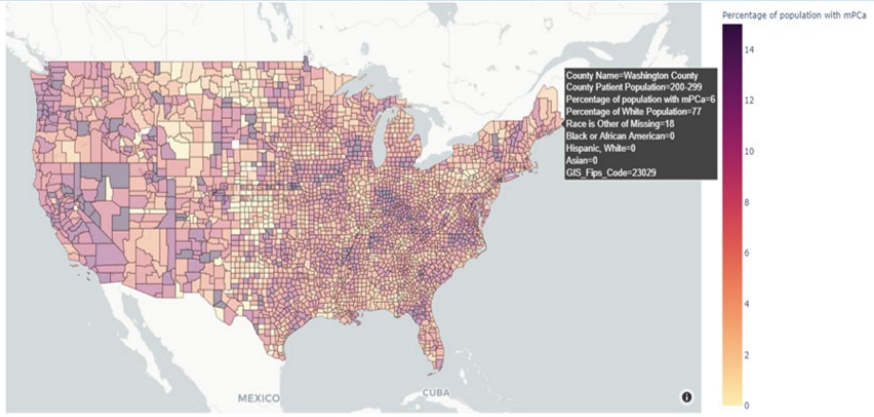


Friesen, Cancer Letters 2001

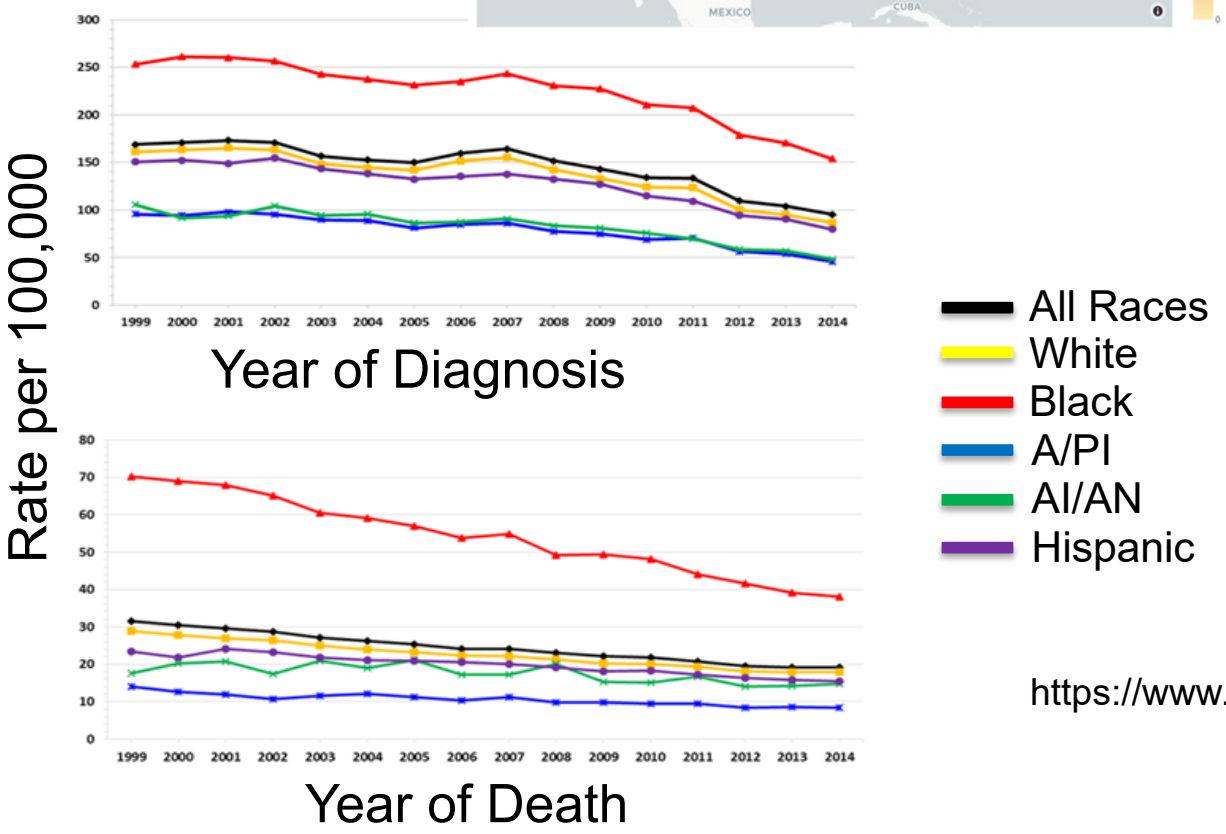
Rohrman S CEBP 2015

Tantamango-Bartley, CEBP 2013

Prostate Cancer Disparities Among Racial Groups



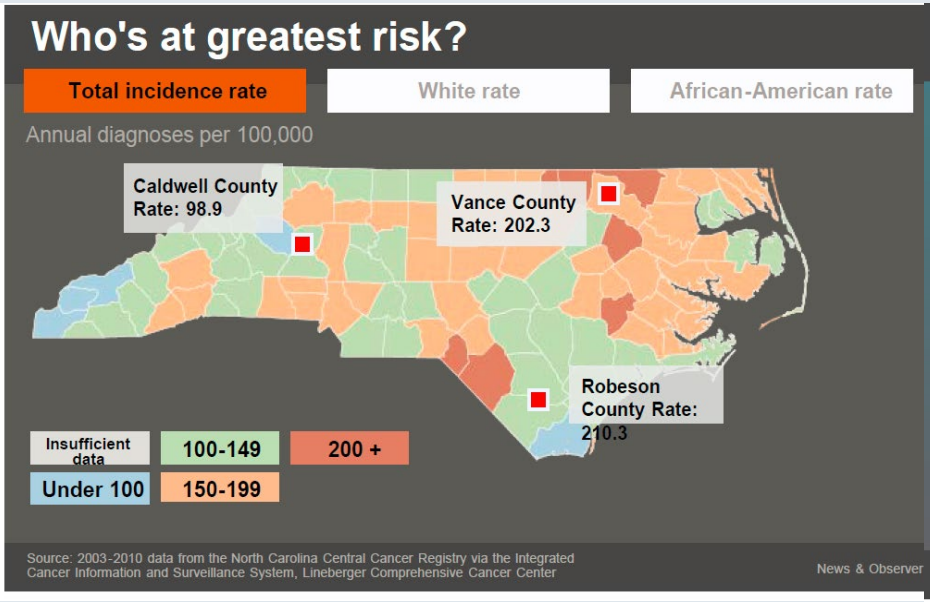
Incidence Rates by Race and Ethnicity US, 1999-2014

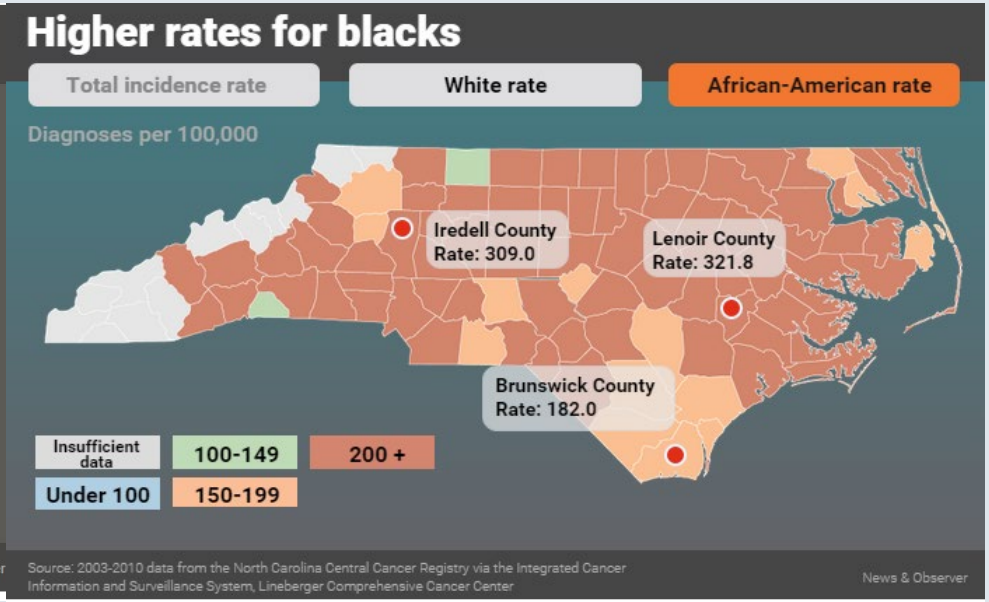


Death Rates by Race and Ethnicity US, 1999-2014

https://www.cdc.gov/

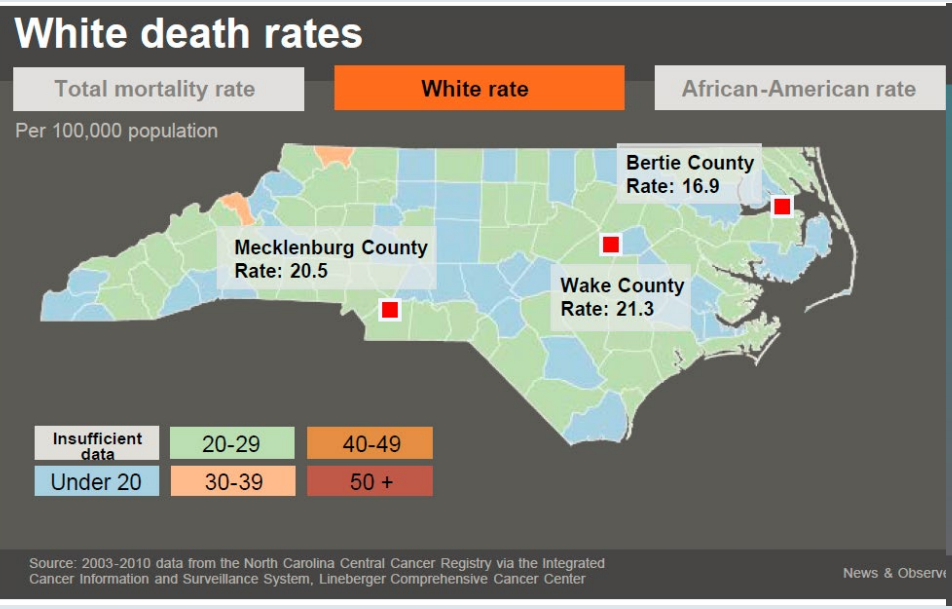
Prostate cancer affects African Americans at 1.5 greater rate than Caucasians

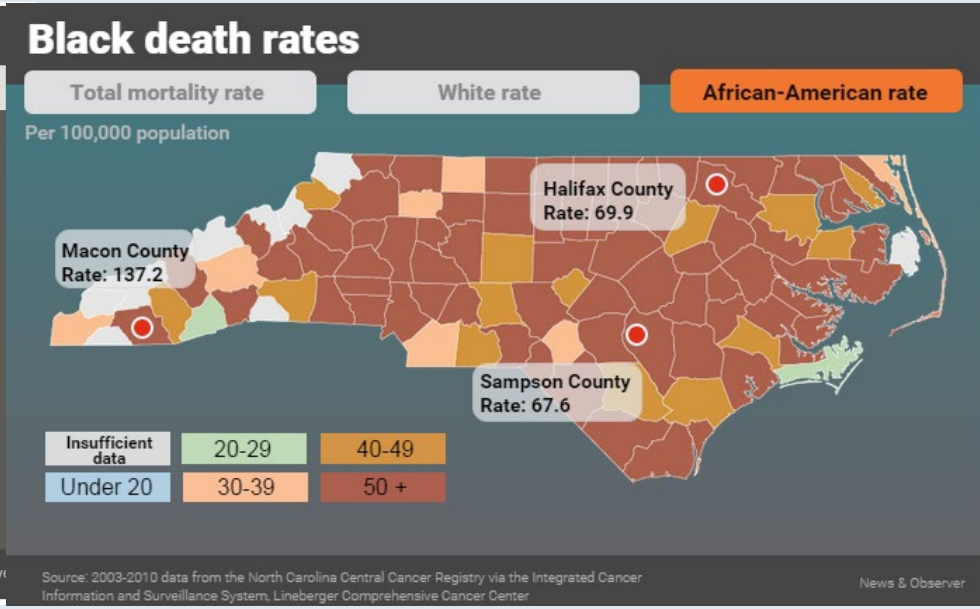




General population data does not reflect the risk in disproportionately affected populations like African Americans

Death from prostate cancer – an even greater disparity

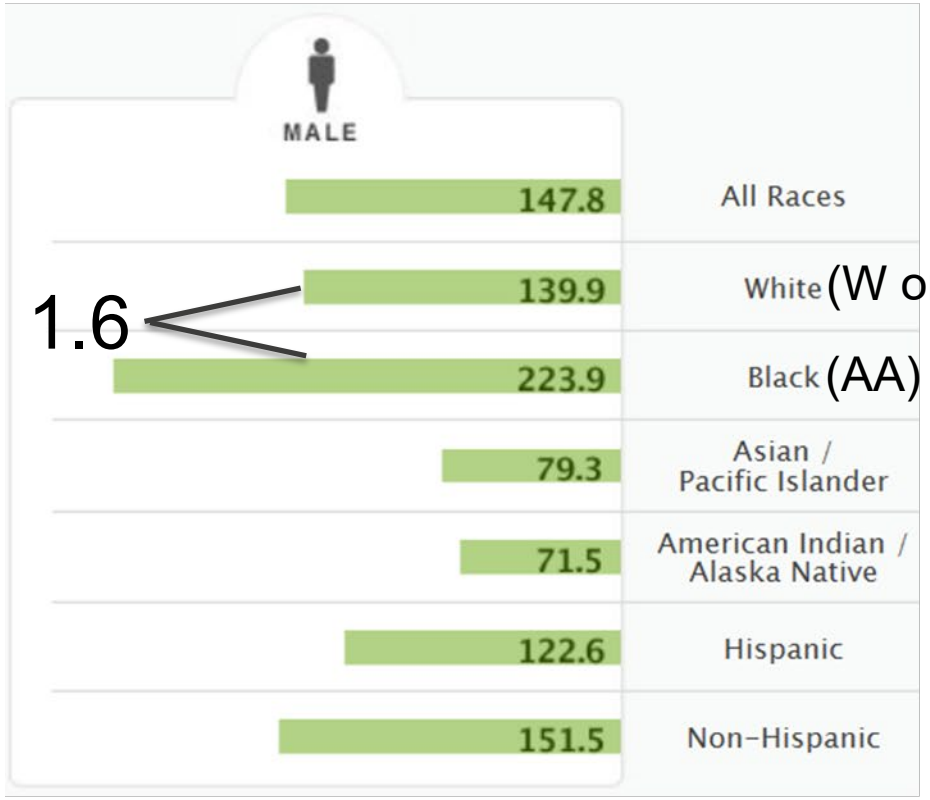




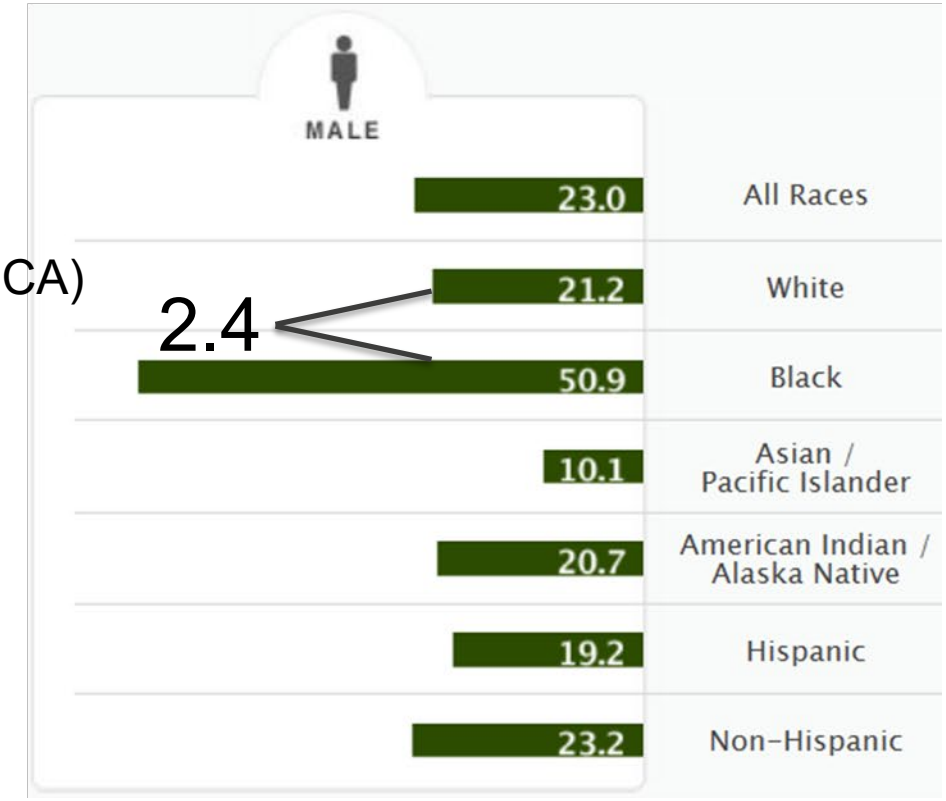
AAM have 2.5 greater risk of death from prostate cancer than CM

Prostate cancer (PC) health disparities among racial groups

Number of New Cases per 100,000 Persons

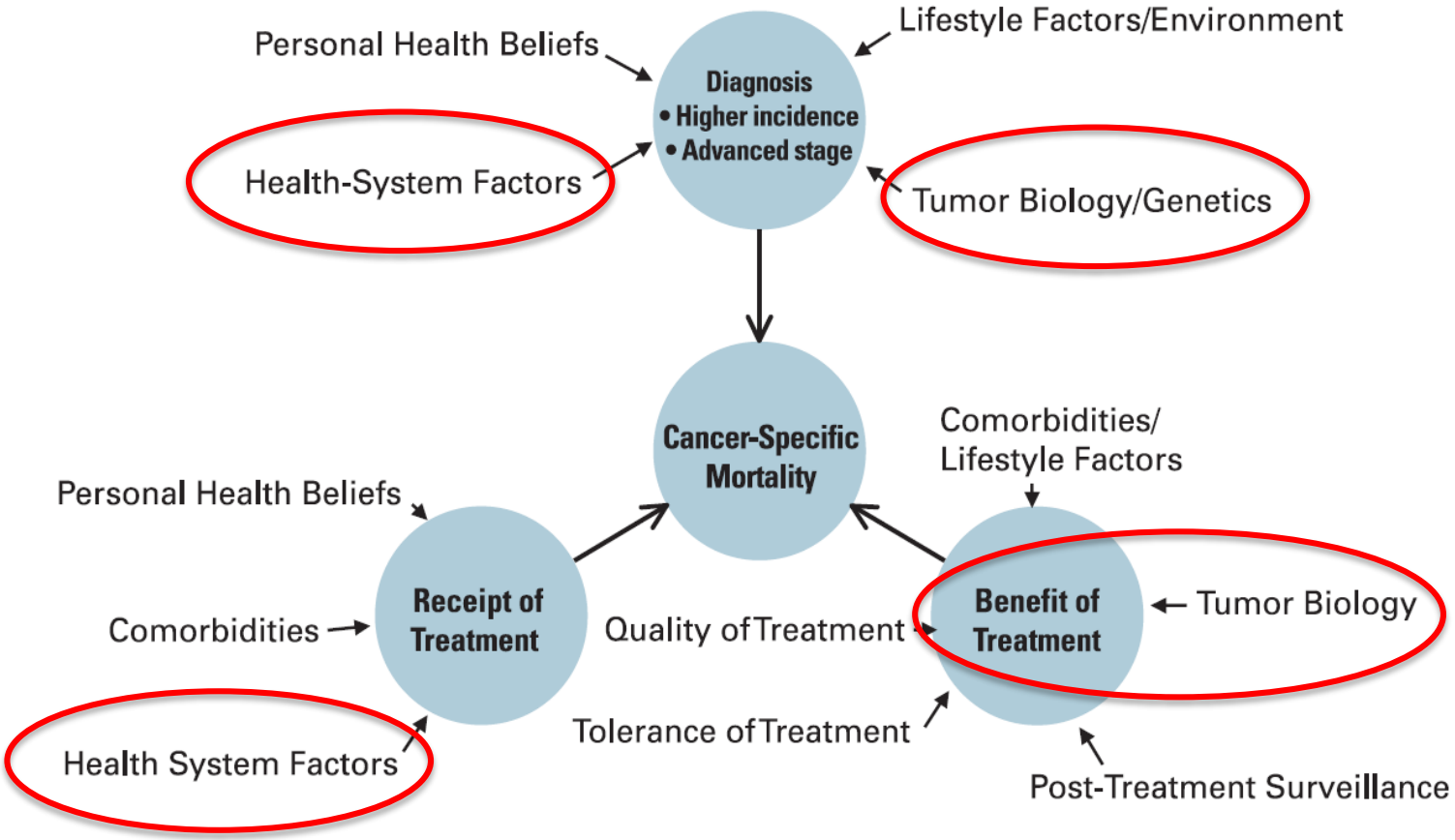


Number of Deaths per 100,000 Persons



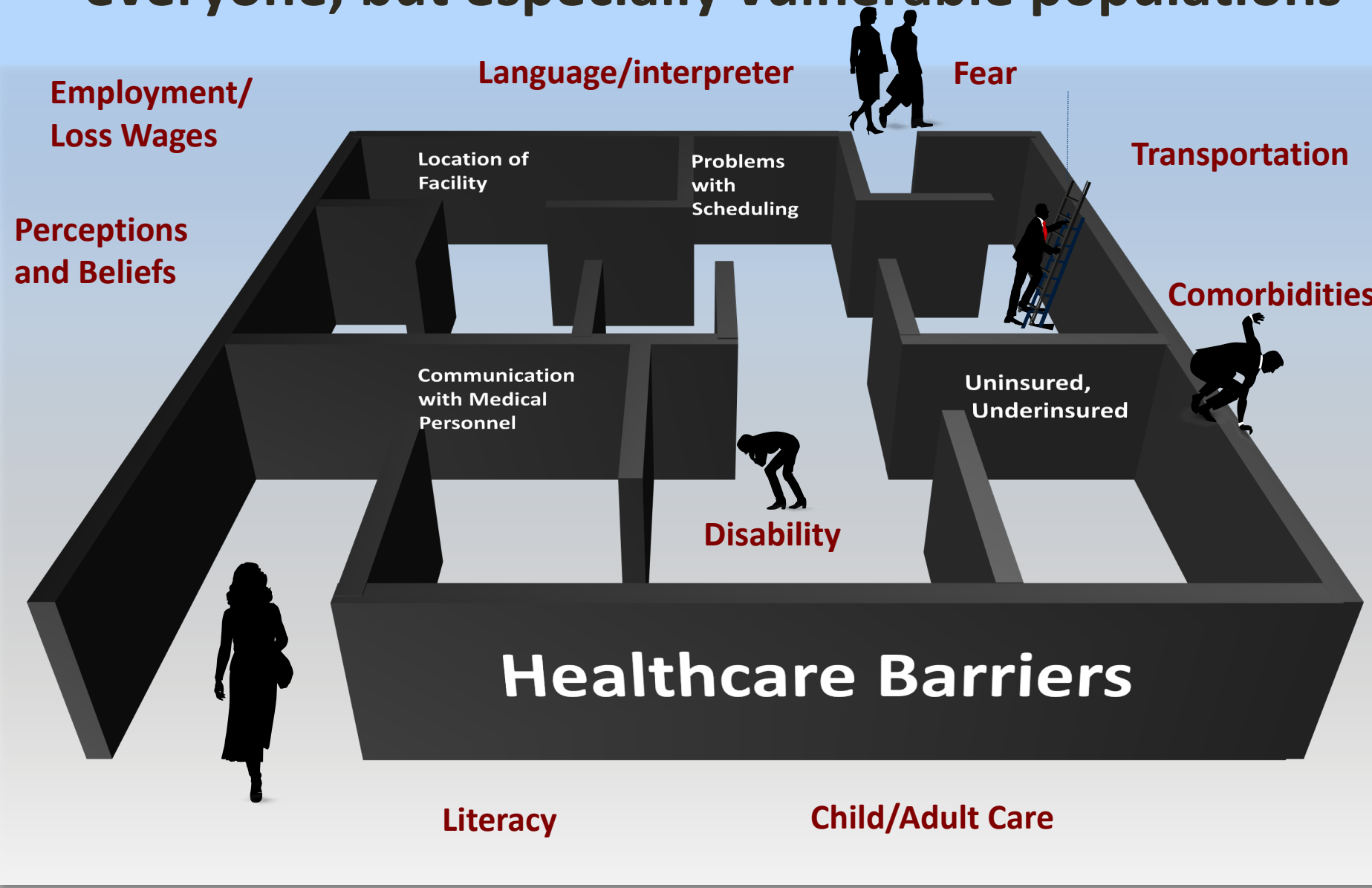
SEER Stat Fact Sheets: Prostate. Available from: http://seer.cancer.gov/statfacts/html/prost.html

Oncology Health Disparities Model



Polite *et al.*, J Clin Oncol, 2006, 24(14), p.2179-87

The Healthcare System Maze Needs a GPS for everyone, but especially vulnerable populations



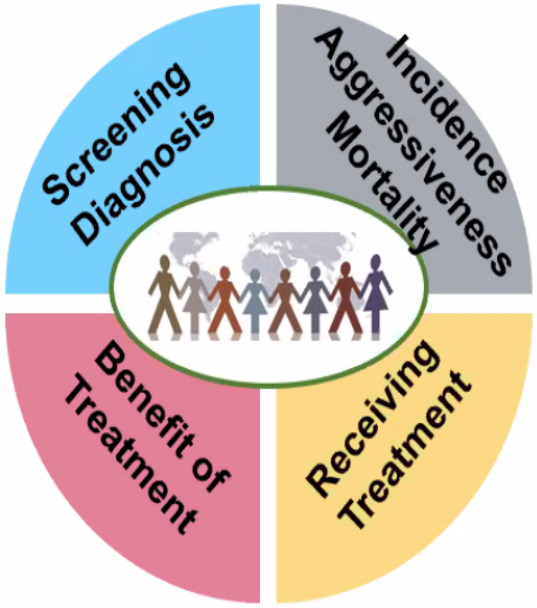
Multi-Factorial Contributors to Cancer Disparities

Social & Environmental

Personal Health Beliefs
Individual Responsibility
Socioeconomic Status
Environmental Exposures

Biological

Germline/Somatic
Genome
Epigenome
Transcriptome
Proteome
Metabolome



Illustrates the need for new methodologies in intersectionality and "convergence science"

Lifestyle

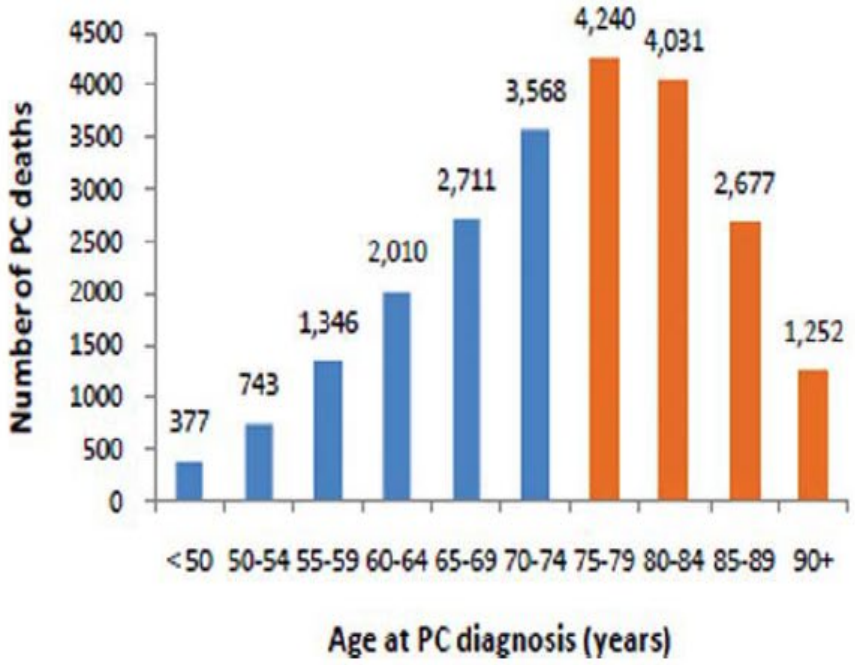
Smoking Status
Diet
Exercise
Obesity
Comorbidities
Physical Environment

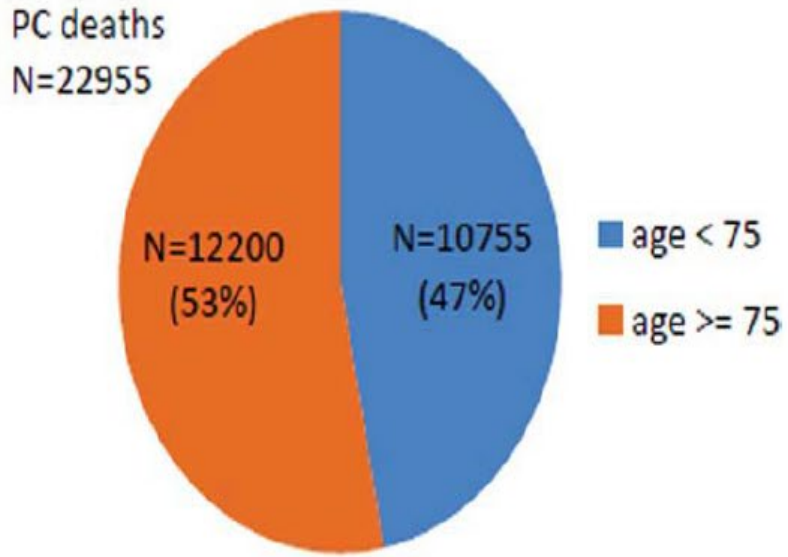
Structural

Health System
Access To Care
Policy
Physical Environment

Courtesy of Drs. Jennifer Freedman & Steven Patierno

Age and Lethal Prostate Cancer





- 47 percent of all PC deaths occur in men over 75
- 11, 18, and 27 percent of <u>all male deaths</u> are related to prostate cancer in the 80-84, 85-89, and >90 year old age groups, respectively

Scosyrev E, Cancer 2011

PSA

- Blood test that measures a protein made by the normal prostate and prostate cancer cells
- Using cutoff of 4.0 ng/dl, suffers from many false positive and negative results as a high level can indicate a big prostate and many cancers can have low PSA levels
- Indicates more prostate volume than cancer risk
- Using lower cutoffs will increase detection but also false positive rate and unnecessary biopsies
- However, PSA remains our best screening test to date
- High risk men may benefit from lower cutoff and earlier screening (ie age 40-45)
- Other PSA isoforms may help to risk stratify patients (free PSA, pro-PSA, bPSA, age adjusted PSA, PSA density)

PSA Screening: Cancer May be Present even at Low PSA Levels

Table 1
Prostate Cancer (CaP) in Men with Low Prostate-Specific Antigen (PSA)

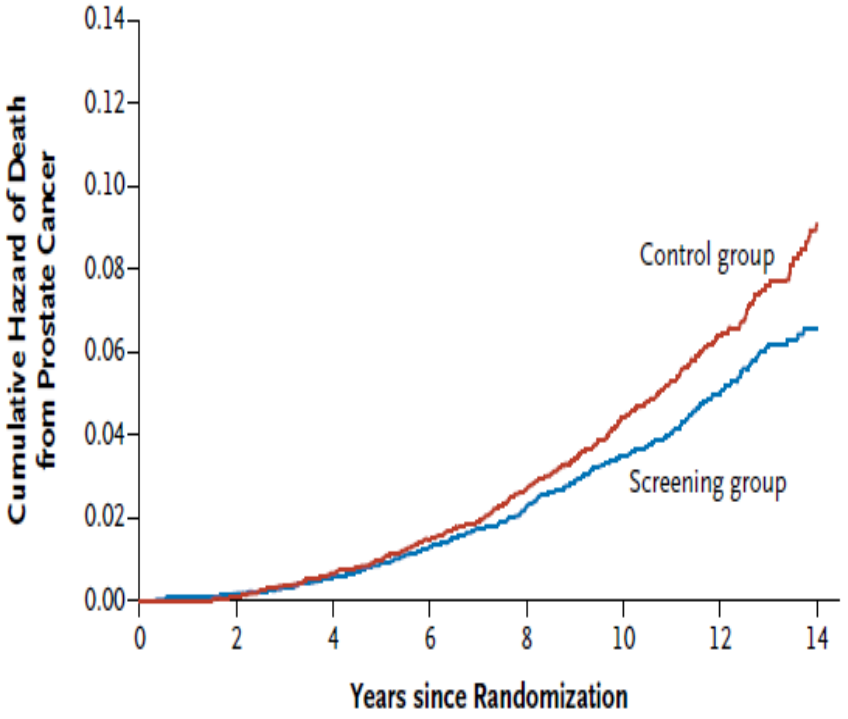
PSA level (ng/mL)	Men with CaP (%)	High-grade CaP (%)
< 0.5	6.6	12.5
0.6-1.0	10.1	10.0
1.1-2.0	17.0	11.8
2.1-3.0	23.9	19.1
3.1-4.0	26.9	25.0

Reprinted from Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per milliliter. *N Engl J Med.* 2004;350:2239-2246.

Prostate Cancer Screening Trials

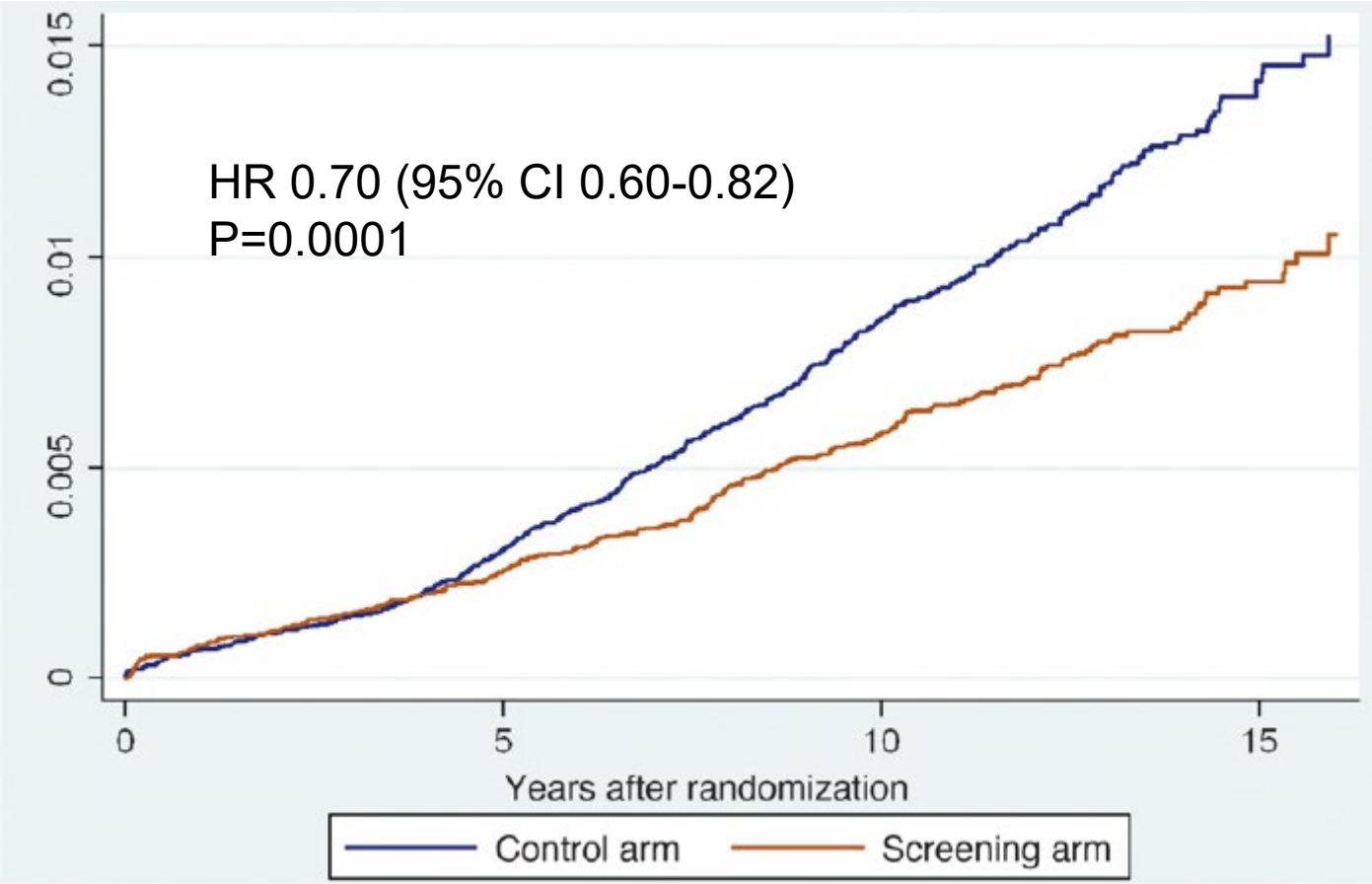
ERSPC. Collection of many large trials pooled across Europe, in which 182,160 men were randomized to screening according to various definitions (ie once every 4 years +/- DRE) or no screening

- Median f/u 11 years, median age 62
- PC diagnosed in 8.2% of screened men vs. 4.8% in control group (RR 1.63)
- Relative risk of death from PC was 0.79 favoring screening, p=0.001
- High risk PC less likely in screen arm (7 vs. 11%)
- Overdiagnosis in ~50% of men
- Number needed to screen=1055
- Number needed to treat (RP, seeds, radiation, AS) = 37
  (lower for various PSA cut-points, longer follow up)



Schroder et al, NEJM 2012;366

Does Screening Prevent Metastatic Disease?



Largely an effect noted at diagnosis rather than in follow-up
Number needed to screen to prevent one metastasis: 328
Number needed to diagnose: 12

Schroder FH, Eur Urol 2012

ERSPC follow up: 2014

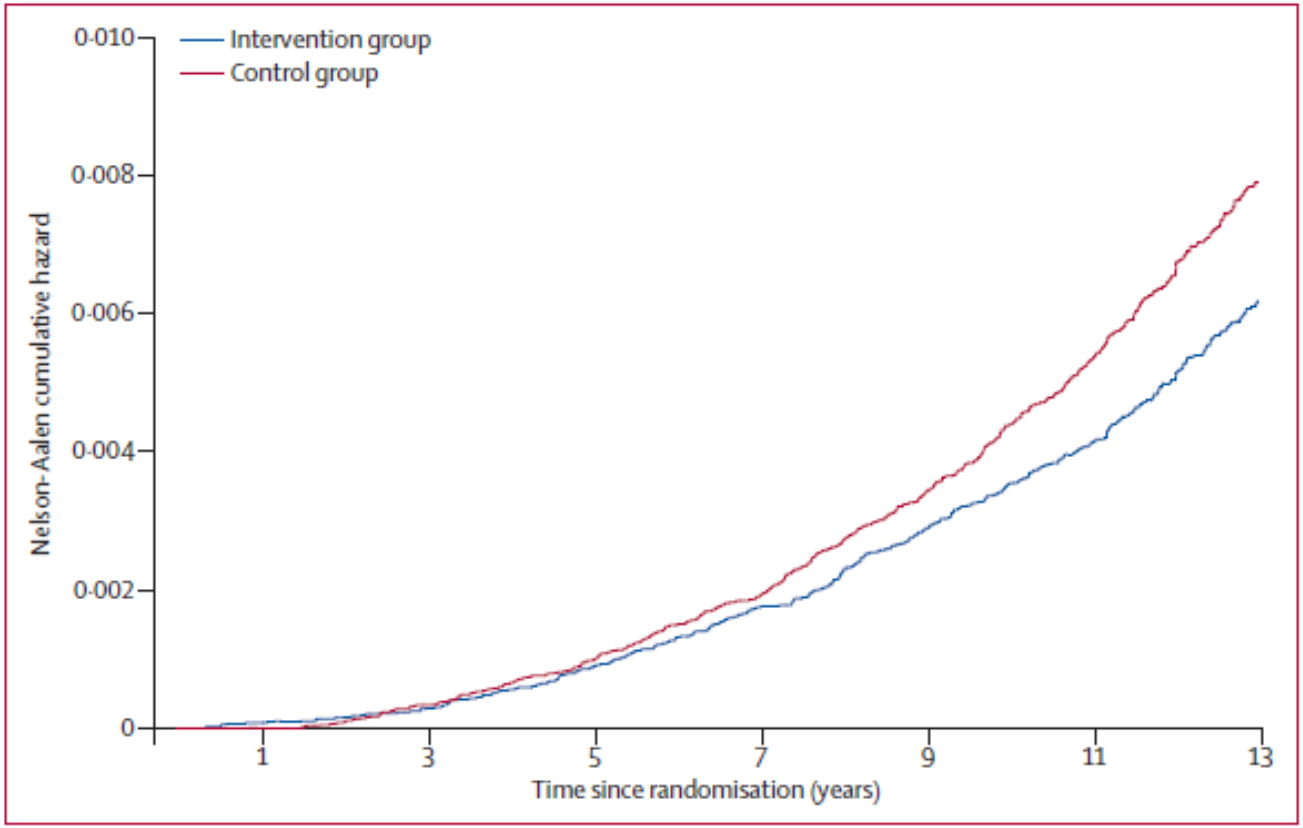


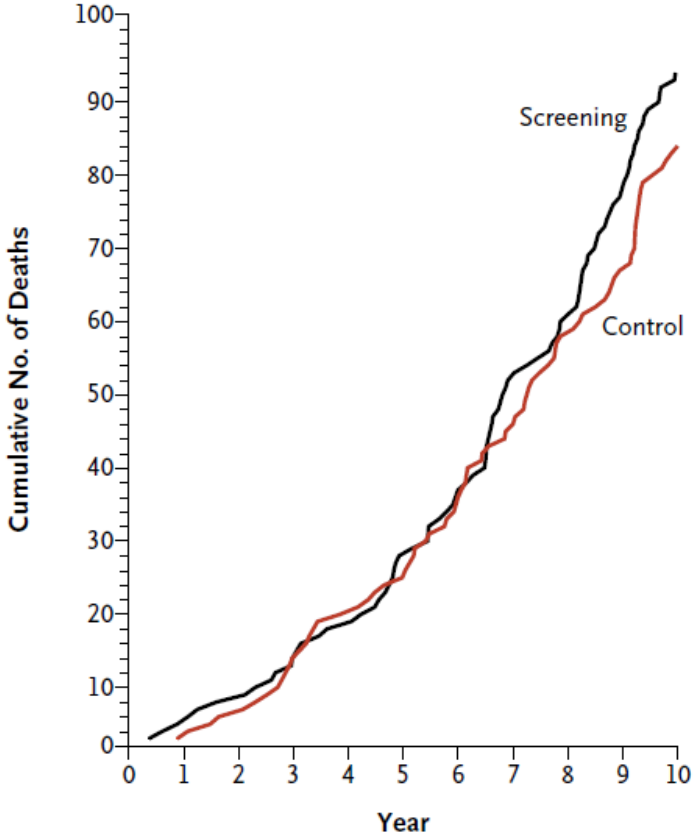
Figure 2: **Nelson–Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)**

Schroder, F. H., et al. (2014). "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**(9959): 2027-2035

Prostate Cancer Screening Trials

PLCO (US) Trial: 76,693 men randomized to intensive annual screening (80-90% compliant) vs. less intensive ad hoc screening (>50% screening)

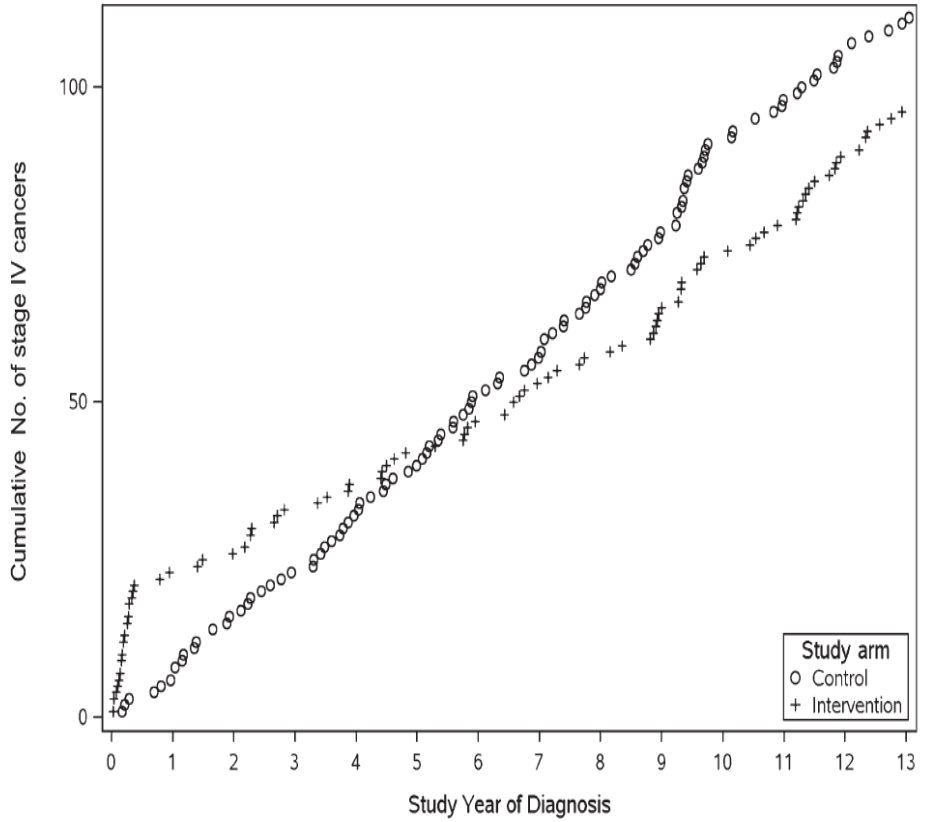
- Median f/u 7 years
- Rate ratio for PC diagnosis was 1.22 (116 per 10K vs 95) favoring control
- Rate ratio for death was 1.13 favoring control (but only 94 deaths reported)
- No difference in any outcome measures



Andriole et al, NEJM 2009;360

PLCO Long Term Follow Up

- 13 year follow up
- 75% of cases occurred in men over 65
- Despite more PC cases being diagnosed in the screening arm (4250 vs. 3815), no difference observed in overall or PC-specific survival
- No clear prevention of metastases
- No interactions seen by age or comorbidity



Andriole GL JNCI 2011
Prorok PC et al JNCI 2012

Conflicting Results: Why?

PLCO: No mortality benefit	ERSPC: 20% mortality benefit
n = 76,000	n = 182,000
PSA threshold: 4.0	PSA threshold: 3.0
Biopsied 50% of screen^{+} subjects	Biopsied 85% of screen^{+} subjects
PSA contamination 52%	PSA contamination 20%

Grubb, et al *BJUI* 2008 Andriole, et al. *NEJM* 2009

Schröder, et al. *NEJM* 2012 Hayes & Barry *JAMA* 2013

Benefits of PSA screening improved over time

	Follow-up		
	9 year	11 year	13 year
ARR for prostate-cancer death	0.71/ 1000 men	1.07/ 1000 men	1.28/ 1000 men
NNS to prevent 1 death	1410	1055	781
NNT to prevent 1 death	48	37	27

Schroder, F. H., J. Hugosson, M. J. Roobol, T. L. Tammela, S. Ciatto, V. Nelen, M. Kwiatkowski, M. Lujan, H. Lilja, M. Zappa, L. J. Denis, F. Recker, A. Berenguer, L. Maattanen, C. H. Bangma, G. Aus, A. Villers, X. Rebillard, T. van der Kwast, B. G. Blijenberg, S. M. Moss, H. J. de Koning and A. Auvinen. "Screening and Prostate-Cancer Mortality in a Randomized European Study." *N Engl J Med* 360, no. 13 (2009): 1320-8.

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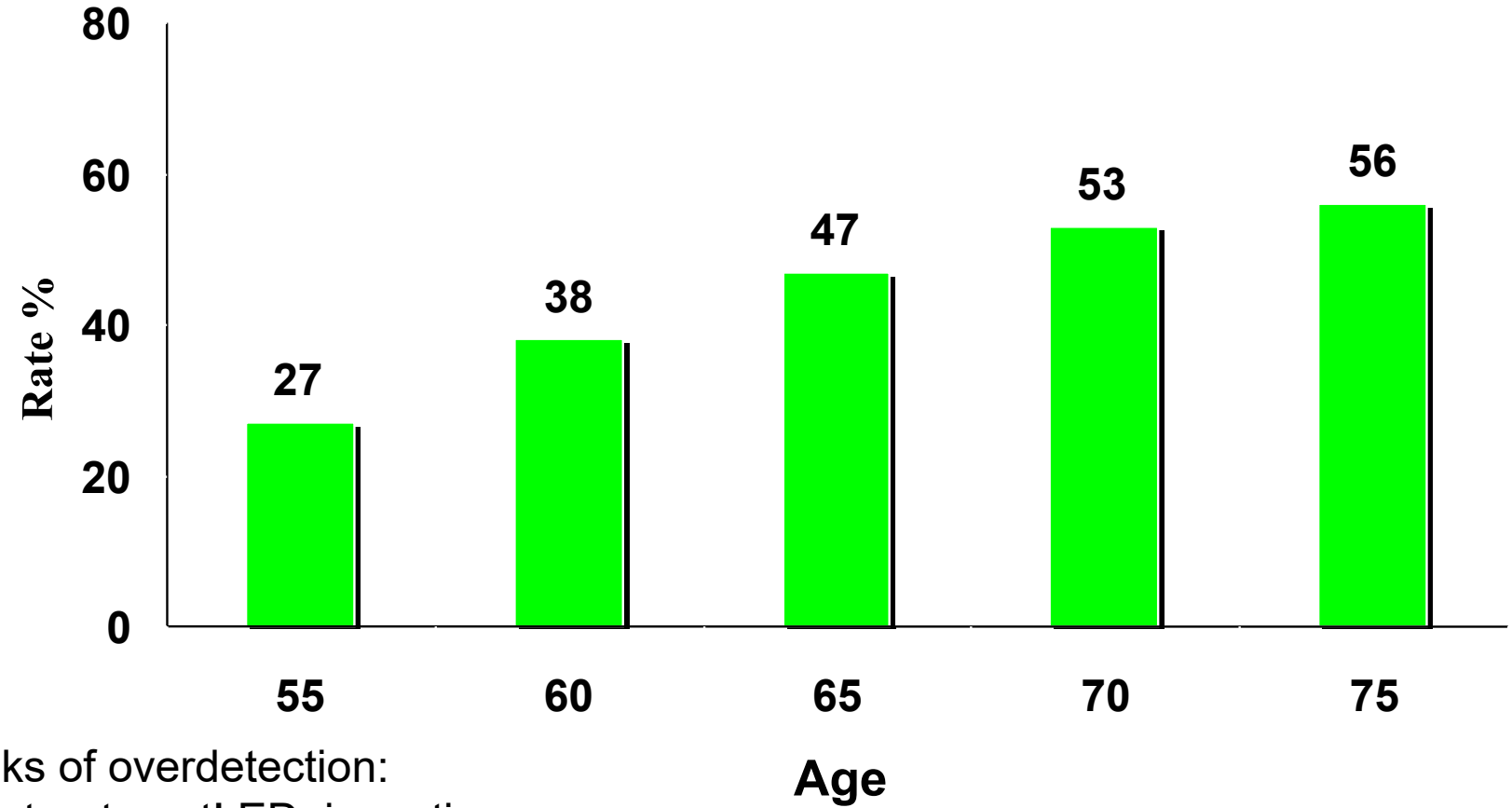
Age-dependent Overdetection Rate in a Screening Population

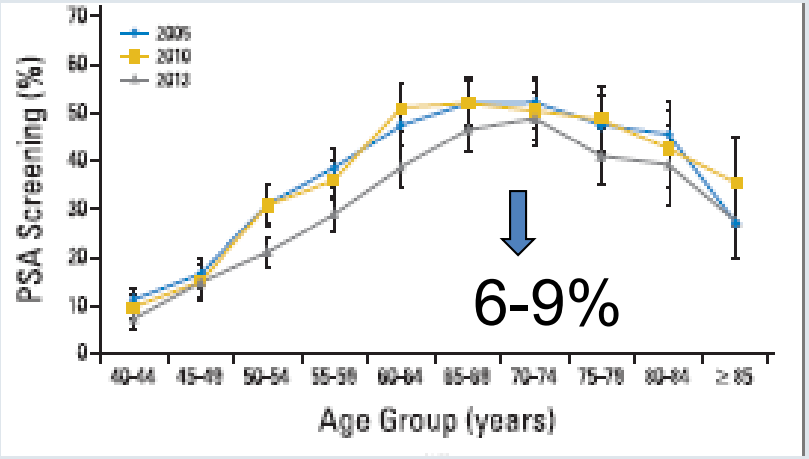
European Randomized Study of Screening for Prostate Cancer

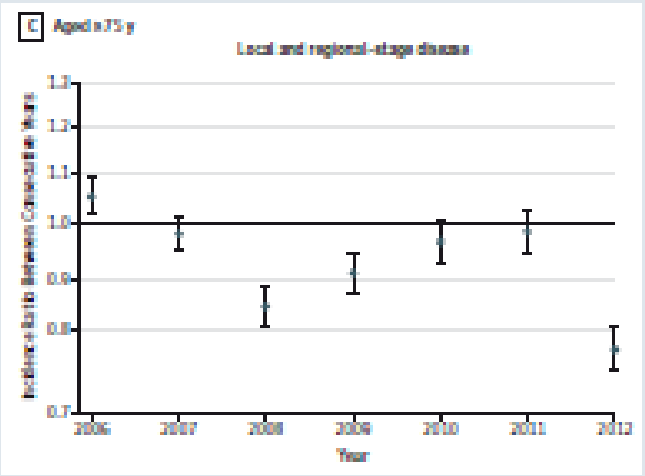


Risks of overdetection: overtreatment! ED, incontinence, worry, surgical risks

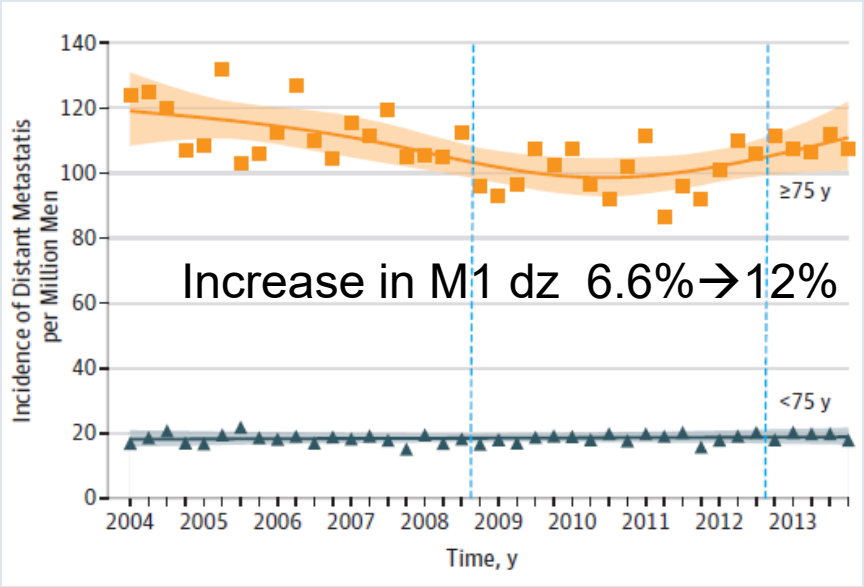
Draisma G, et al. J Natl Cancer Inst. 2003 Jun 18;95(12):868-78.

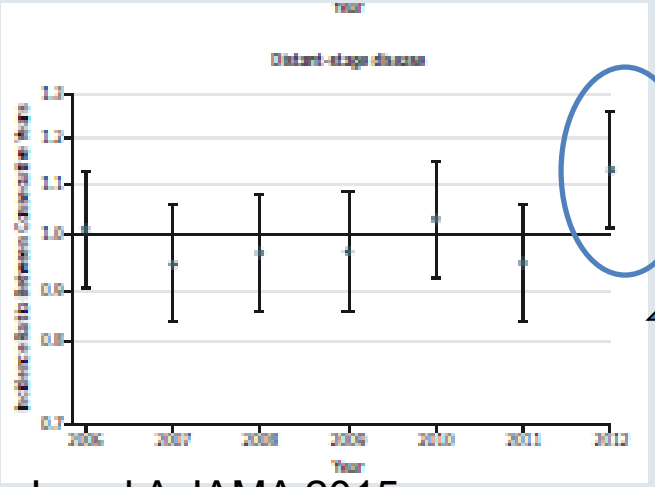
IMPACT of Decline in Screening Rates





Incidence





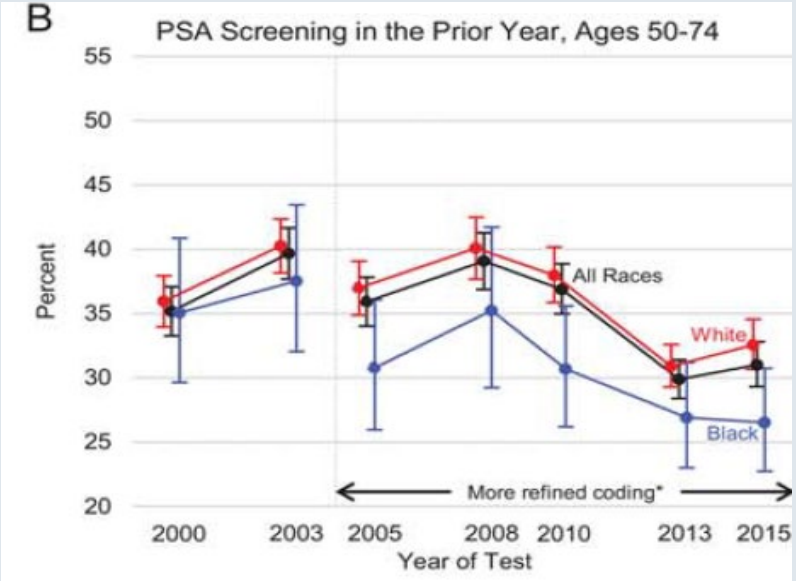
10-20% increase

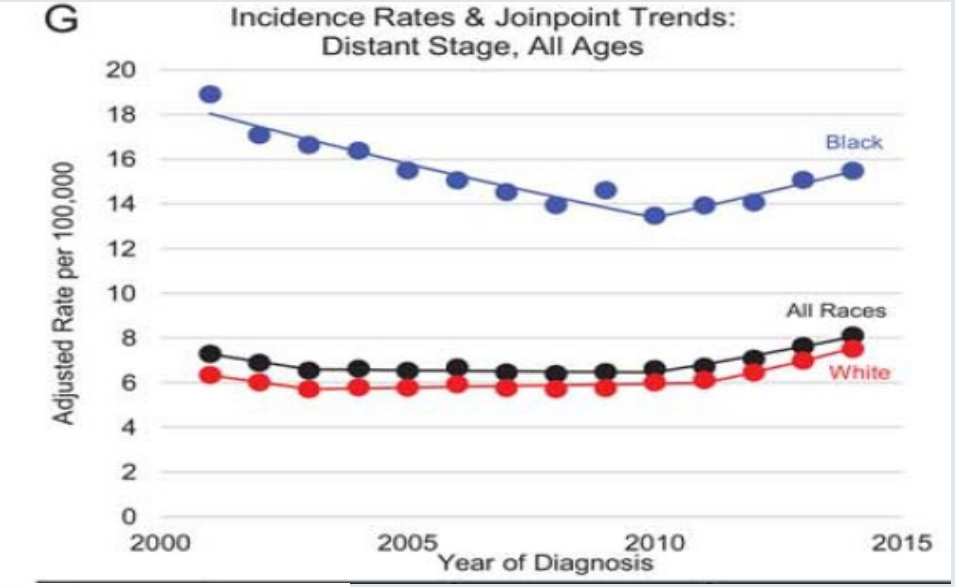
Lethal disease

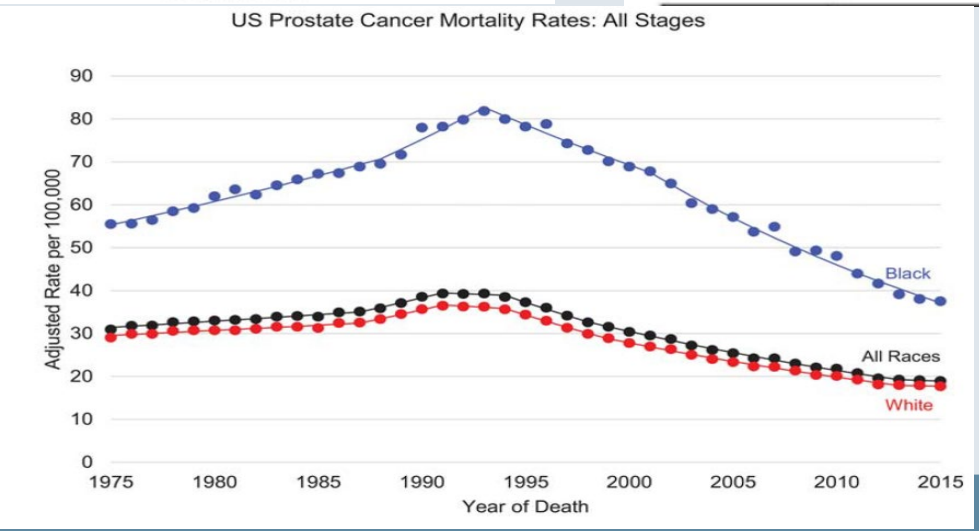
Jemal A JAMA 2015

Drazer MW JCO 2015; Hu JC et al JAMA Oncol 2016

Recent Trends in the Wrong Direction







Negoita S Cancer 2018

Plateau in declining death rates

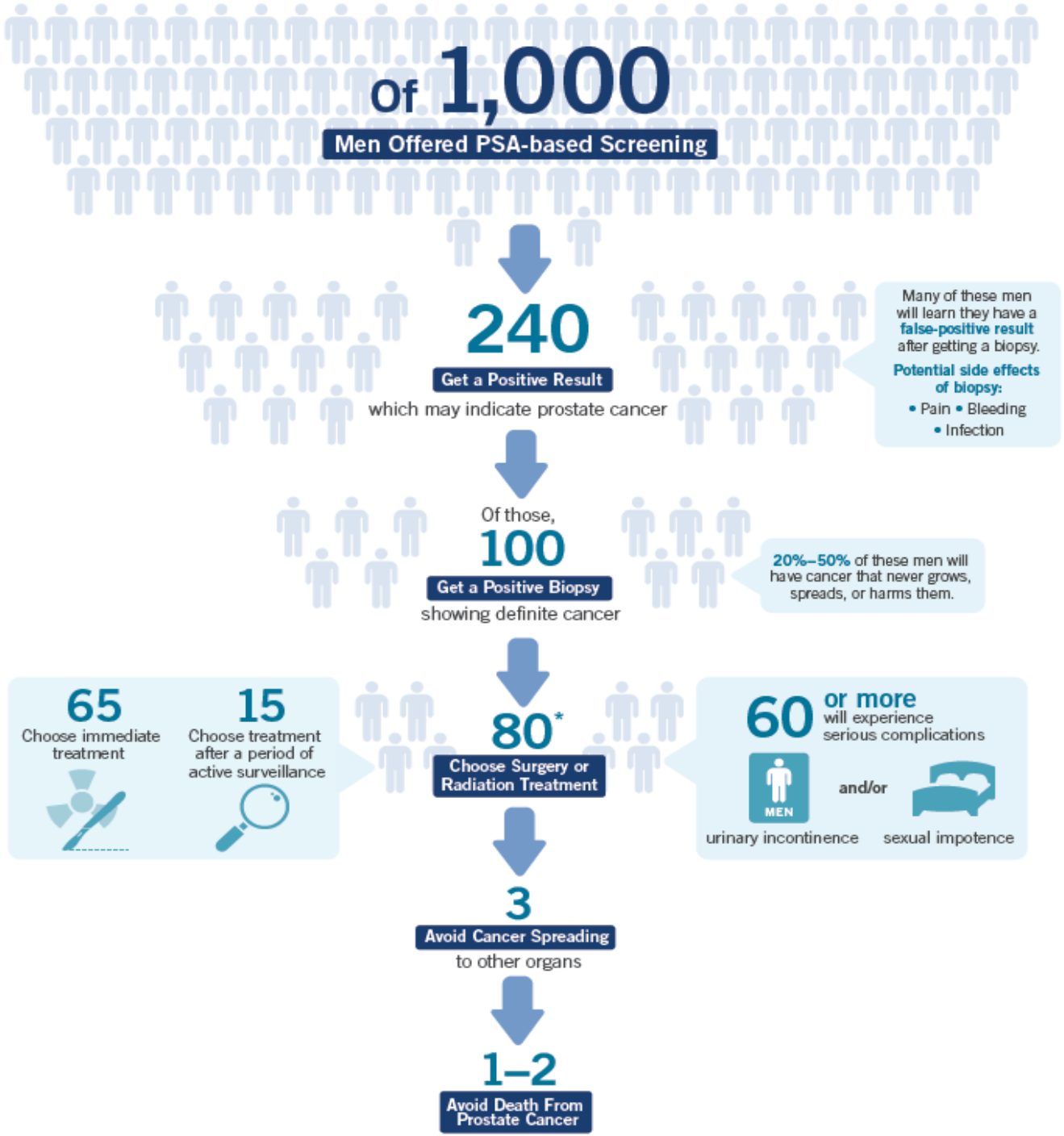
Summary of PSA screening guidelines

Society	Year	Baseline test (age)	Invitation to screen (age)*	High risk groups (age)**	Screening Interval	PSA threshold for biopsy (ng/mL)
ACS	2010	None	50 if life expectancy ≥ 10 yrs	40 if life expectancy ≥ 10 yrs	Annually if PSA ≥ 2.5 Every 2 yrs if PSA < 2.5	-2.5 in select patient -4.0 in most patients
USPSTF	2012	None	55-69 (C recommendation)	55-69 (C)	Unclear	Unclear
AUA	2013	None	55-69	40-69	Q2 yrs	None
EAU	2013	40-45	Any age if life expectancy ≥ 10 yrs	Any age if life expectancy ≥ 10 yrs	-Q2-4 yrs if baseline PSA > 1 -Q8 yrs if baseline PSA ≤ 1 ng/mL	None
ACP	2013	None	50-69	40-69	Annually if PSA ≥ 2.5	None
NCCN	2014	45-49	- 50-70 - 70-75 if life expectancy ≥ 10 yrs	Consider change in biopsy threshold	40-49 yrs -Q1-2yrs if PSA >1 -Repeat at 50 if PSA ≤ 1 50-70 yrs: - Q1-2 yrs	3.0 < 3.0 with excess risk based on family hx, race, PSA kinetics
MCS	2014	40-49	- 50-69 - 70+ if life expectancy ≥ 10 yrs	Use to better risk stratify men	None	None
Canada	2014	None	None	None	None	None
ESMO	2015	None	None	None	None	None

The US Preventive Services Task Force 2017 Draft Recommendation Statement on Screening for Prostate Cancer
An Invitation to Review and Comment

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances. Age 55-69
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service. Age ≥70
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

JAMA 2017


Of 1,000
Men Offered PSA-based Screening
240
Get a Positive Result
which may indicate prostate cancer
Many of these men will learn they have a false-positive result after getting a biopsy.
Potential side effects of biopsy:
• Pain • Bleeding
• Infection
Of those,
100
Get a Positive Biopsy
showing definite cancer
20%–50% of these men will have cancer that never grows, spreads, or harms them.
65
Choose immediate treatment
15
Choose treatment after a period of active surveillance
80*
Choose Surgery or Radiation Treatment
60 or more
will experience serious complications
MEN
and/or
urinary incontinence
sexual impotence
3
Avoid Cancer Spreading
to other organs
1–2
Avoid Death From Prostate Cancer

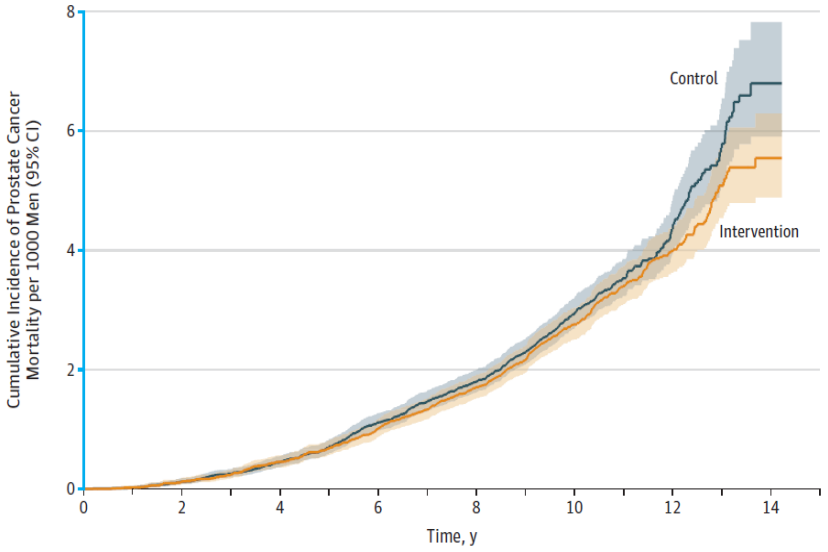
Concerns about Prostate Cancer Screening Studies

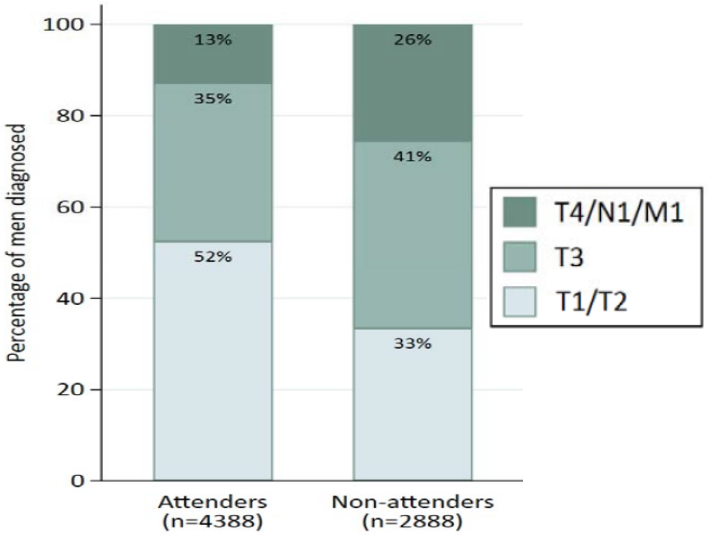
- Largely neglected AA men who have a higher risk of the disease and more aggressive disease
- Suffered from screening in the control group
- Insufficient follow up times until recently to show a survival benefit
- Did not account for other health issues, life expectancy

CAP Study: Adding to the Controversy

- The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) included 419,582 men aged 50-69 years in 573 PCP practices in the UK
- Single PSA test vs. no testing
- 189K screened, 219K not screened
  - 35% (64K) of the screening group had valid PSA testing done, of whom 11% had a PSA > 3
  - 20% of control group had screening
- 4.3 vs. 3.6% of men diagnosed with PC
- Primary endpoint was PC Mortality at 10 yrs: RR 0.96 [0.85-1.08], p=0.50
- However, screened men were less likely to have advanced/metastatic disease and more likely to have organ confined low risk disease!

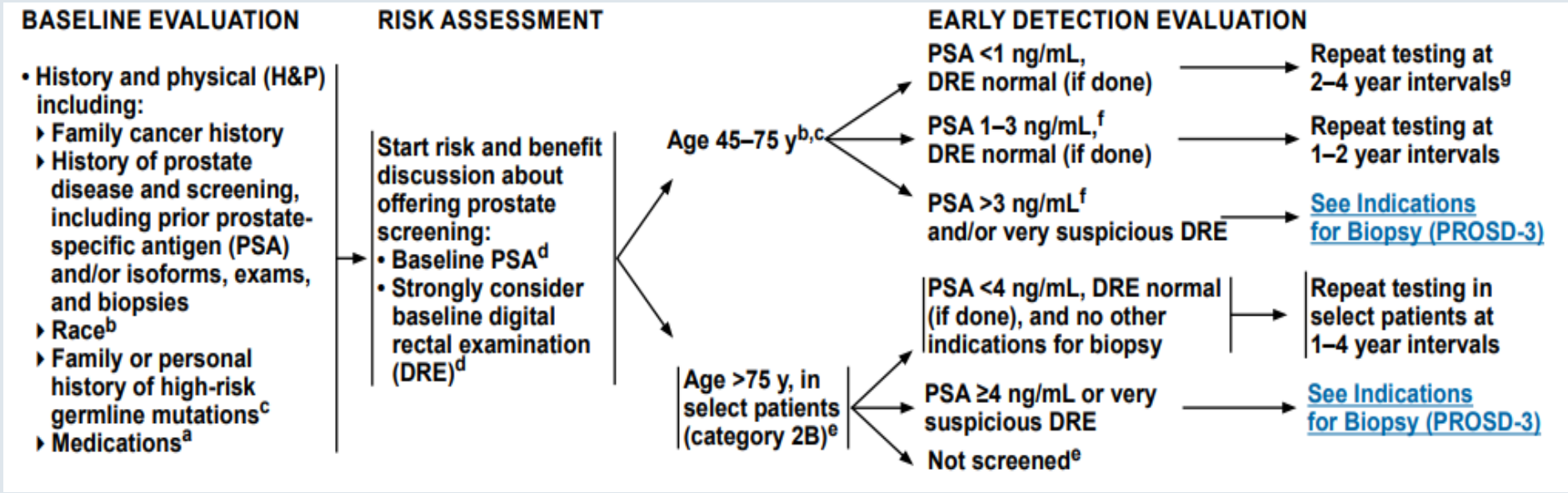
PC Mortality





Martin et al JAMA 2018

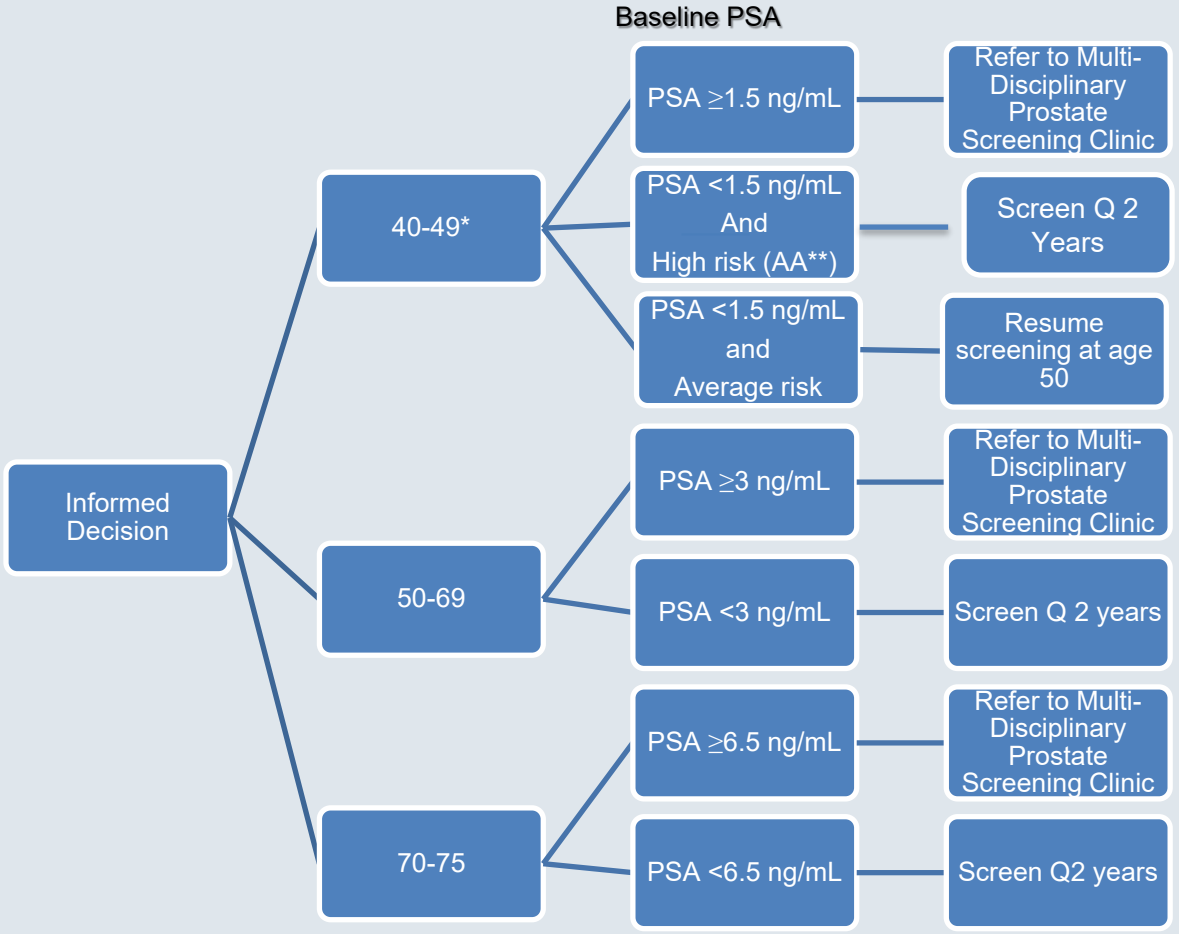
NCCN Guidelines



*An abnormal DRE prompts referral to Urology for work up

National Comprehensive Cancer Network. Prostate Cancer Early Detection (Version 2020).

Duke Cancer Institute PSA Screening Algorithm

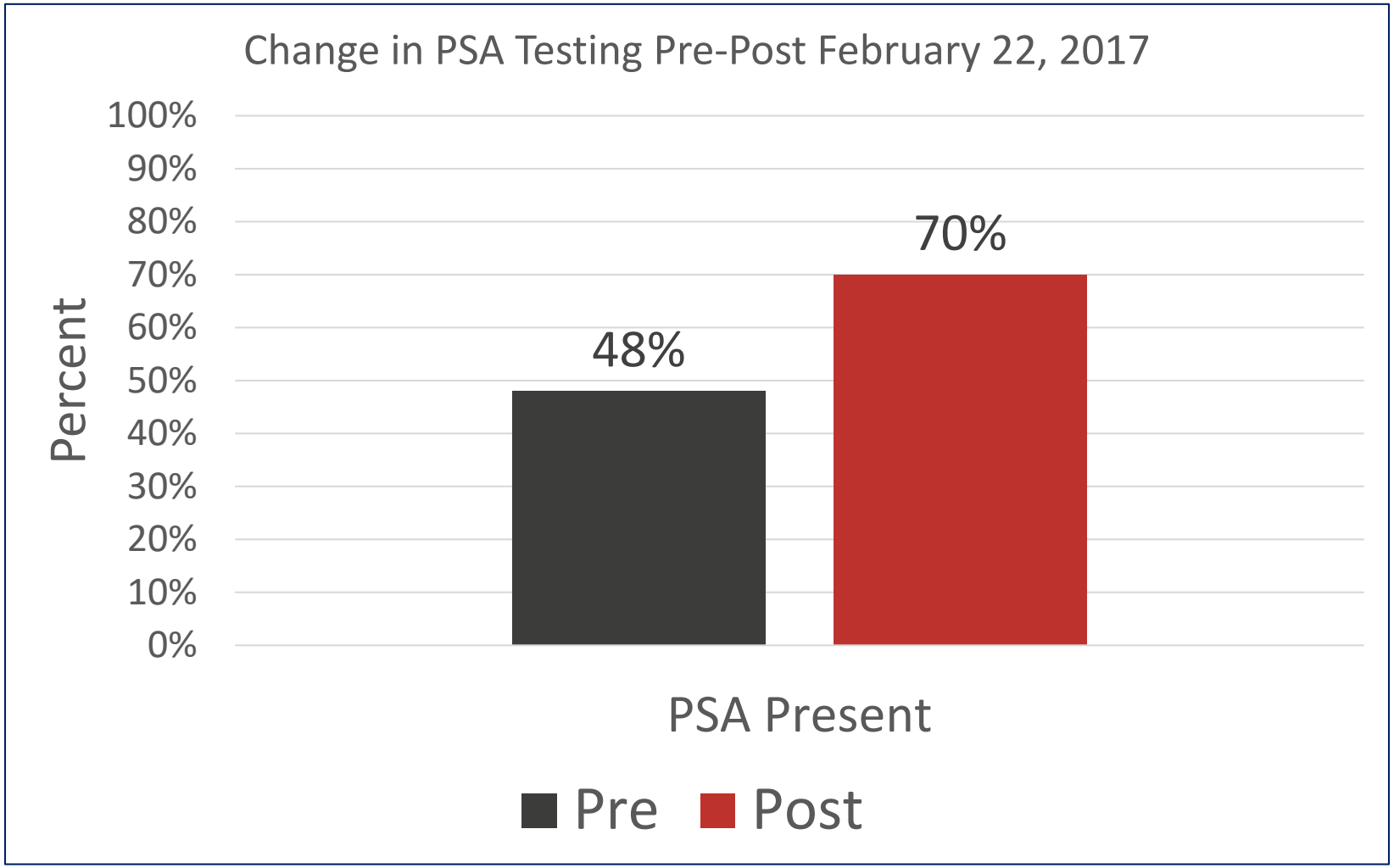


*A **single** PSA test is sufficient to establish the baseline level

** AA – African American

Gann PH, Hennekens CH, and Stampfer MJ: A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA 273: 289–294, 1995
The Baltimore Longitudinal Study
Low levels of prostate-specific antigen predict long-term risk of prostate cancer: resultsfrom the Baltimore Longitudinal Study of Aging. Fang J, Metter EJ, Landis P, Chan DW, Morrell CH, Carter HB. Urology. 2001 Sep;58(3):411-6. NCCN, AUA, EUA guidelines
Serum prostate-specific antigen in a **community-based population** of **healthy men**. Establishment of age-specific reference ranges.
Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM.
JAMA. 1993 Aug 18;270(7):860-4.

Implementation Resulted in Increased Screening



- Data covers nearly 60K men between ages 40 and 75 seen by DPC providers
- Data does not include men who “meet” the health maintenance topic
- Represents an incremental 21K PSA tests ordered this year

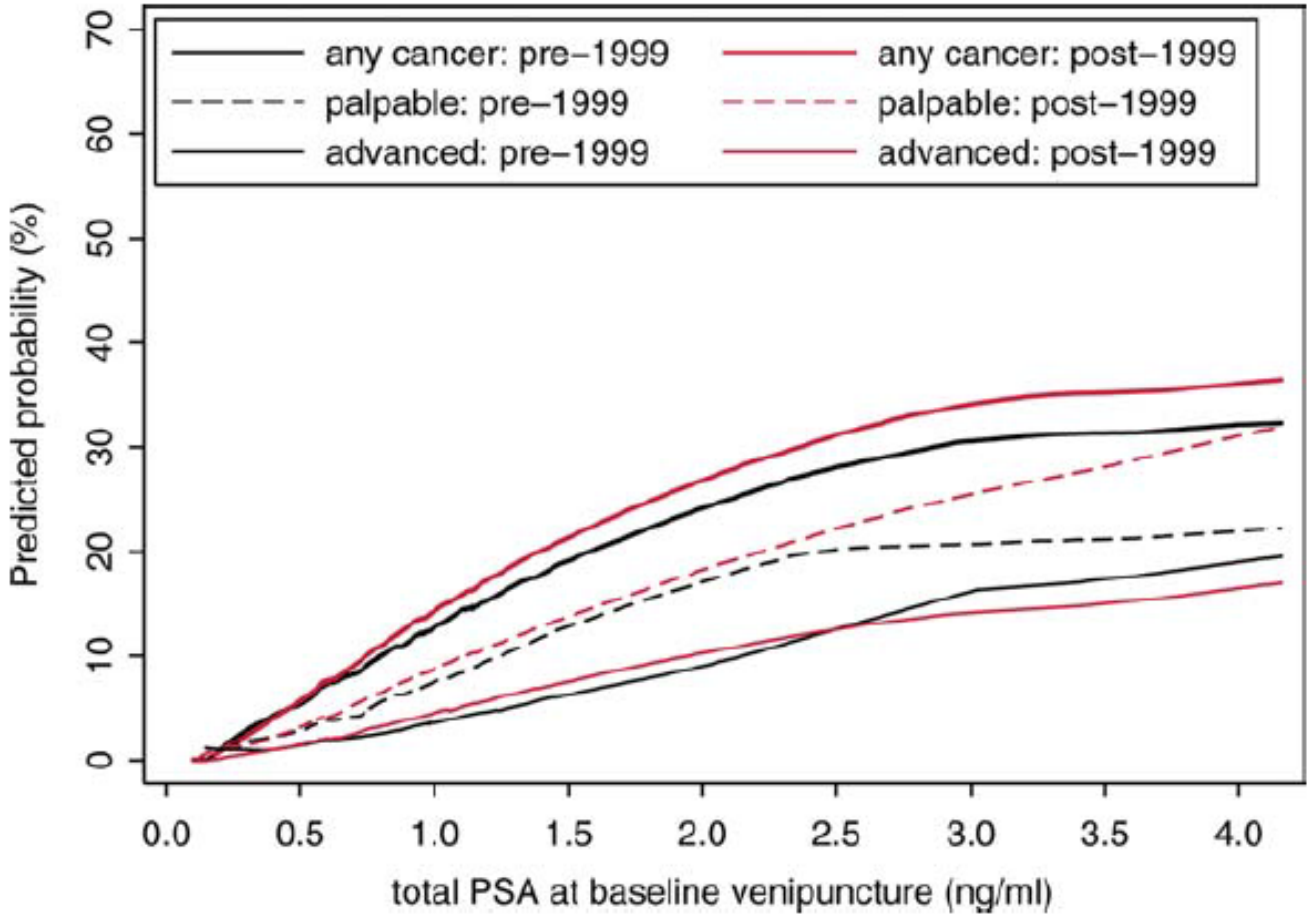
Age

- Increasing rate of harm to benefit ratio
  - **< 40yrs**
  - **40-50yrs**
  - **50-69yrs**
    - The best studied population is 55-69
  - **70+yrs**

Baseline PSA

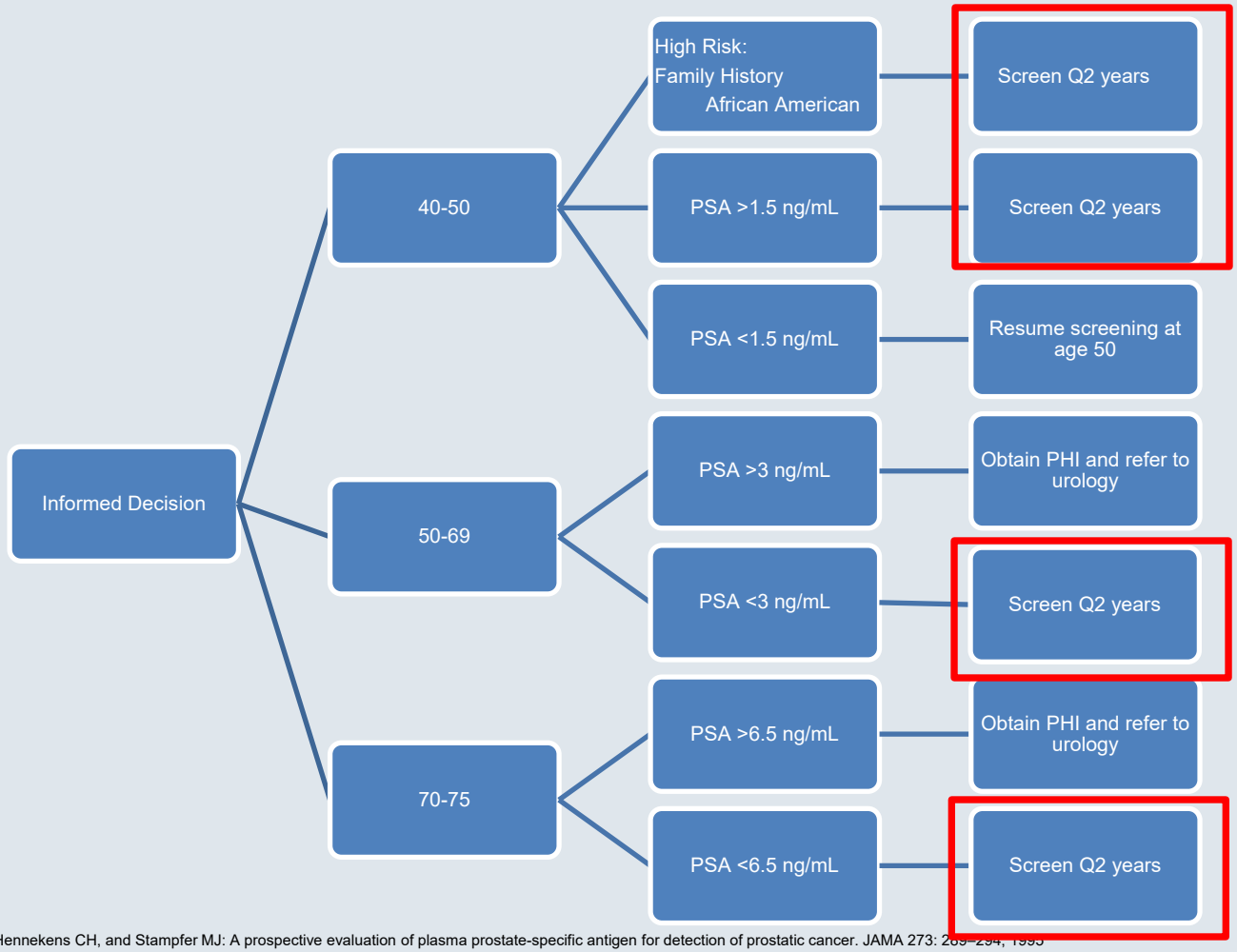
- The 1.0 ng/mL cutpoint
  - **Median PSA in a 40 year old is 0.7 ng/mL**
  - **95th percentile is 1.5 ng/mL**

Baseline PSA (age 40-60) and Risk of PC 20-30 years later



Lilja H Cancer 2011

Complete Algorithm for Normal DRE



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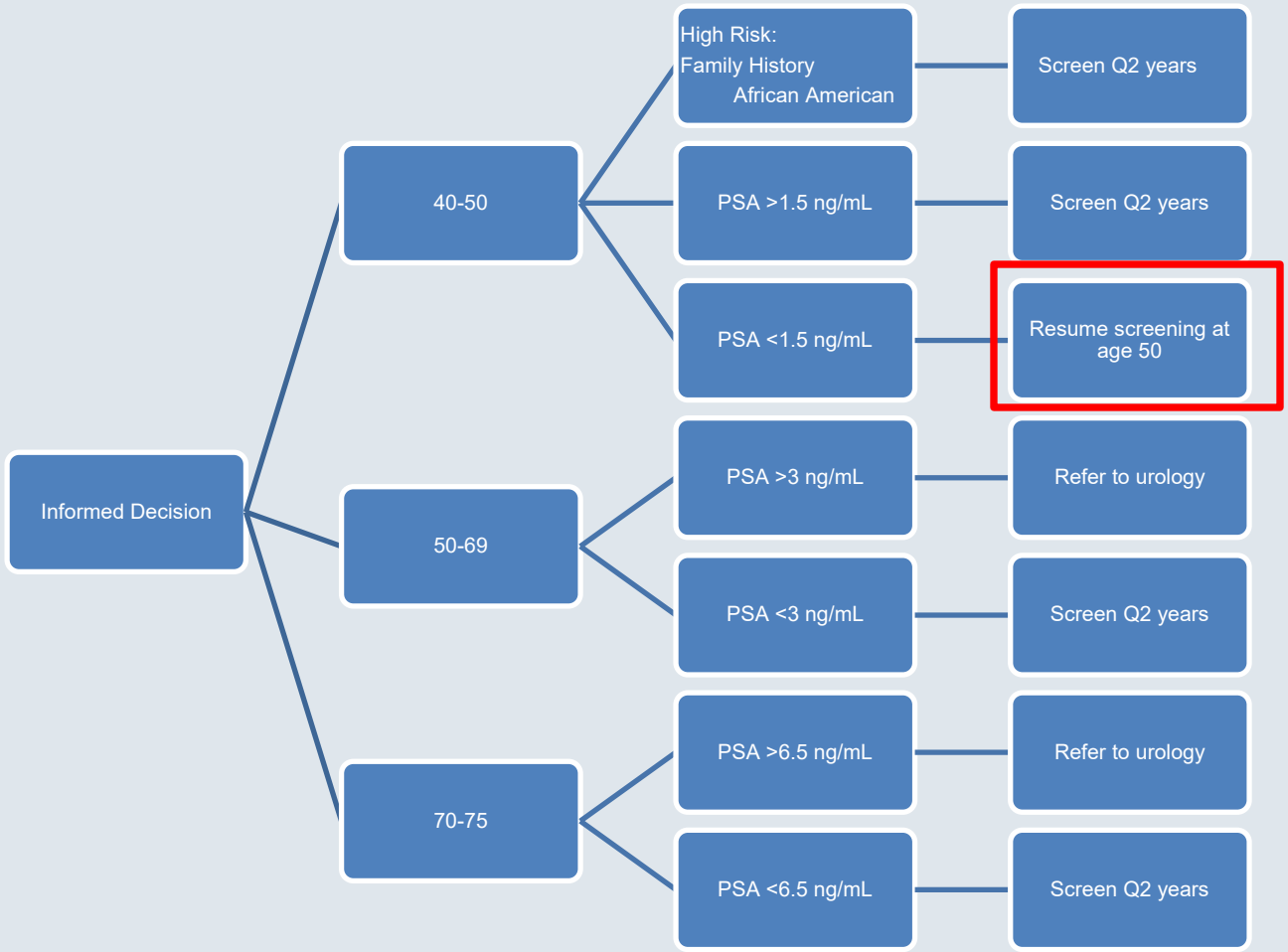

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JAMA. 1993 Aug 18;270(7):860-4.

8 Year Interval

TABLE I.
Distribution of PSA levels at second and third screening (screening interval 4 years) of 1703 men with initial PSA ≤1.0 ng/mL

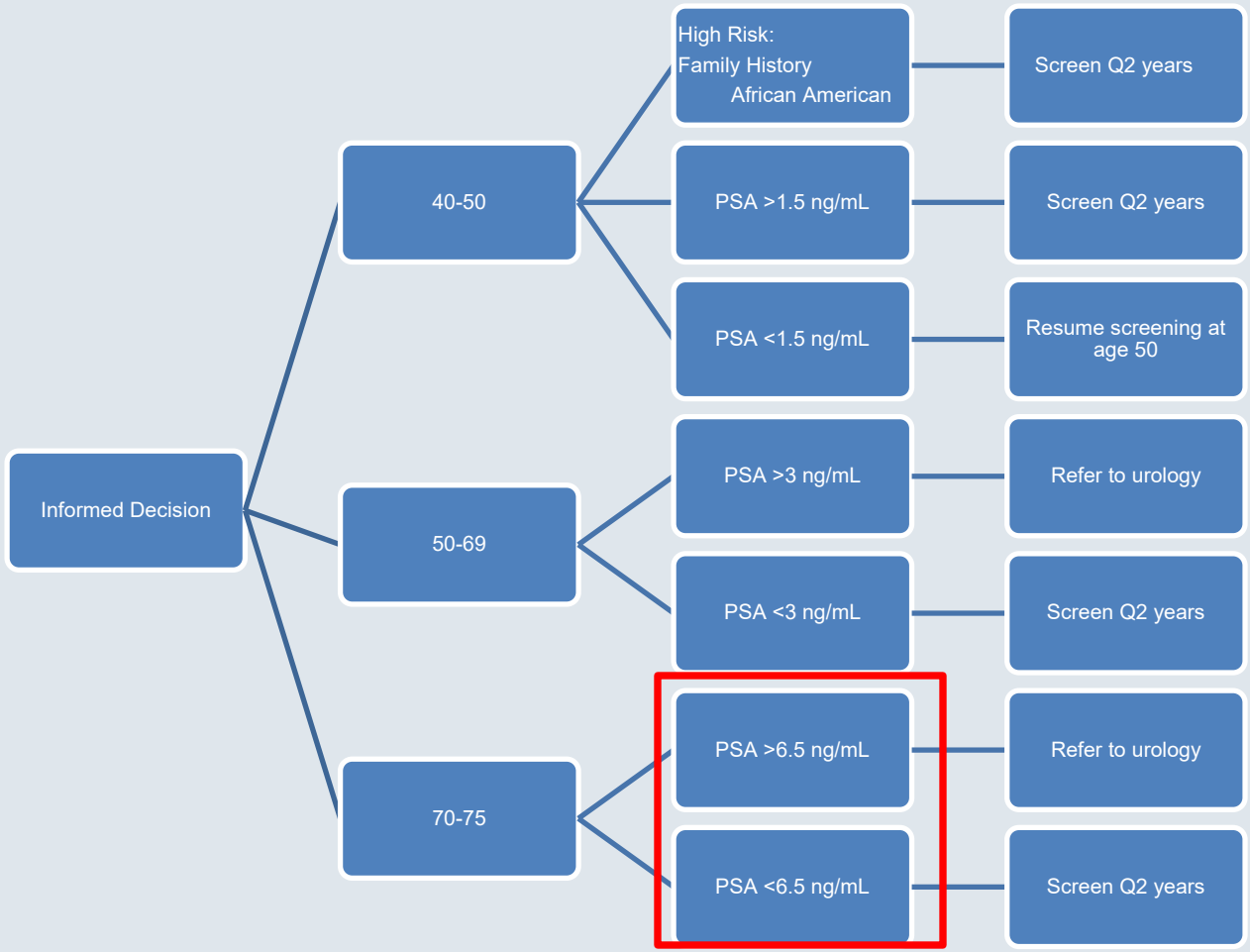
Initial Screen	Second Screen	Third Screen							
PSA (ng/mL)	Men (A)	Lost (% of A)	Men (B)	PSA2 ≤1.0 ng/mL (% of B)	PSA2 1.1–2.9 ng/mL (% of B)	PSA2 ≥3.0 ng/mL (% of B)	PC (n)	Lost (% of B)	Me (C)
0.1	29 (1.7)	7 (24.1)	22	21 (95.5)	1 (4.5)	—		4 (18.2)	18
0.2	69 (4.1)	10 (14.5)	59	55 (93.2)	4 (6.8)	—		18 (30.5)	41
0.3	145 (8.5)	30 (20.7)	115	111 (96.5)	4 (3.5)	—		20 (17.4)	95
0.4	199 (11.7)	41 (20.6)	158	142 (89.9)	16 (10.1)	—		40 (25.3)	11
0.5	230 (13.5)	46 (20.0)	184	161 (87.5)	22 (12.0)	1 (0.5)		38 (20.6)	14
0.6	238 (14.0)	54 (22.7)	184	153 (83.2)	30 (16.3)	1 (0.5)		41 (22.3)	14
0.7	208 (12.2)	43 (20.7)	165	127 (77.0)	37 (22.4)	1 (0.6)	1	33 (20.0)	13
0.8	209 (12.3)	49 (23.4)	160	104 (65.0)	53 (33.1)	3 (1.9)		46 (28.8)	11
0.9	184 (10.8)	44 (23.9)	140	62 (44.3)	76 (54.3)	2 (1.4)		34 (24.3)	10
1.0	192 (11.3)	52 (27.1)	140	40 (28.6)	95 (67.9)	5 (3.5)	2	33 (23.6)	10
Total	1703 (100.0)	376 (22.1)	1327	976 (73.5)	338 (25.5)	13 (1.0)	3	307 (23.1)	10

KEY: PSA = prostate-specific antigen; PC = prostate cancer.

Data presented as number of men, with percentages in parentheses.

Roobol MJ, Roobol DW, Schröder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology. 2005 Feb;65(2):343-6.

Complete Algorithm for Normal DRE



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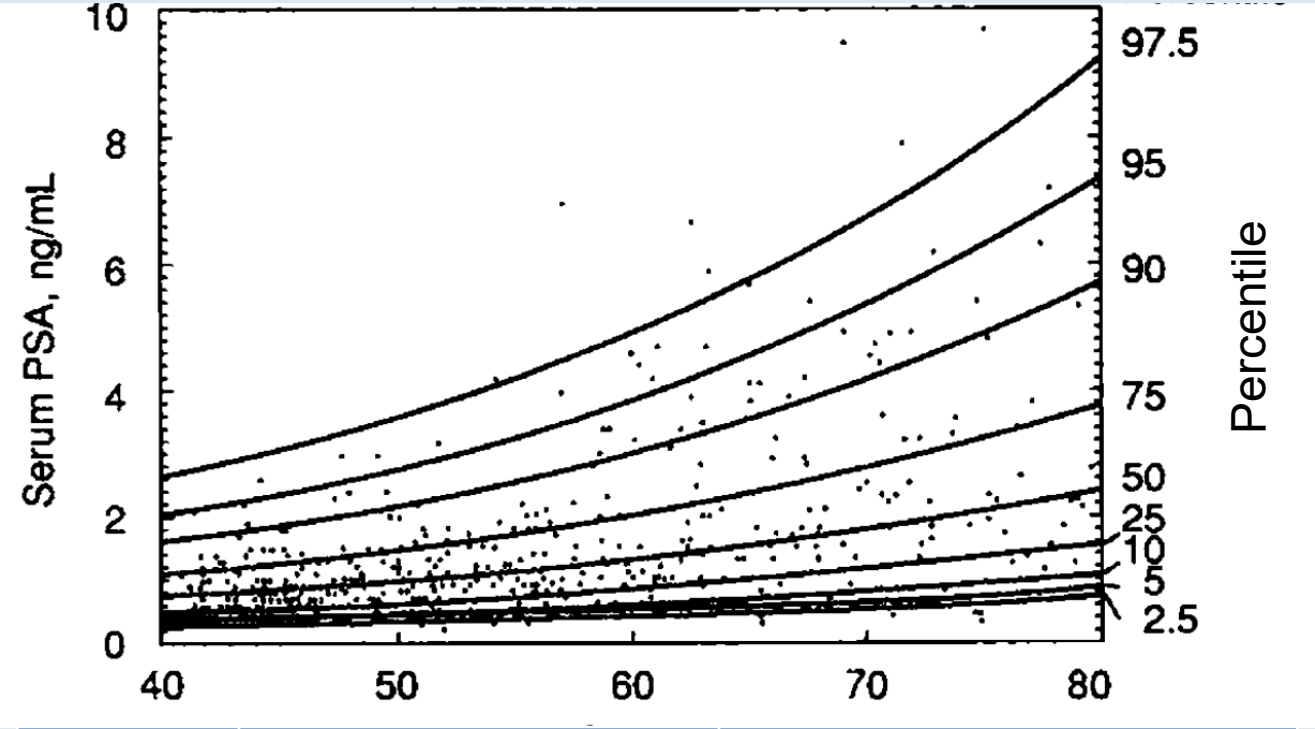
PSA goes up with Age



Age	0-4 ng/mL %(Abnormal/No. of Men)	0-6.5 ng/mL %(Abnormal/No. of Men)
70-79	19 (13/68)	7(5/68)

Serum prostate-specific antigen (PSA) concentration as a function of patient age. Scattergram of the individual serum PSA values for all 471 men, with the nomogram demonstrating the 2.5th, 5th, 25th, 50th, 75th, 95th, and 97.5th percentiles for serum PSA according to age.

Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA. 1993 Aug 18;270(7):860-4.

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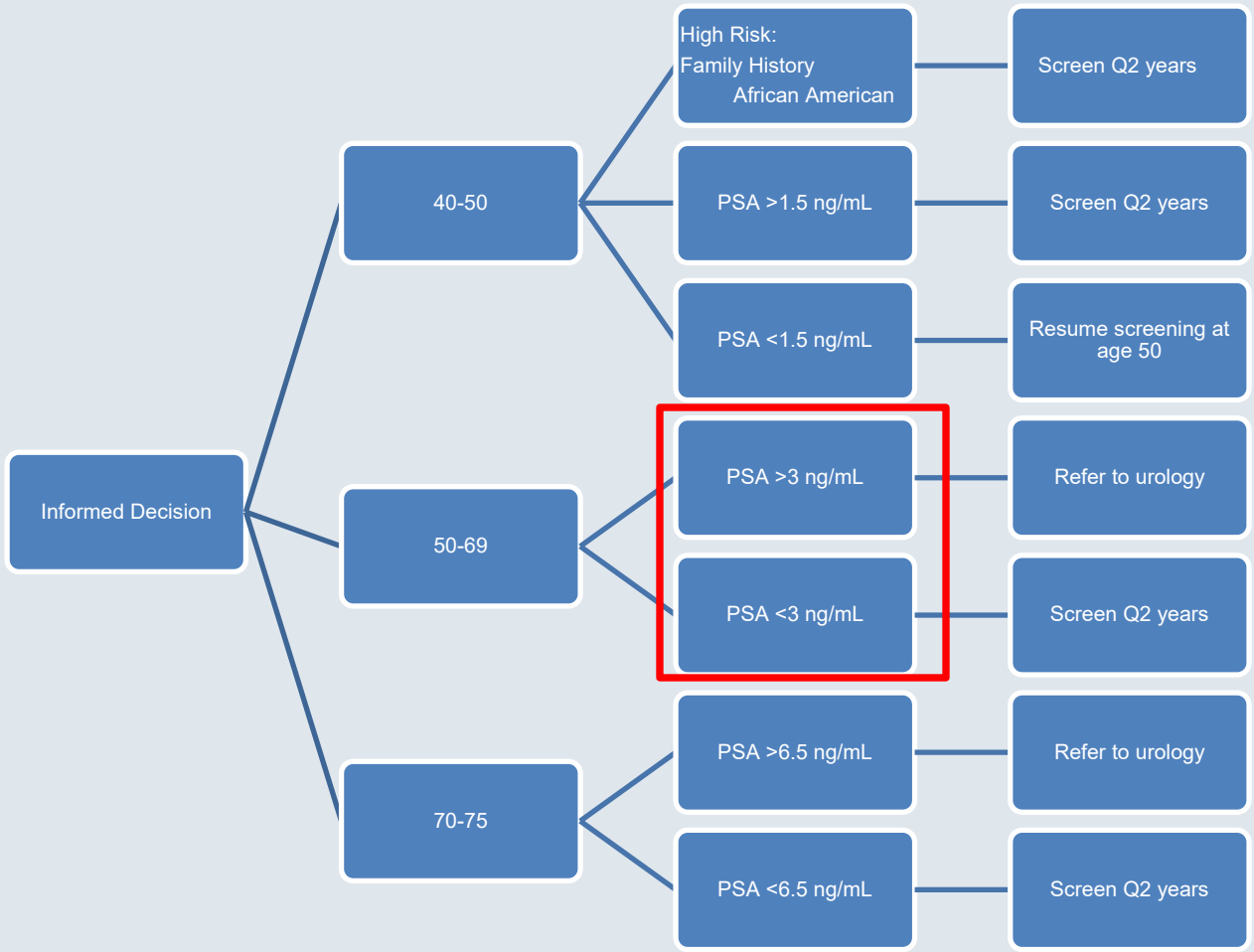

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JAMA. 1993 Aug 18;270(7):860-4.

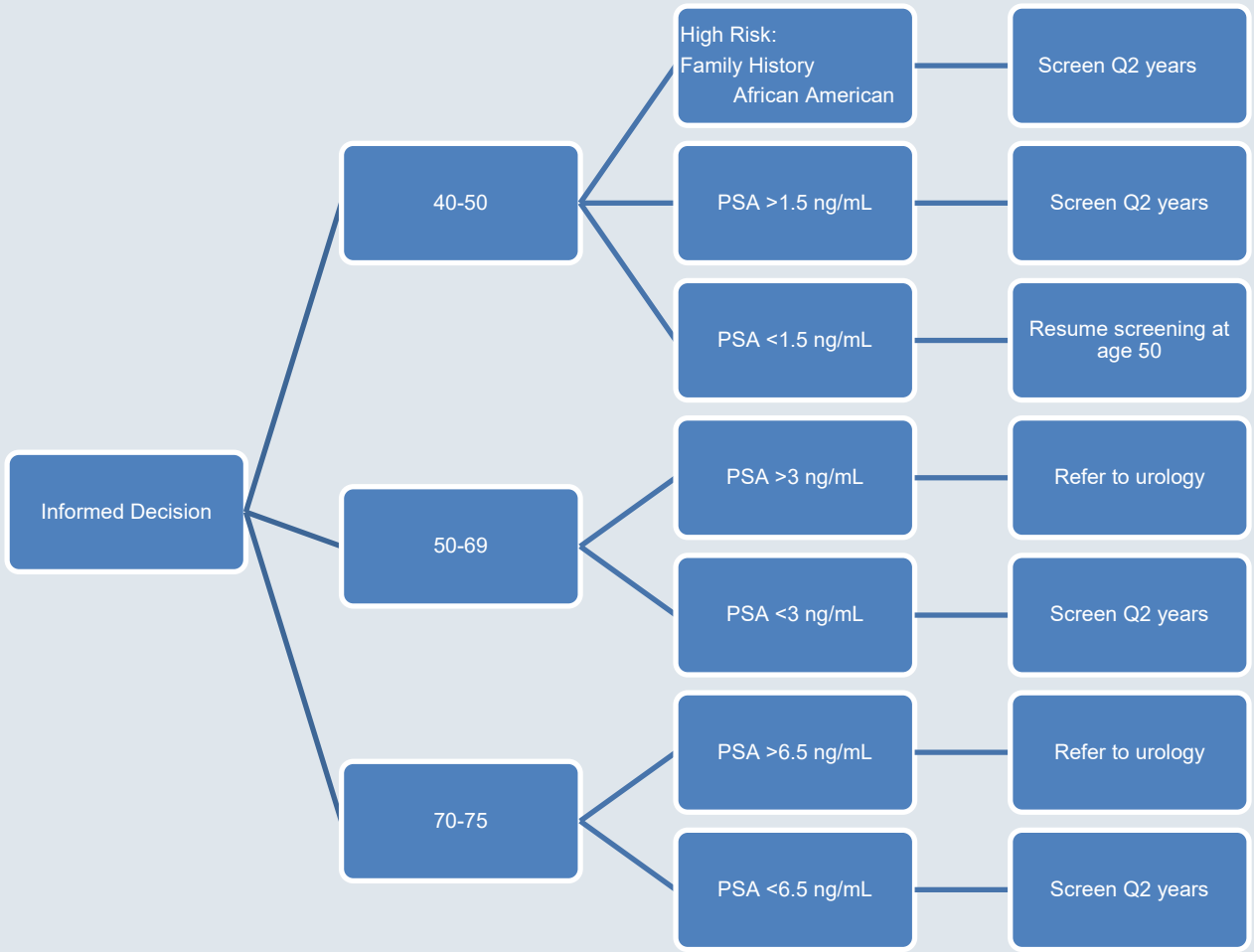
PSA level of 3 is the new 4

- New assay has the same sensitivity and specificity as the value of 4 in the traditional assay
- The ERSPC study demonstrating a reduction in death from prostate cancer used a PSA cutoff of 3.0

Schroder FH, Hugosson J, Roobol MJ et al: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; **360:** 1320.

Stephan C, Kopke T, Semjonow A, et al. Discordant total and free prostate-specific antigen (PSA) assays: does calibration with WHO reference materials diminish the problem? Clin Chem Lab Med 2009;47:1325–31.

Complete Algorithm for Normal DRE



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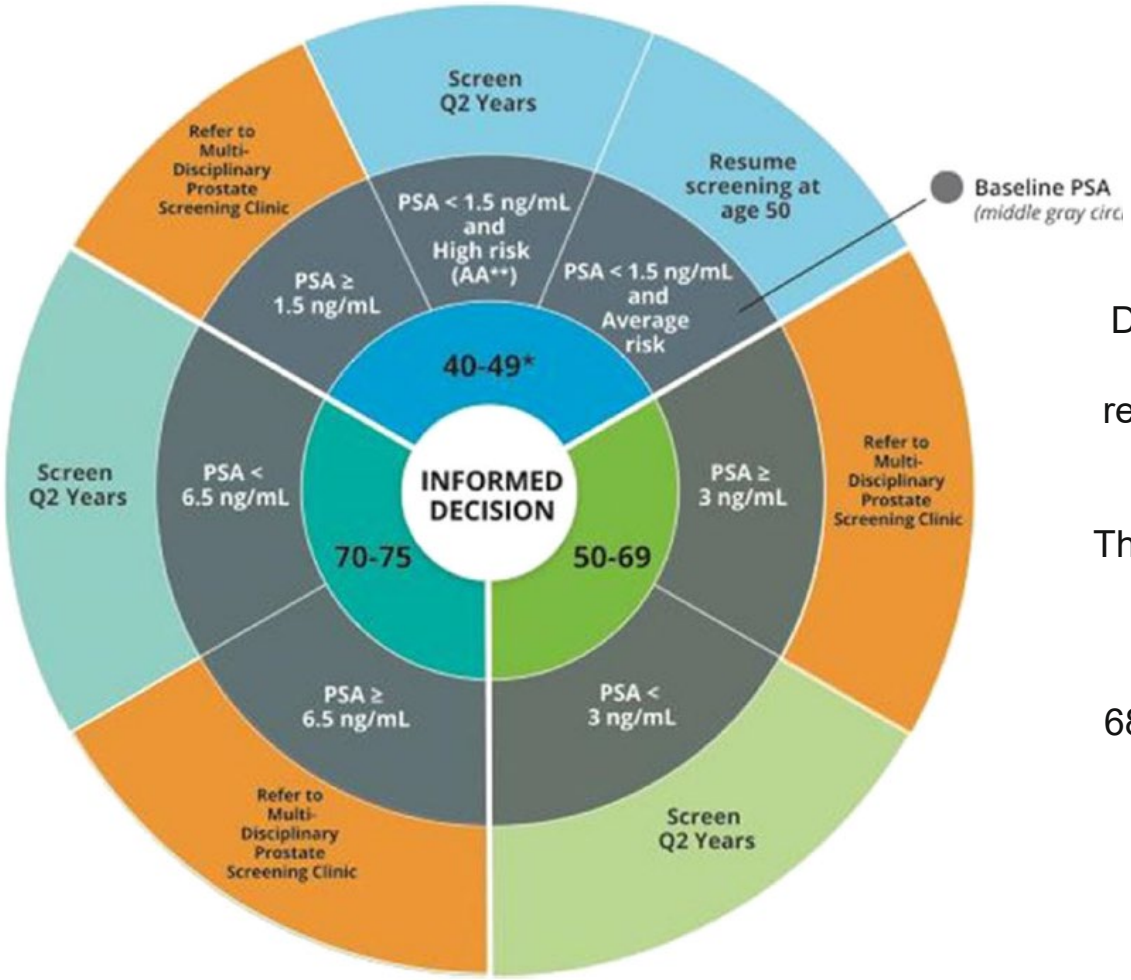
Duke Prostate Cancer Screening Algorithm



During the pre- and postimplementation periods, 49,053 and 49,980 men, respectively, were seen across 26 clinics (20.6% African American).

The proportion of men who met screening algorithm
criteria increased from 49.3% (pre-implementation) to
68.0% (post-implementation) ($p < 0.001$)

Implementation and Impact of a Risk-Stratified Prostate Cancer Screening Algorithm as a Clinical Decision Support Tool in a Primary Care Network

Anand Shah, MD, MBA[1], Thomas J. Polascik, MD[1], Daniel J. George, MD[1], John Anderson, MD, MPH[1], Terry Hyslop, PhD[1], Alicia M. Ellis, PhD[1], Andrew J. Armstrong, MD, MSc[1], Michael Ferrandino, MD[1], Glenn M. Preminger, MD[1], Rajan T. Gupta, MD[1], W. Robert Lee, MD, MS[1], Nadine J. Barrett, PhD[1], John Ragsdale, MD[1], Coleman Mills, MA, CCRP[1], Devon K. Check, PhD[1], Alireza Aminsharifi, MD[1,2], Ariel Schulman, MD[1,3], Christina Sze, MD, MS[1,4], Efrat Tsivian, MD[1], Kae Jack Tay, MD[1,5], Steven Patierno, PhD[1], Kevin C. Oeffinger, MD[1], and Kevin Shah, MD, MBA[1]

[1]Duke University, Durham, NC, USA; [2]Cleveland Clinic, Cleveland, OH, USA; [3]Maimonides Medical Center, New York, NY, USA; [4]Weill Cornell Medical College, New York, NY, USA; [5]SingHealth, Duke-NUS, Singapore, Singapore.

Shah et al JGIM 2020

Results of the Screening Algorithm

Table 2 Percent of Men Meeting Algorithm-Based Screening and with PSA Completed in Pre- and Post-implementation Periods

Category	Pre-implementation		Post-implementation		% difference
Date range	**2/1/2016–2/1/2017**		**2/2/2017–2/21/2018***		
Men meeting algorithm-based screening	*N*	*%*	*N*	*%*	
Total	24,193	49.3	33,976	68.0	18.7*
Race					
African American	5464	54.0	7360	71.5	17.4*
Caucasian	16,998	48.9	23,753	67.3	18.4*
Asian	806	40.4	1375	66.6	26.1*
Age categories (year)					
40–44	1168	18.3	1972	47.7	29.4*
45–49	2360	32.9	4425	56.8	23.9*
50–59	8828	58.9	11,577	73.3	14.4*
60–69	8561	60.9	11,032	74.2	13.3*
70–75	3276	50.6	4970	67.1	16.5*
Men with PSA completed					
Total	27,146	55.3	27,498	55.0	− 0.3
Race					
African American	6130	60.6	5811	56.4	− 4.2
Caucasian	19,116	55.0	19,314	54.8	− 0.2
Asian	870	43.7	1162	56.2	12.6
Age categories (year)					
40–44	1242	19.4	1726	41.7	22.3*
45–49	2545	35.5	3680	47.3	11.8*
50–59	9744	65.1	9001	57.0	− 8.0
60–69	9689	69.0	9010	60.6	− 8.4
70–75	3926	60.7	4081	55.1	− 5.6

*$p < 0.001$
†*Post-implementation data pull on 2/22/18*
PSA, prostate-specific antigen

Importantly, the percent of men who had a PSA did not change: 55.3% pre-implementation, 55.0% post-implementation.
The adjusted odds of meeting algorithm-based screening was **6.5-times** higher in the post-implementation period than in the preimplementation period (95% confidence interval, 5.97 to 7.05).

Shah et al JGIM 2020

Disparities in Localized Disease Outcomes
Population Studies vs Equal Access Centers vs. Clinical Trials

Figure 2. Forest Plot of Fine-Gray Competing-Risk Subdistribution Hazard Ratios (sHRs) of Prostate Cancer–Specific Mortality (PCSM)

Cohort (No. Black/White)	10-y Absolute Difference In PCSM, Black Minus White (95% CI), %	sHR (95% CI)	P Value
SEER (52840/243433)			
Age weighted	1.30 (0.9 to 1.6)	1.30 (1.23-1.37)	<.001
Age and stage weighted	0.80 (0.5 to 1.2)	1.17 (1.11-1.24)	<.001
Fully weighted	0.50 (0.2 to 0.9)	1.09 (1.04-1.15)	<.001
VA (1513/2459)			
Age weighted	-0.50 (-1.6 to 0.6)	0.88 (0.57-1.34)	.55
Fully weighted	-0.60 (-1.8 to 0.5)	0.85 (0.56-1.30)	.46
RCT (1129/4725)			
Age weighted	-1.60 (-3.6 to 0.4)	0.90 (0.74-1.09)	.27
Fully weighted	-2.20 (-4.3 to -0.1)	0.81 (0.66-0.99)	.04

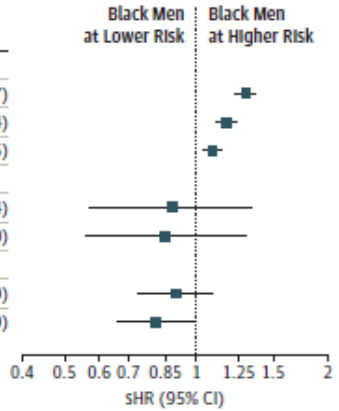
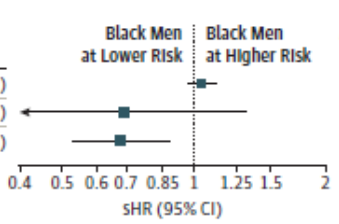
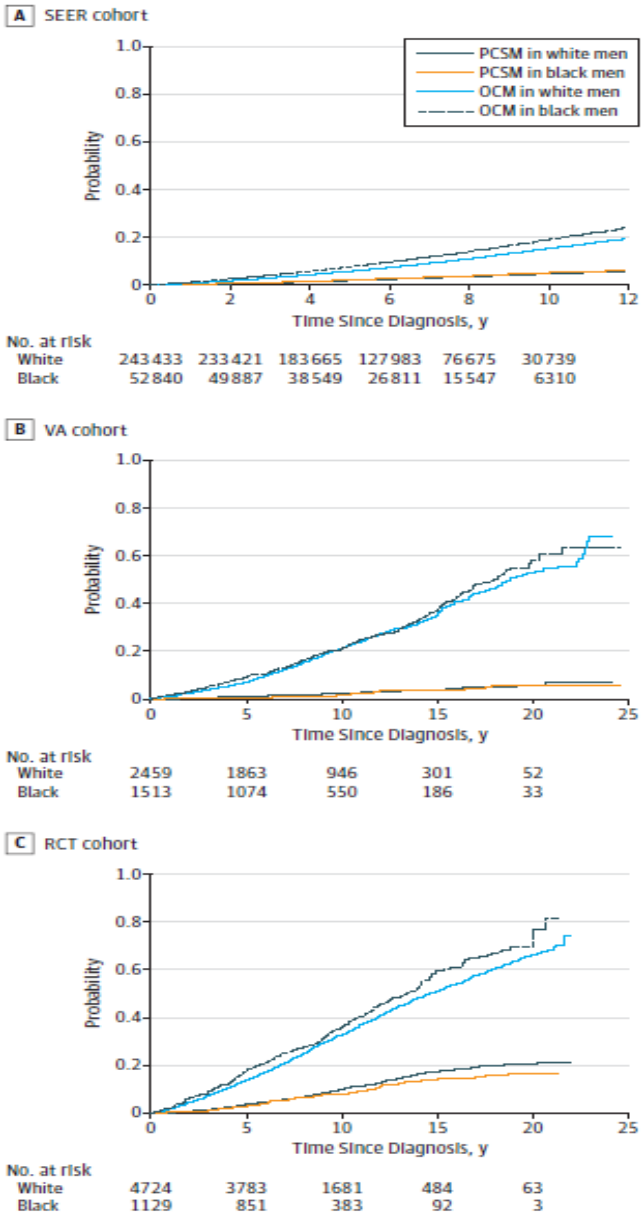


Figure 3. Forest Plot of Fine-Gray Competing-Risk Subdistribution Hazard Ratios (sHRs) of Prostate Cancer–Specific Mortality (PCSM) by National Comprehensive Cancer Network High-Risk Subgroup

Fully Weighted Cohort (No. Black/White)	10-y Absolute Difference In PCSM, Black Minus White (95% CI), %	sHR (95% CI)	P Value
SEER (11557/53904)	0.5 (-0.6 to 1.7)	1.04 (0.97-1.12)	.29
VA (278/468)	-1.2 (-5.6 to 3.3)	0.69 (0.36-1.32)	.36
RCT (487/2074)	-5.1 (-8.5 to -1.7)	0.68 (0.53-0.88)	.003





Dess et al JAMA Oncol 2019

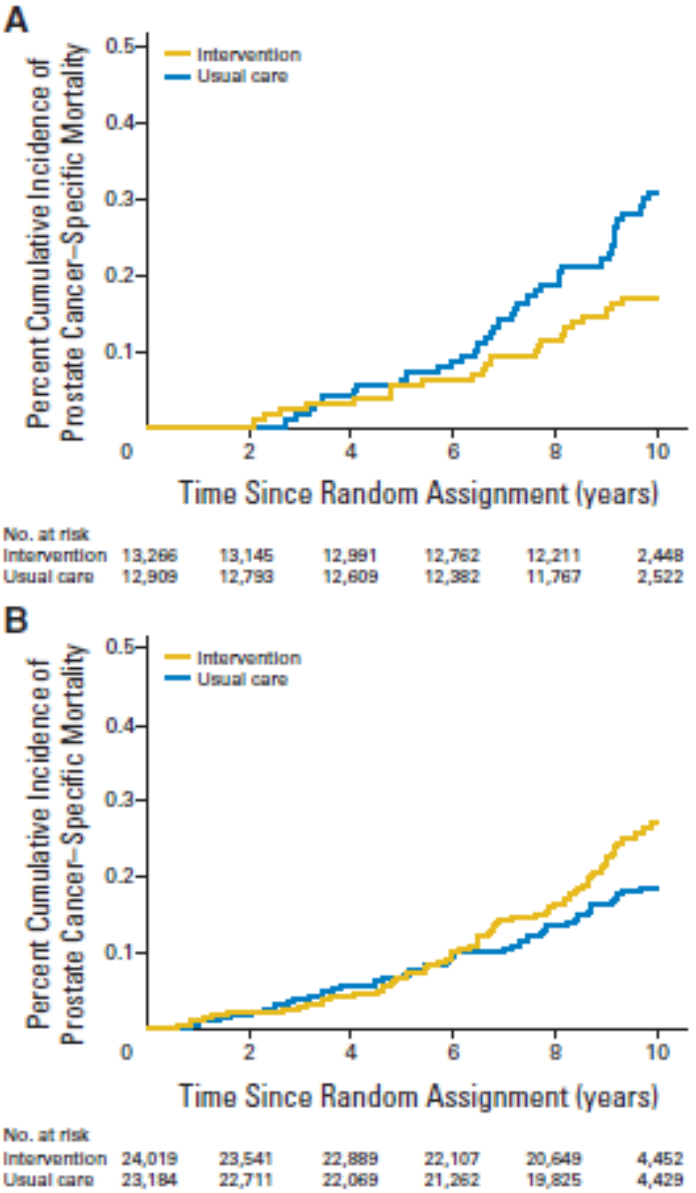
Why did the prior USPSFT recommend against PSA screening?

1. Harms related to screening
   - False positive related anxiety (suicidality perhaps)
   - Risk of biopsies: urosepsis in 1-3%, urinary retetion in 1%, gross hematuria in 0-1%, need for catheter), pain, fever, or UTI (in up to 1/3), hospitalization in 1-2%
2. Harms related to treatment
   - Underutilization of active surveillance for low risk PC
   - Overtreatment: over 90% of men are treated in the US!
   - Side effects of treatment: death (<0.5%), ED, urinary symptoms
   - Overutilization of primary ADT for localized PC in the elderly
3. Lack of proof of benefit in the elderly
   - While most men who die of PC are elderly (>70), RCTs have not shown a survival benefit in this population

USPSTF May 2012
Pinkhasov GI BJUI 2012
Rosario DJ BMJ 2012

Screening only Healthy Men?

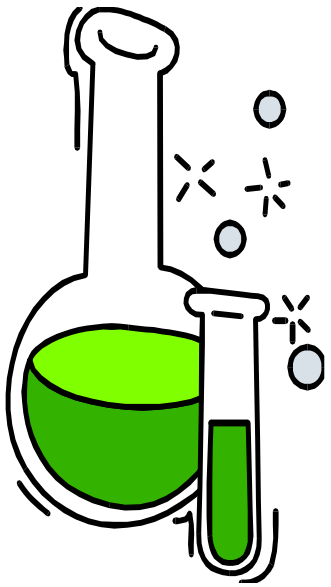
- PLCO trial retrospectively analyzed for an interaction between PC-related mortality and comorbidity
- 10 year follow up: 164 out of 9,565 deaths from PC
- Decrease PCSM in men with 0-minimal comorbidity (AHR 0.56 p=0.03), NNT of 5
- No benefit and possibly harm with screening in men with at least one significant comorbidity (AHR 1.43 p=0.08)
  - But depends on criteria used!



Crawford ED JCO 2010

Screening Recommendations

- Most guidelines now recommend informed decision making and consideration of PSA for all men at 40-55 to set baseline risk (USPSTF 2017 at 55)
- Individual discussions based on risk and benefits are recommended starting at age 50 (average risk) and age 40-45 (high risk family, African American men)
- **Initial PSA at a younger age (40-60) may be useful to guide further screening decisions and necessity of screening later**
- When to stop screening is controversial: 70 is recommended but may be tailored to “biologic age” and comorbidities



Elevated PSA Work Up

- DRE: low Se/Sp by PCPs
- Clearly helpful in some cases (low PSA aggressive tumors) but these are uncommon
- False positives are common (BPH)
- Should be performed by those competent in the procedure and interpretation (urology generally)
- A positive DRE for a nodule should prompt referral for biopsy regardless of the PSA

Table 4. Summary Findings and Meta-Analysis of Diagnostic Accuracy of DRE for Prostate Cancer Screening in Primary Care Settings

Study, Year	Sensitivity	Specificity	PPV	NPV
Al-Azab et al,[16] 2007	0.50	0.61	0.49	0.62
Brett,[17] 1998	0.67	N/A	N/A	N/A
Crawford et al,[18] 1999	0.65	0.37	0.29	0.72
Elliott et al,[19] 2008	0.65	0.65	0.52	0.64
Faria et al,[20] 2012	0.24	0.72	0.36	0.59
Kirby et al,[21] 1994	0.73	N/A	N/A	N/A
Pederson et al,[22] 1990	N/A	N/A	0.26	N/A
Pooled analysis[a]				
Estimate (95% CI)	0.51 (0.36-0.67)	0.59 (0.41-0.76)	0.41 (0.31-0.52)	0.64 (0.58-0.70)
Heterogeneity: I^2, %	98.4	99.4	97.2	95.0

DRE = digital rectal examination; NPV = negative predictive value; N/A = not available; PPV = positive predictive value.

[a] Pooled analysis of data from 6 studies of 3,304 patients total for sensitivity; 4 studies of 5,877 patients total for specificity; 6 studies of 4,581 patients total for positive predictive value; and 4 studies of 4,634 patients total for negative predictive value.

Ann Fam Med 2018;16

Elevated PSA: Serum Markers

- Prostate health index (phi) is available to identify men at high risk for PC who have an elevated PSA.
- Serum marker combines total PSA, free PSA, and [-2]proPSA:
  - ([-2]proPSA/free PSA) × √PSA = phi
- Se of 80-95%, greater specificity than PSA, AUC 0.70 for clinically significant PC, leading to FDA approval in the PSA 4-10 range, but also works in 2-10 range
  - Threshold of ~25-35% provides greatest net benefit/harm reduction
- Can reduce the number of unnecessary biopsies by ~15%
- May be first reflect step in work up of a man with an elevated PSA

Loeb et al The Adv Urol 2014

Reducing Harms of Screening: Increased Active Surveillance of low risk prostate cancer (turtles)

Pathology of Prostate Cancer

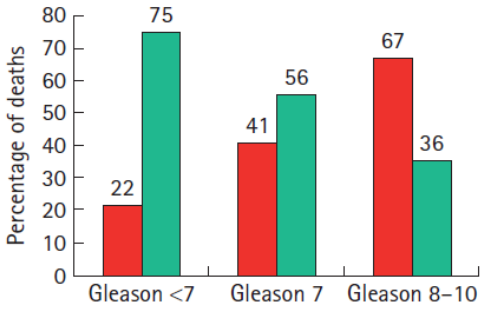
Important factors noted in prostate biopsy specimens:

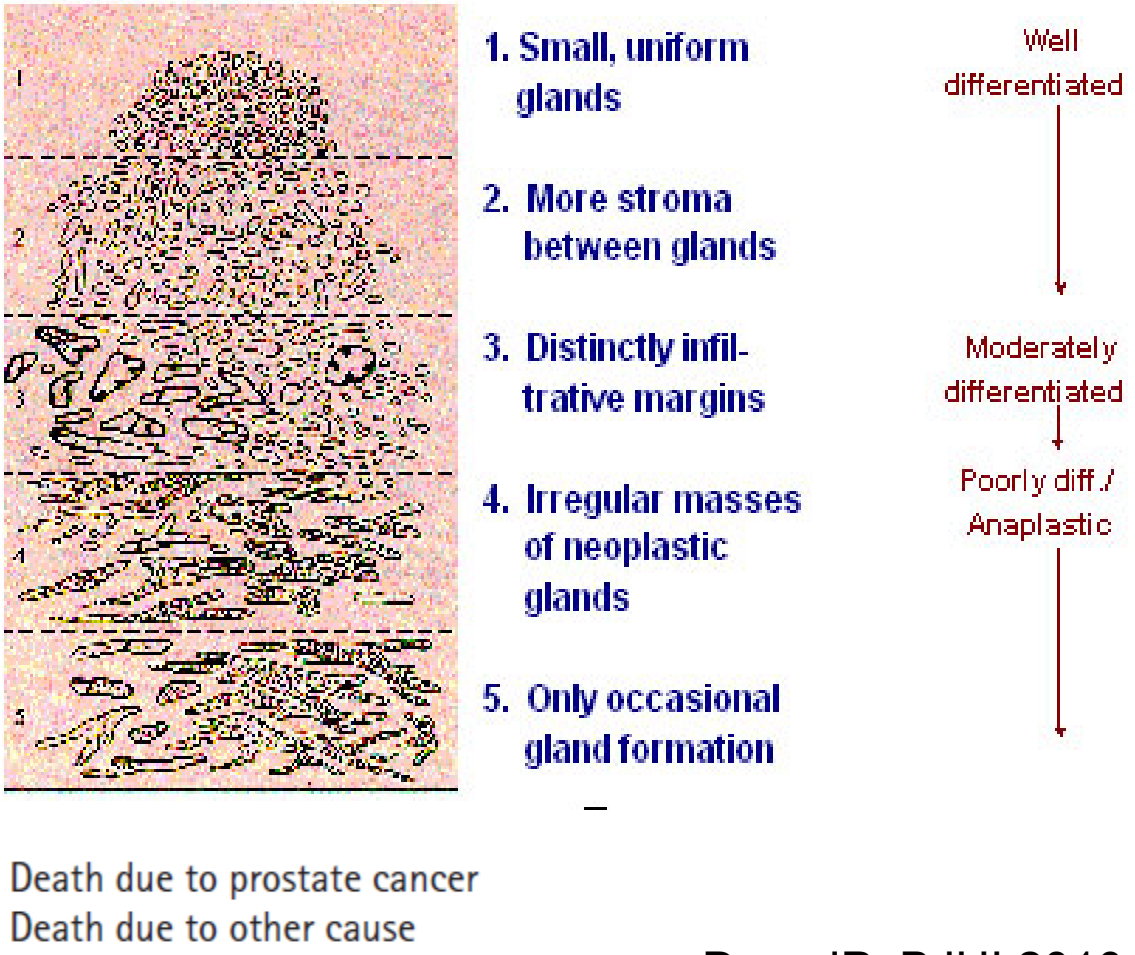
Perineural invasion

Primary and secondary Gleason score

Percent core involvement

# of cores involved

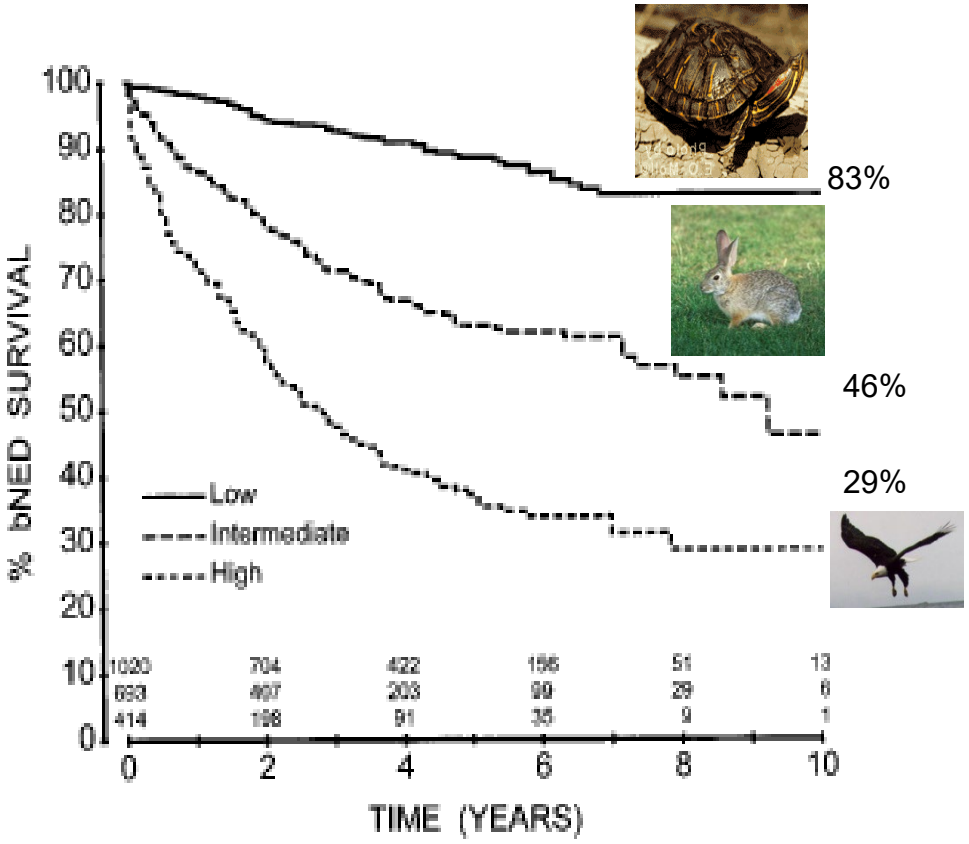




Droz JP, BJUI 2010

Not all prostate cancers are created equally

- Low Risk: T1c-T2a, PSA<10 and Gleason ≤6
- Intermediate: T2b (unilateral more than ½ lobe) or PSA 10-20 or Gleason 7
- High Risk: T2c (bilateral palpable), Gleason ≥8, PSA>20



D'Amico, J Urol 2001

5 Tier Gleason System

Grade group 1: Gleason score ≤6
Only individual discrete well-formed glands

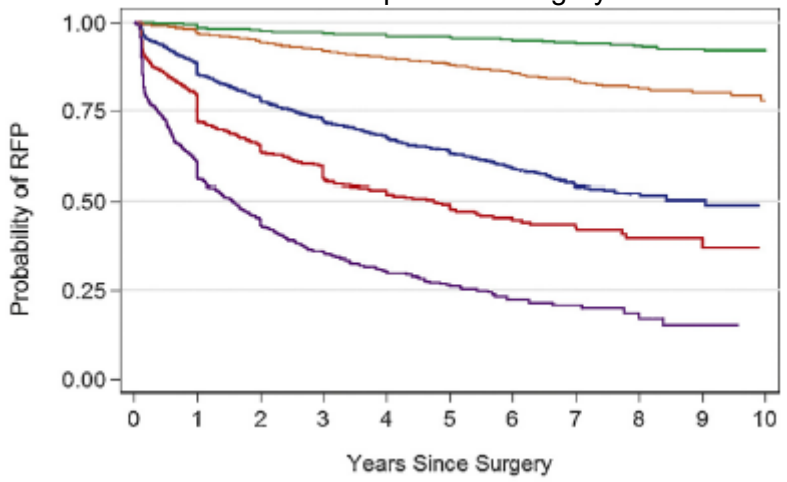
Grade group 2: Gleason score 3+4=7
Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands

Grade group 3: Gleason score 4+3=7
Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands*

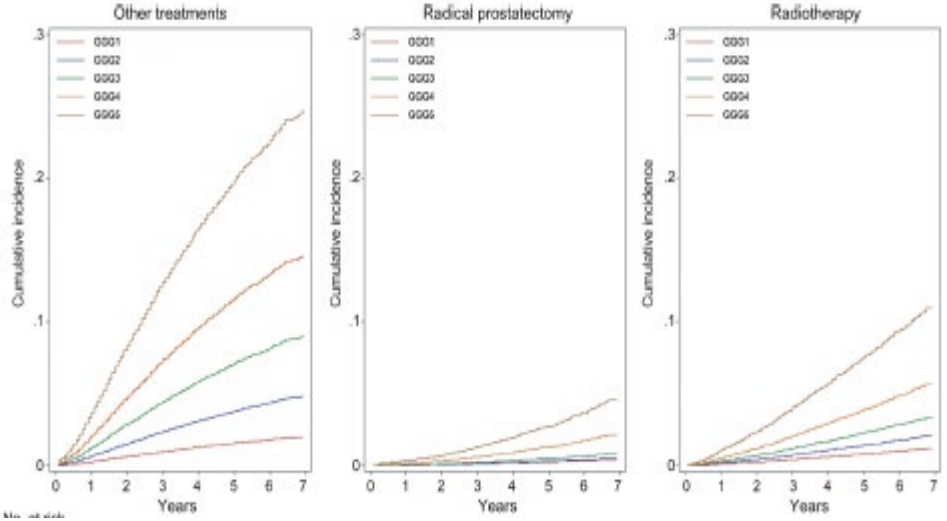
Grade group 4: Gleason score 4+4=8; 3+5=8; 5+3=8
- **Only poorly-formed/fused/cribriform glands or**
- **Predominantly well-formed glands and lesser component lacking glands[1] or**
- **Predominantly lacking glands and lesser component of well-formed glands[1]**

Grade group 5: Gleason score 9-10
Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands[2]

PSA Relapse after Surgery



PC-Specific Mortality Validation



Epstein JI, Egevad L, Amin MB, et al. Am J Surg Pathol 2016;40:244-252.
Epstein JI, Zelefsky MJ, Sjoberg DD, et al. Eur Urol 2016;69:428-435.
He J et al Eur Urol 2017

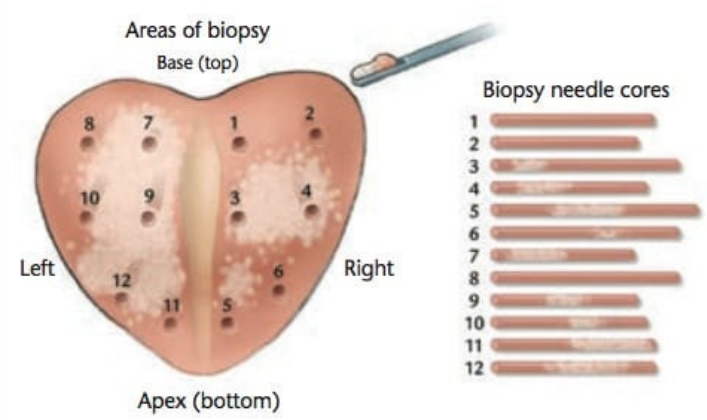
Staging Types

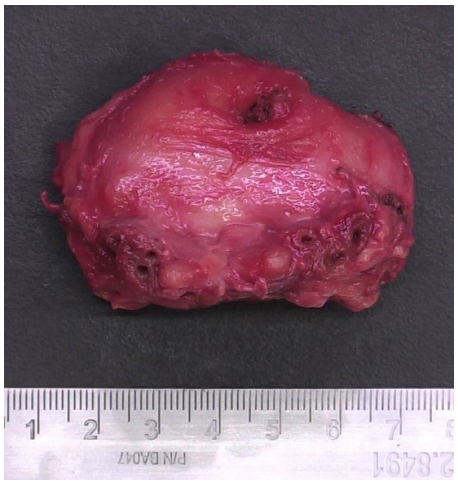
Clinical Staging

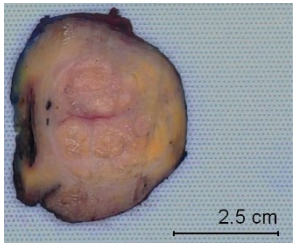
- Applies to patients prior to surgery or those treated with surveillance, radiation, brachytherapy, or other modalities
- Uses imaging (MRI, CT, bone scan), exam, TRUS or MRI biopsies

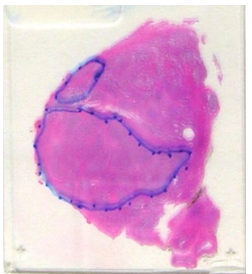
Pathologic staging

- Applies only to radical prostatectomy patients
- Surgical patients have clinical AND pathologic TNM stages
- Pathologic staging considered more definitive, accurate
- Upgrading and downgrading is relatively common

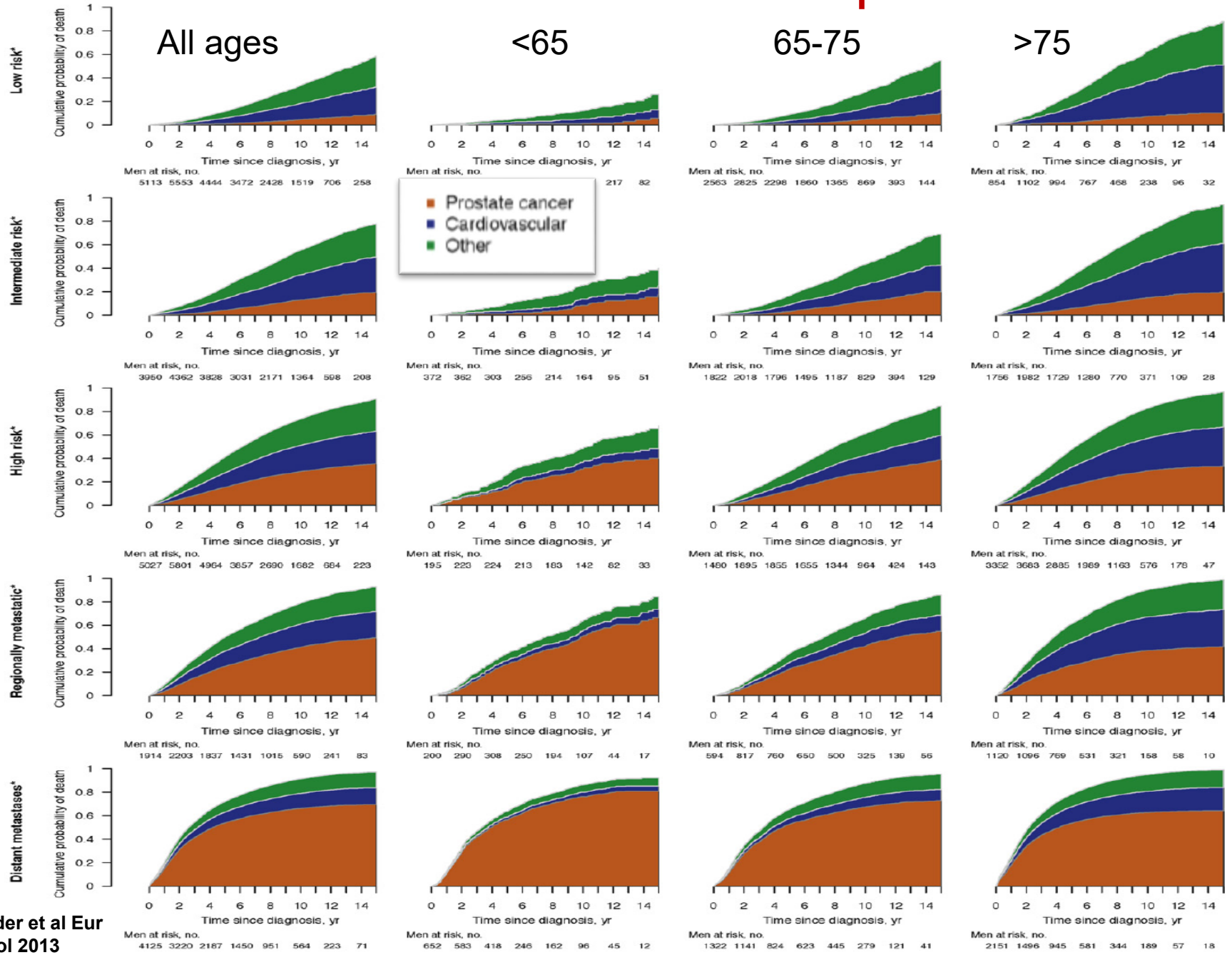








The Middle Ground: Risk Adapted Treatment



Rider et al Eur Urol 2013

Bottom Line

- Early detection of more aggressive prostate cancer saves lives and should be offered as part of shared decision making
- Age and risk based guidelines are patient-centric
- Increasing use of imaging, serum biomarkers, and active surveillance is minimizing harms associated with screening and early detection and maximizing benefits to all men but particularly for disproportionately impacted men


Thank you!
Duke Cancer Institute