Controversies in Prostate Cancer Screening

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PSA Screening Recommendations

- **Pro-Screening**
- American Cancer Society
- American Urological Association
- National Comprehensive Cancer Network
- American College of Radiology

- **Anti-Screening**

American College of Physicians

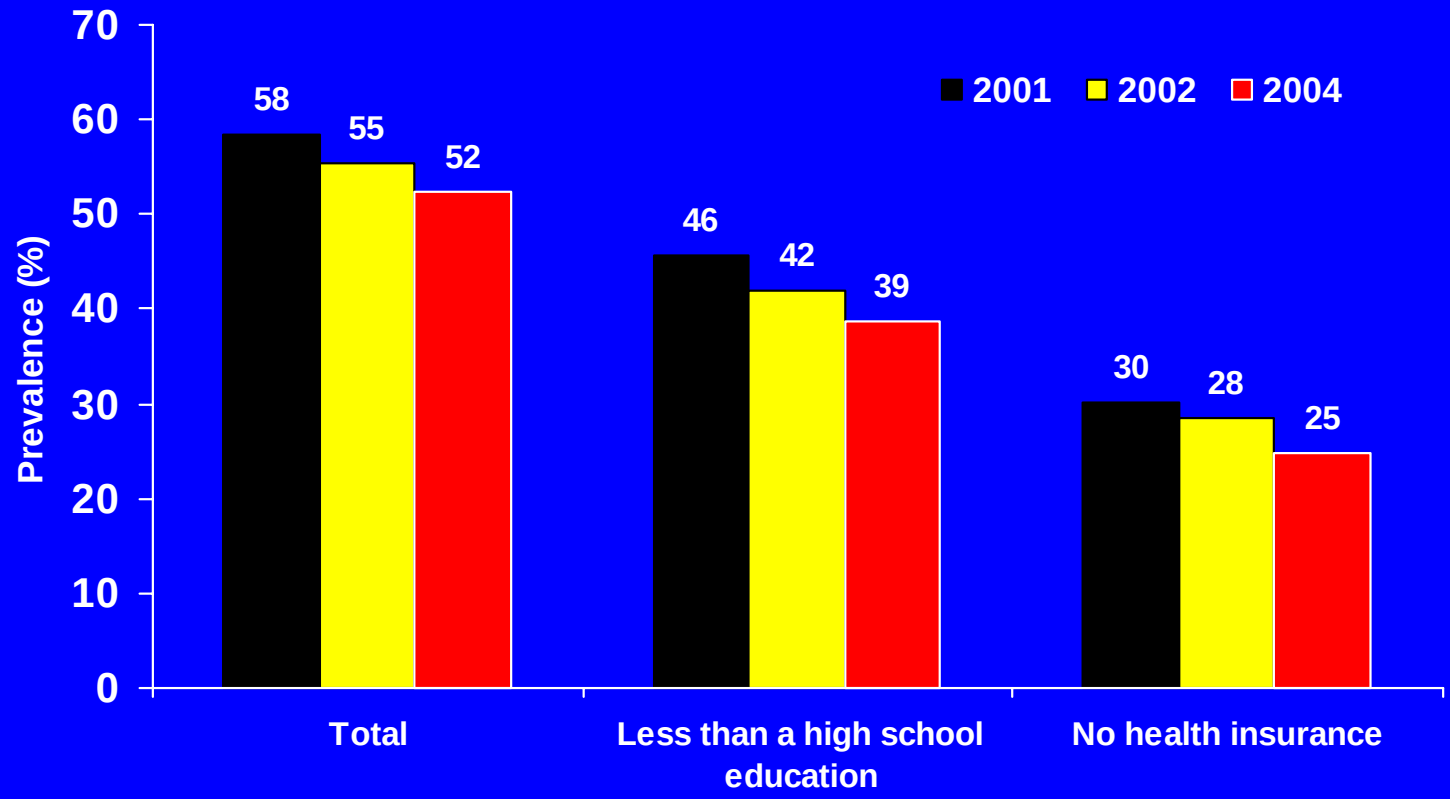
United States Preventive Services Task Force

Neutral

NIH

CDC

Recent* Prostate-Specific Antigen (PSA) Test Prevalence (%) Men 50 Years and Older, US, 2001-2004



*A prostate-specific antigen (PSA) test within the past year. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.

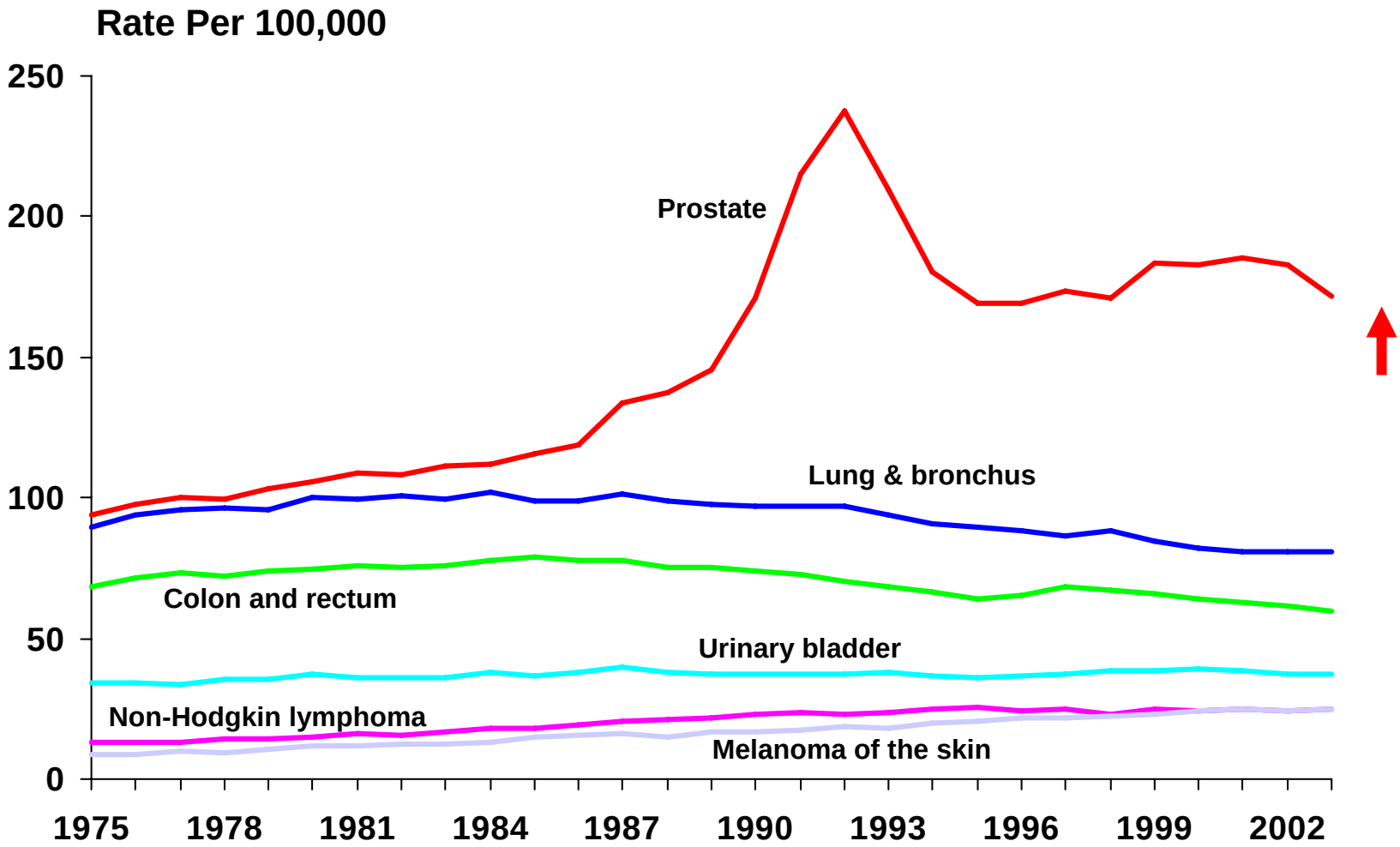
Source: Behavioral Risk Factor Surveillance System Public Use Data Tape (2001, 2002, 2004), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2002, 2003, 2005.

PSA Testing in Physicians

- **87%** of male physicians age ≥ 50 years had a PSA test

Chan EC et al J Gen Intern Med Epub Jan 20, 2006; Walsh PC J Urol 176:583, 2006

Cancer Incidence Rates* for Men, 1975-2003

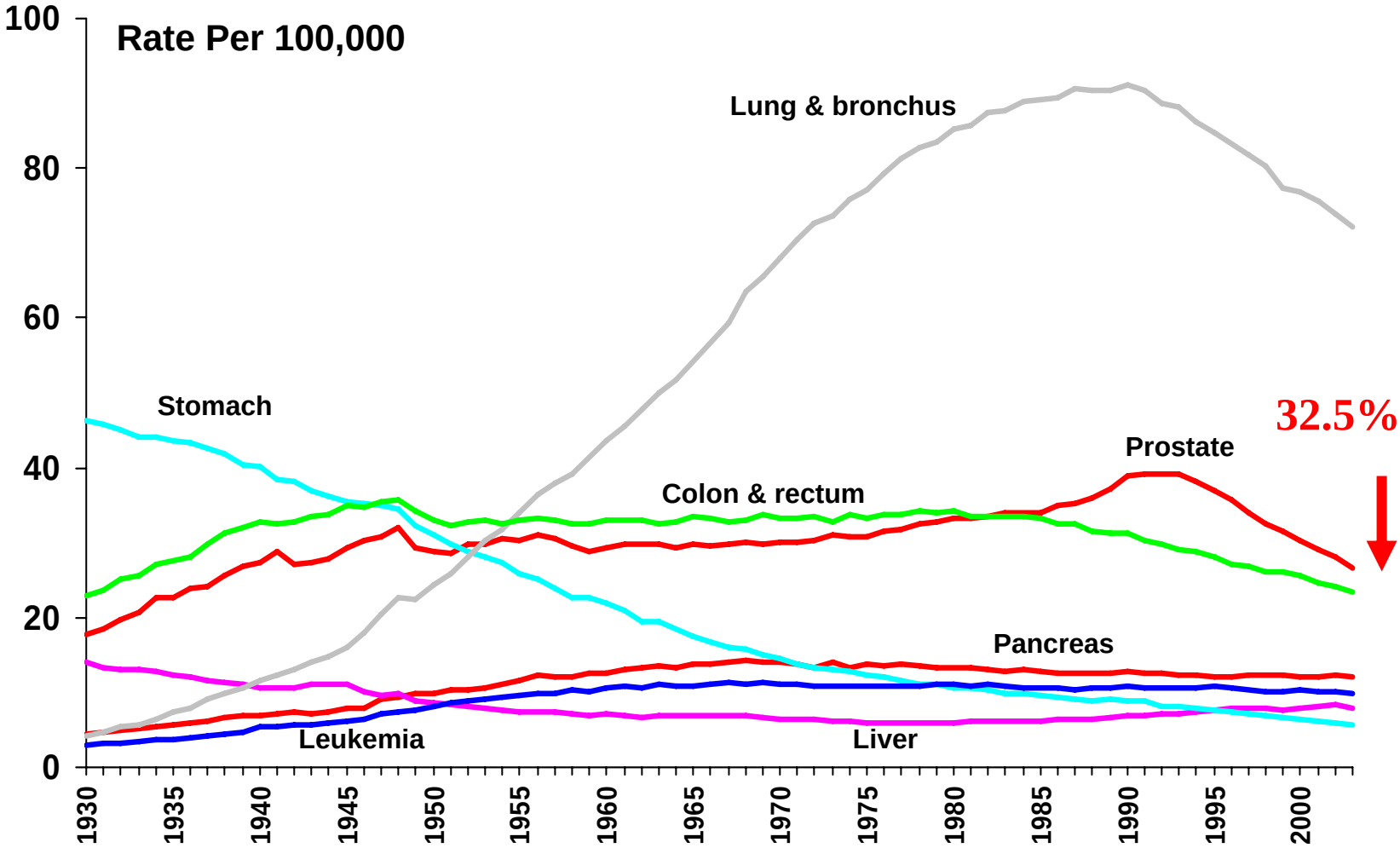


*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2003, Division of Cancer Control and Population Sciences, National Cancer Institute, 2006.

First Sign of Success of PSA Screening: Stage Migration

- **A 70% reduction in metastatic disease at diagnosis since the beginning of the PSA era**

Cancer Death Rates*, for Men, US,1930-2003



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2003, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

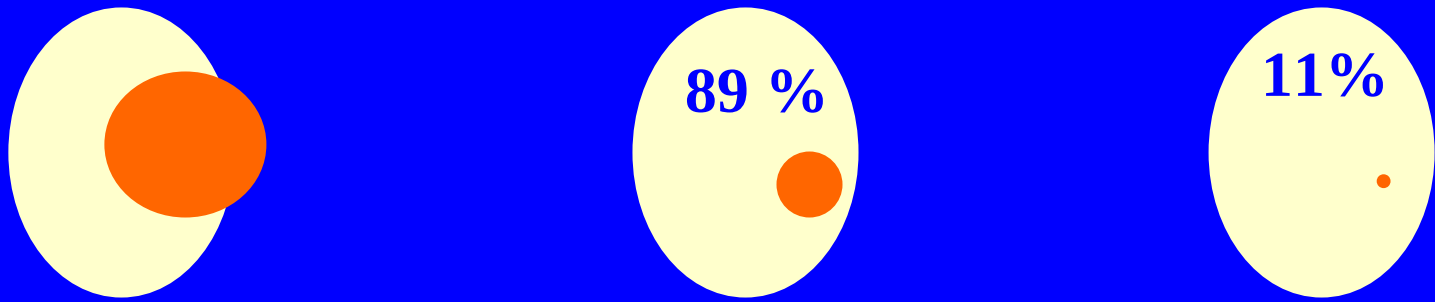
Jemal A et al, Cancer Epidemiol Biomarkers Prev 2005;14:590

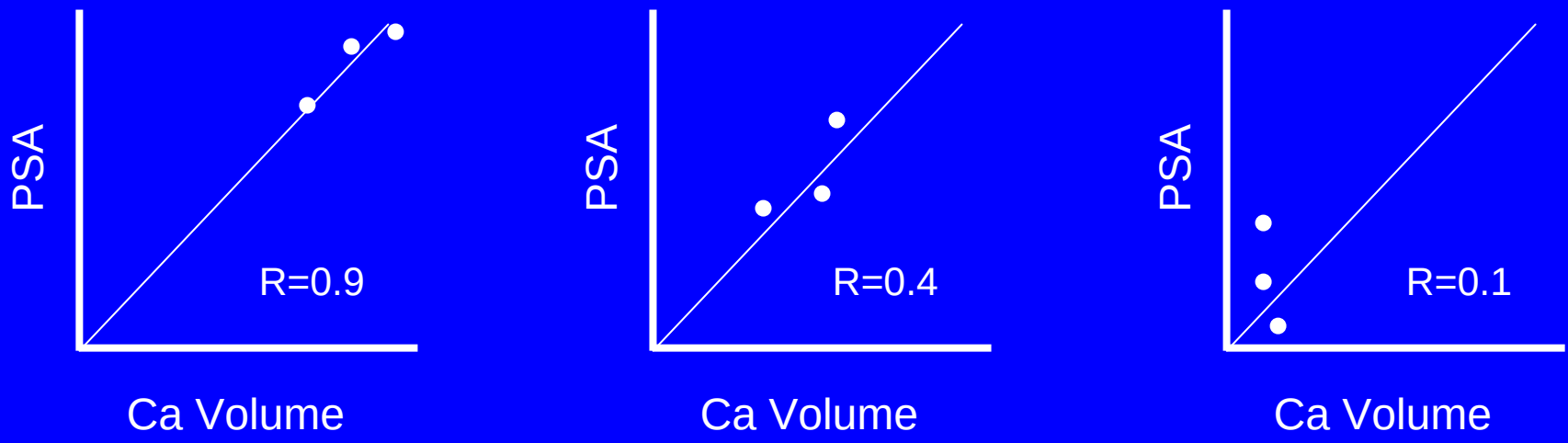
Examined relation of PSA screening to stage at diagnosis and prostate cancer death rates in 30 population-based US cancer registries (30 states, District of Columbia & Atlanta: ~ 68% of US population)

- *The more PSA testing, the less late-stage disease, and the lower the prostate cancer death rate*

Has PSA become a victim of its own success?

Over-diagnosis





“Over-Diagnosis”

- **Over-diagnosis**
- Epidemiological criteria: ≥ 25%-85%
- Clinical and pathologic criteria: 3%-18%
- **Under-diagnosis –** 20% to 30%
- >20% extra-prostatic tumor extension or positive surgical margins in radical prostatectomy series
- > 30% require further treatment after surgery

Graif T et al J Urol 178:88, 2007; Pelzer AE et al J Urol 178: 93,2007

“Insignificant” Cancer

- Patients with low-grade cancer (Gleason < 7) rarely suffer and die from prostate cancer

Albertsen PC et al JAMA 1995. 274:626; Johansson JE et al JAMA 2004 291 :2713

“Active monitoring” with deferred treatment

Information Available with Newly Diagnosed PCa

- **PSA, PSAV, PSAD, % free PSA**
- Estimated tumor volume in biopsies
- Biopsy Gleason score
- DRE findings
- Imaging studies (TRUS, MRI, MRS)

European Screening Trial

PSA Range	2-2.9	3-3.9	4-9.9
Volume	0.48	0.7	1.27

Hoedemaeker RF et al. J Urol 164:411-5, 2000

Criteria for Recommending Intervention

- Gleason pattern 4 or 5
- > 2 biopsy cores involved
- > 50% of a biopsy core is involved
- Cancer on every biopsy procedure
- PSA criteria (PSAV, PSAD, % free PSA)

Current Trigger Points

- Patient anxiety from living with untreated cancer
- **Rising PSA level**
- Repeat biopsy results that suggest greater tumor volume or Gleason grade

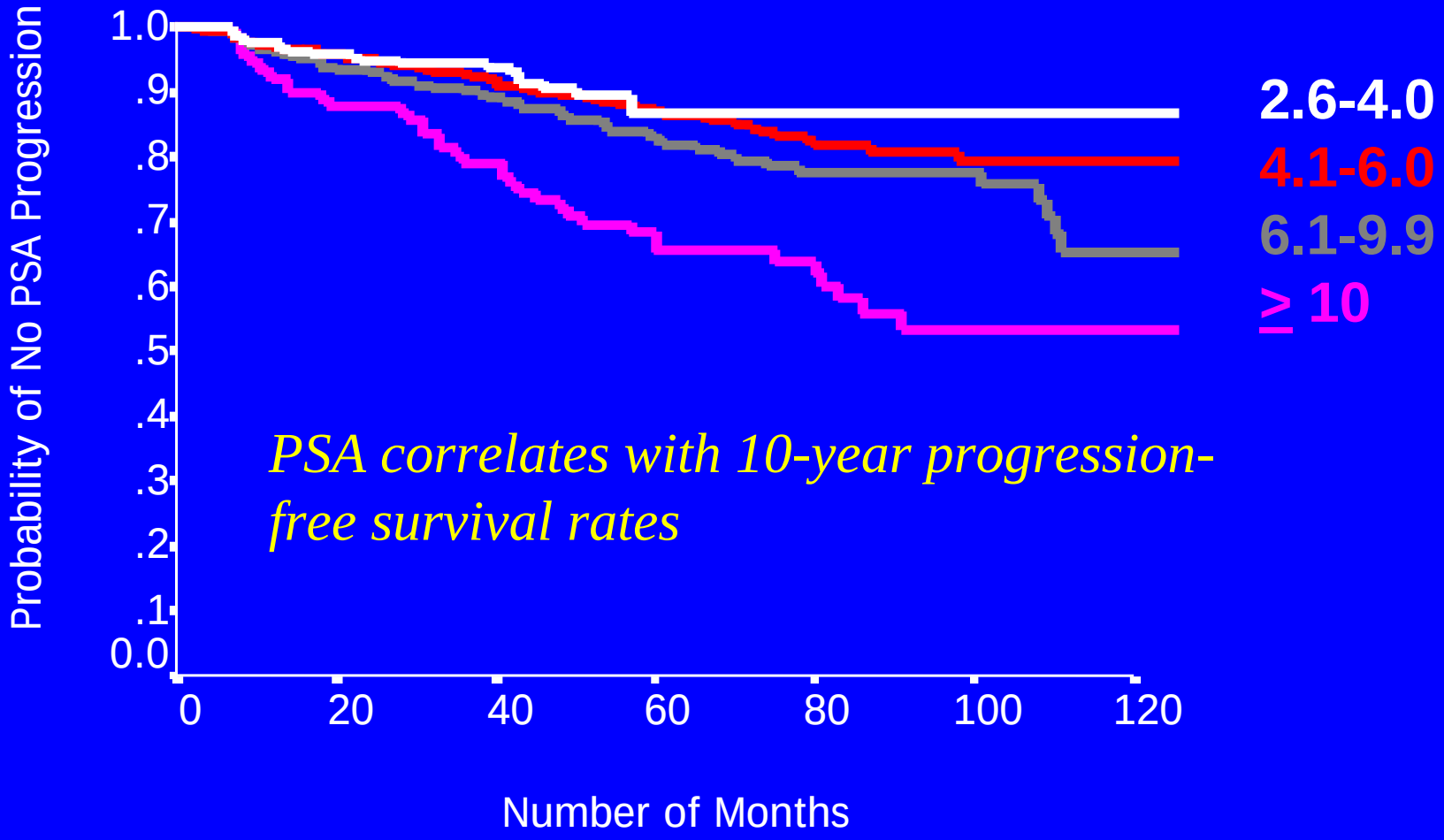
Drawbacks of Active Monitoring

- Repeat biopsies are subject to sampling errors
- **Repeat biopsies might induce inflammatory changes that cause fluctuations in PSA levels**
- May cause scarring that interferes with subsequent nerve-sparing surgery

PSA

- Cancers treated at lower PSA have better progression-free survival than those treated at higher PSA

T1c Patients with RRP by PSA at Diagnosis (PSA Follow-up Study)



Results of Treatment at Progression

- In most studies 25%-50% of patients develop evidence of progression within 5 years
- The percentage of patients with curable cancer at the time of progression has been reported to be 33%-92%

Patel MI, J Urol, 2004.171, 1520; Neulander EZ et al BJU Int, 2000. 85: 699.

PSA Conversion to > 4 ng/ml

	PSA	PSA	PSA	PSA
	0-1	**1-2**	**2-3**	**3-4**
2 yrs	0.5	2.5	**13**	**44**
4 yrs	1.4	6.6	**30**	**77**
5 yrs	1.6	7.6	**35**	**83**

Crawford D et al J Urol 167: 99, 2002 from PLCO Trial

Delayed Treatment after Active Monitoring: Toronto

- >200 patients followed for up to 10 years
- About 60% remained on active monitoring
- But, of patients who underwent radical prostatectomy for progression,
  - **The tumor was organ confined in only 42%**
  - **58% had tumor extension beyond the prostate, and 8% had lymph node metastases**

Klotz L, Urol Oncol 24: 46, 2006

Risk Assessment for Different Age Groups

- Median PSA for age group in men without prostate cancer

Median PSA in Men without Prostate Cancer: PSA Study (32,000 Men)

Age Group	Median PSA
40s	0.7
50s	0.9
60s	1.3
70s	1.7

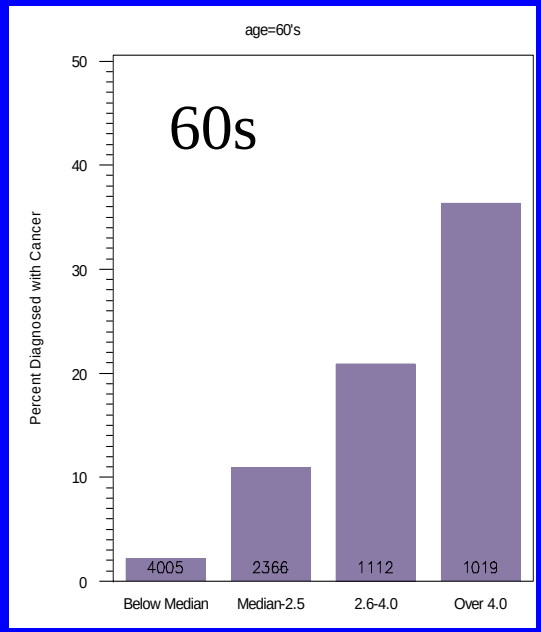
Loeb S et al J Urol 177:1745,2007; Loeb S et al J Urol:177:899, 2007; Loeb et al. Urology 67: 316,2006

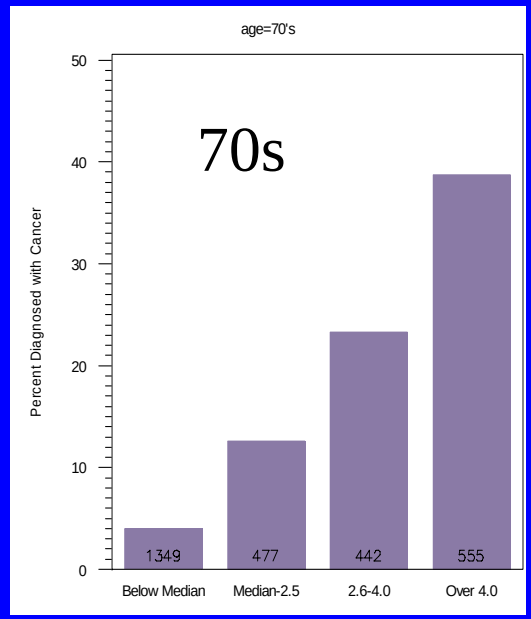
Baseline PSA Predicts Risk and Aggressiveness

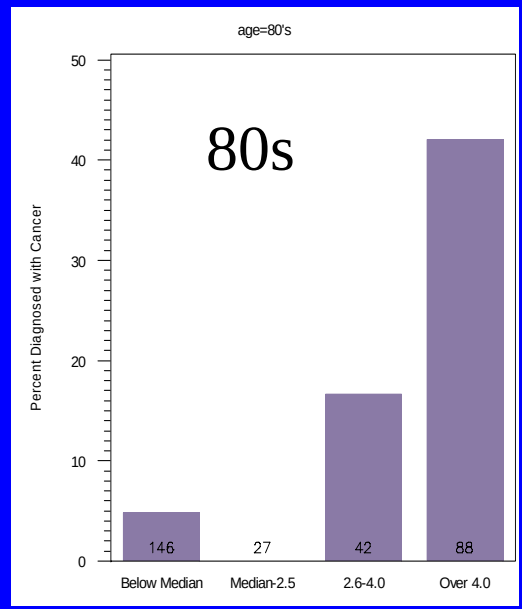
	PSA range ng/ml	Relative Risk
Age 50-59	< 0.9	1
	0.9-2.5	7
	2.6-4.0	27
	> 4.0	44

Loeb S, et al. Urology 67:316-20, 2006

Prostate Cancer Detection Rates by PSA Category



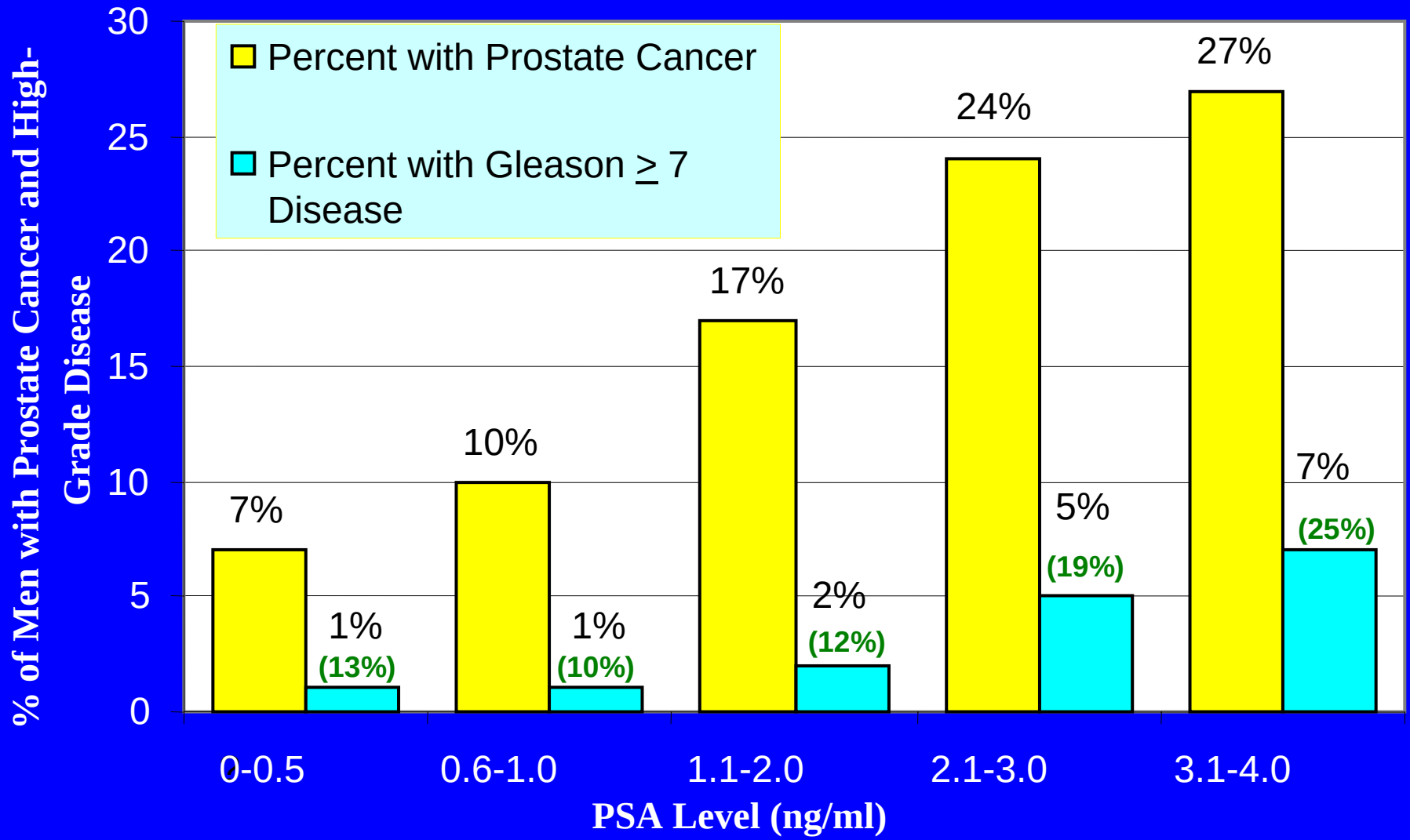




< median median-2.5ng/ml 2.6-4 ng/ml >4ng/ml

Data from PSA Study: 36,000 men followed for up to 12 years

Prevalence of Prostate Cancer with PSA ≤ 4.0 ng/ml.

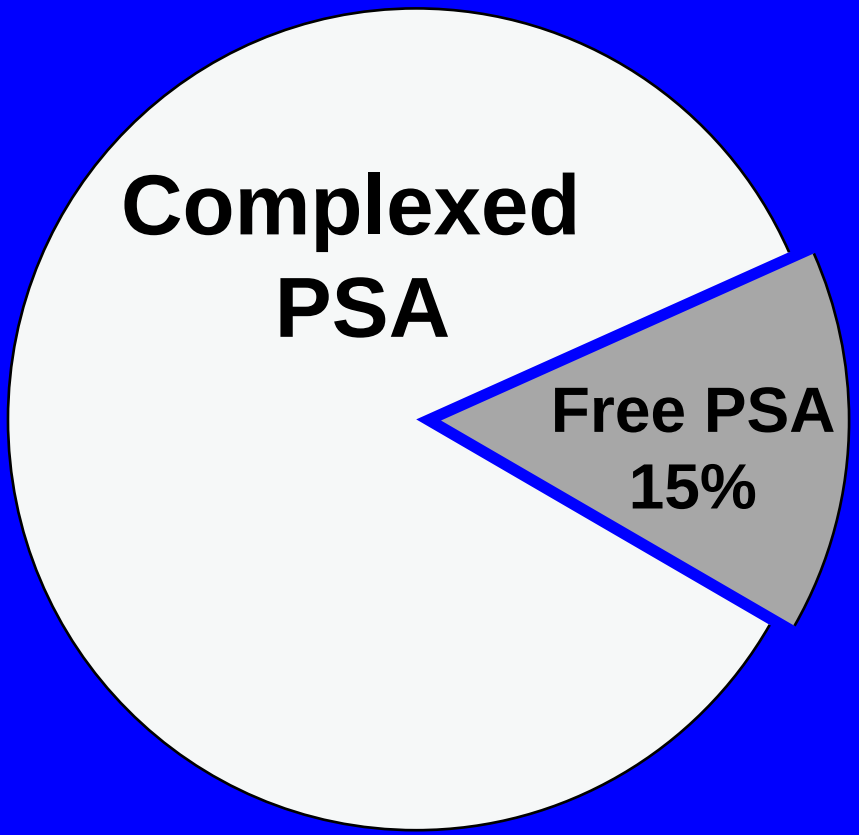


Thompson IM, et al. N Engl J Med. 2004;350:2239-46.

PSA Confounding

- Benign Prostatic Hyperplasia
- Prostatitis
- Ejaculation
- Prostate manipulation
- Assay standardization
- Biologic variation

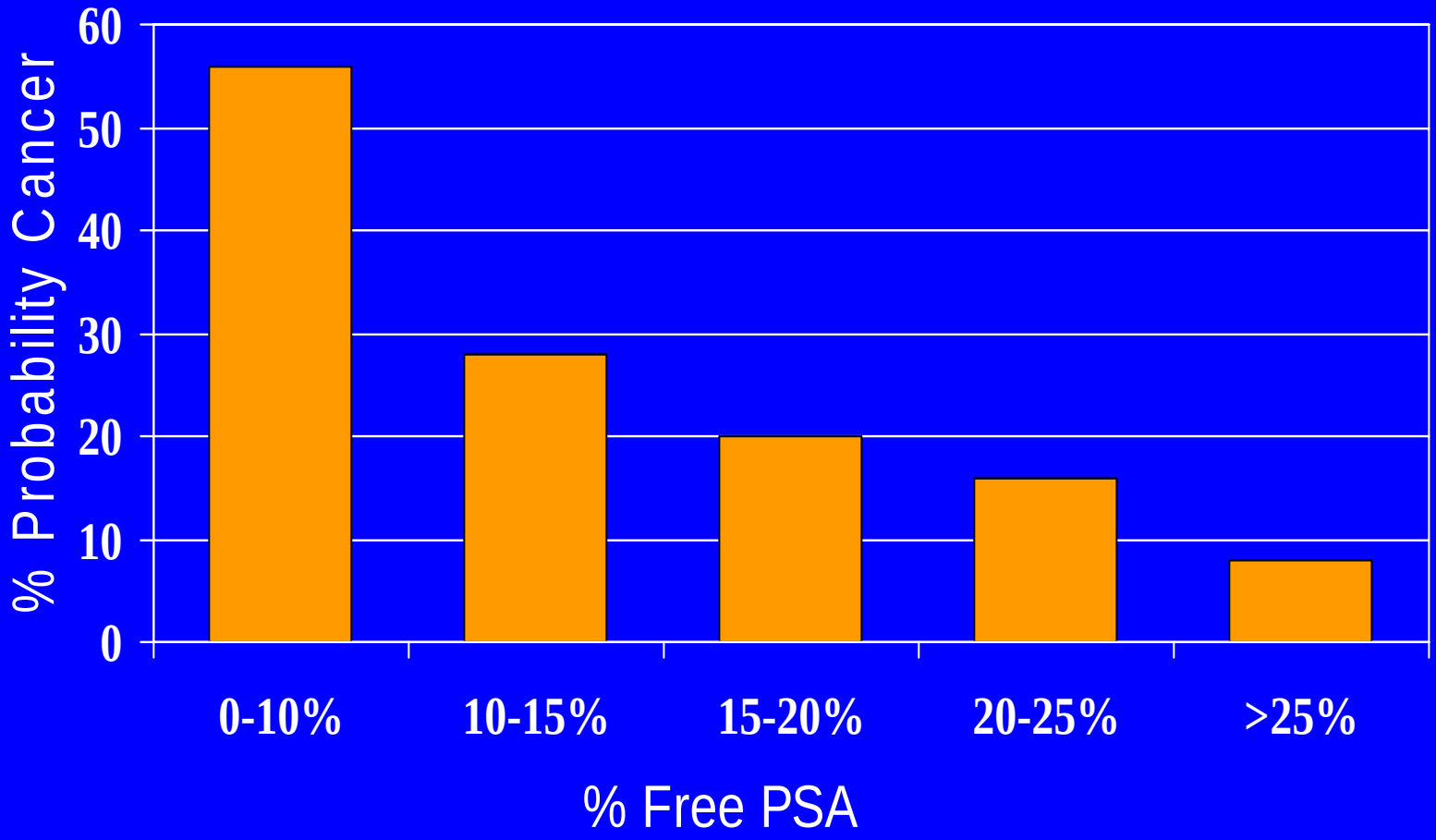
What is Free PSA in Serum?

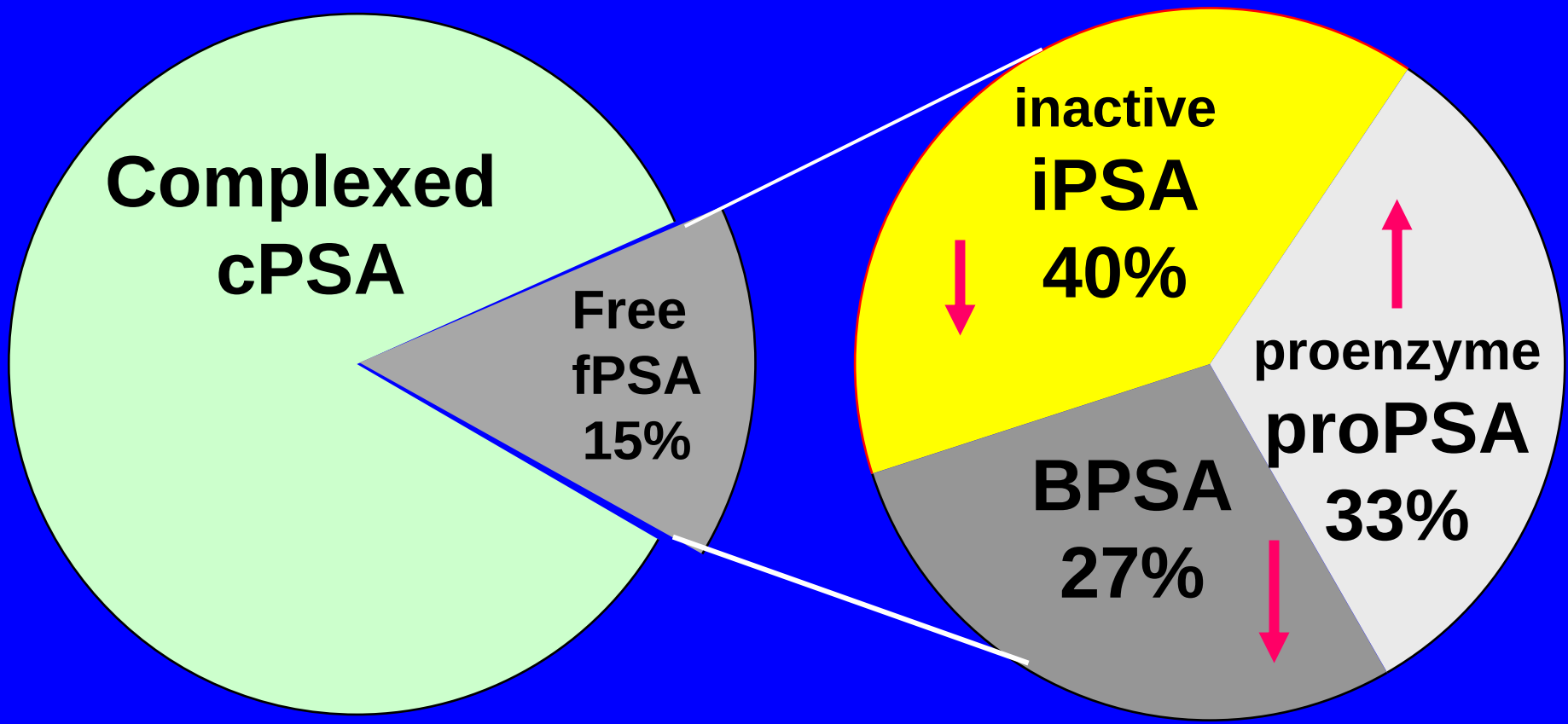


- Enzymatically inactive
- Does not complex with ACT
- Lower % in cancer

Probability of Cancer

PSA 4-10 ng/ml



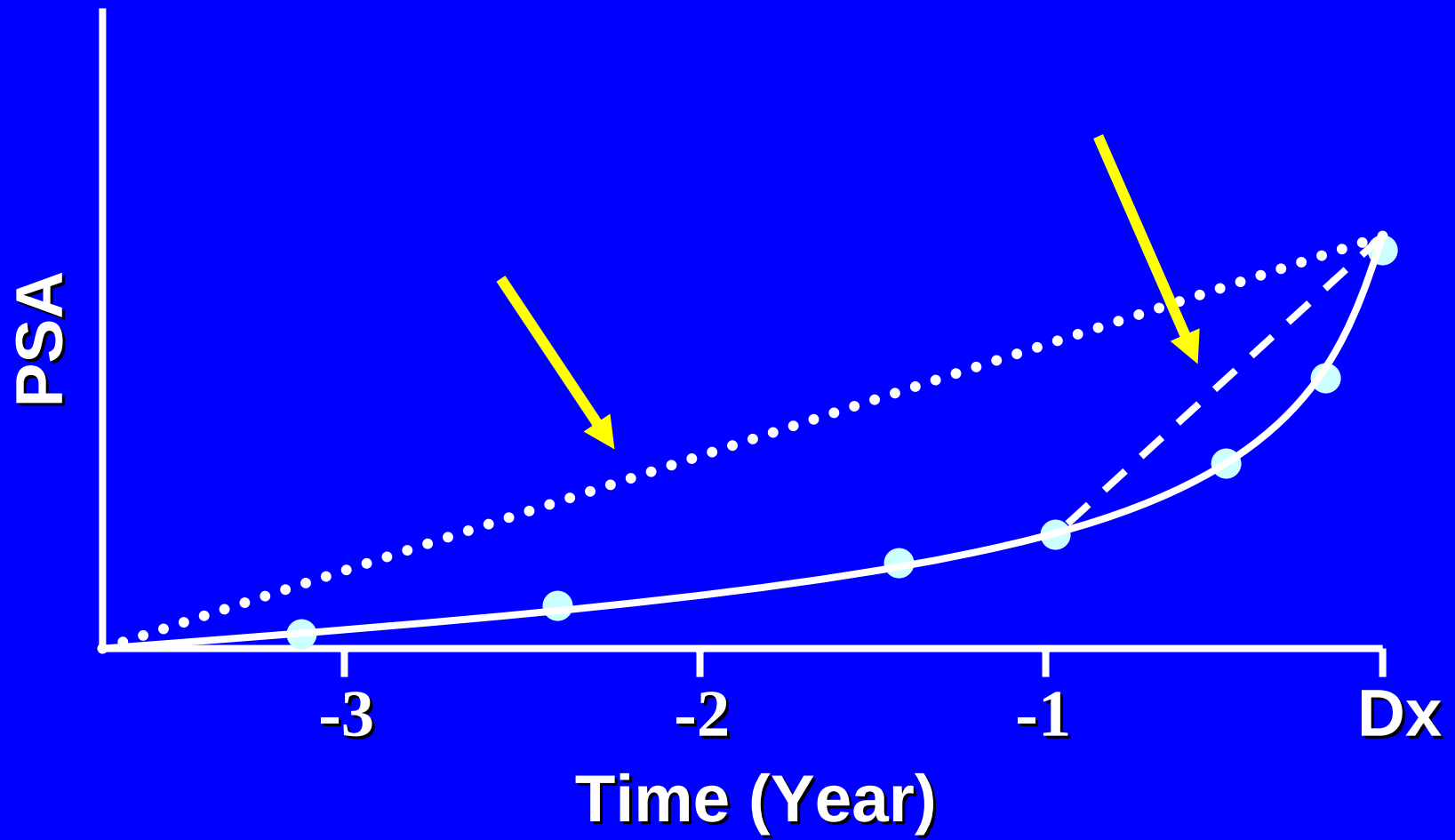

Complexed
cPSA
Free
fPSA
15%
inactive
iPSA
40%
proenzyme
proPSA
33%
BPSA
27%

PSA Density (PSA / Prostate Volume)

- PSA density > 0.10 –0.15 is suspicious for cancer
- PSA density has been shown to correlate with progression-free survival

Kundu SD et al, J Urol 177:505,2007

PSA Kinetics

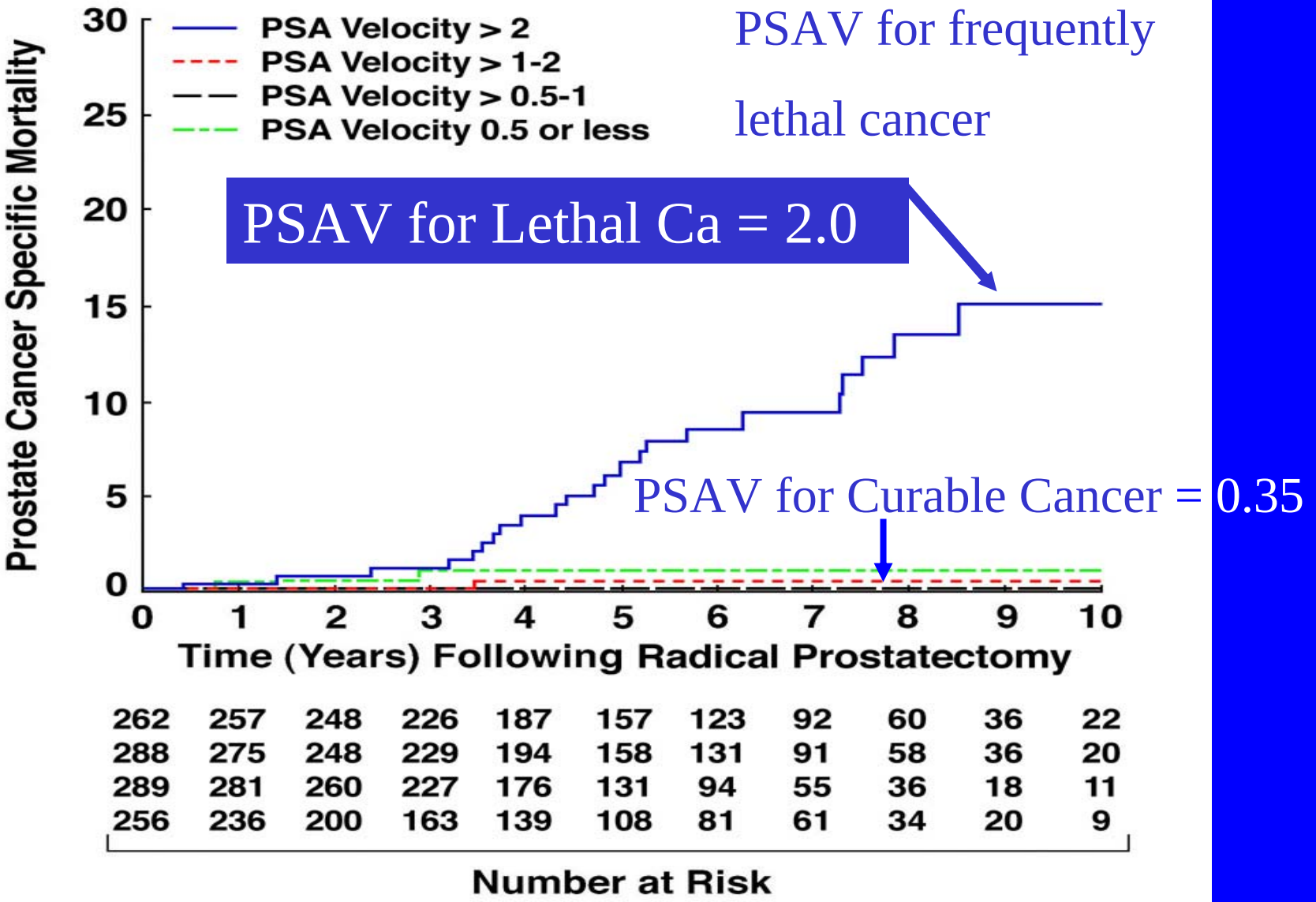


PSA Velocity in PSA Study

	Median PSAV (ng/ml/yr)
Cancer	0.8
Non-Cancer Biopsy	0.1
No Biopsy	0.1

P<0.0001

PSAV for frequently lethal cancer



D'Amico et al, NEJM 351:125, 2004

Long-Term PSAV >0.35 ng/ml/year Correlates with CaP-Specific Mortality Rate

- PSAV calculated in 980 men from Baltimore Longitudinal Study on Aging

- *PSAV >0.35 ng/ml/year associated with 5-fold increased risk prostate cancer death 15 or more years later*

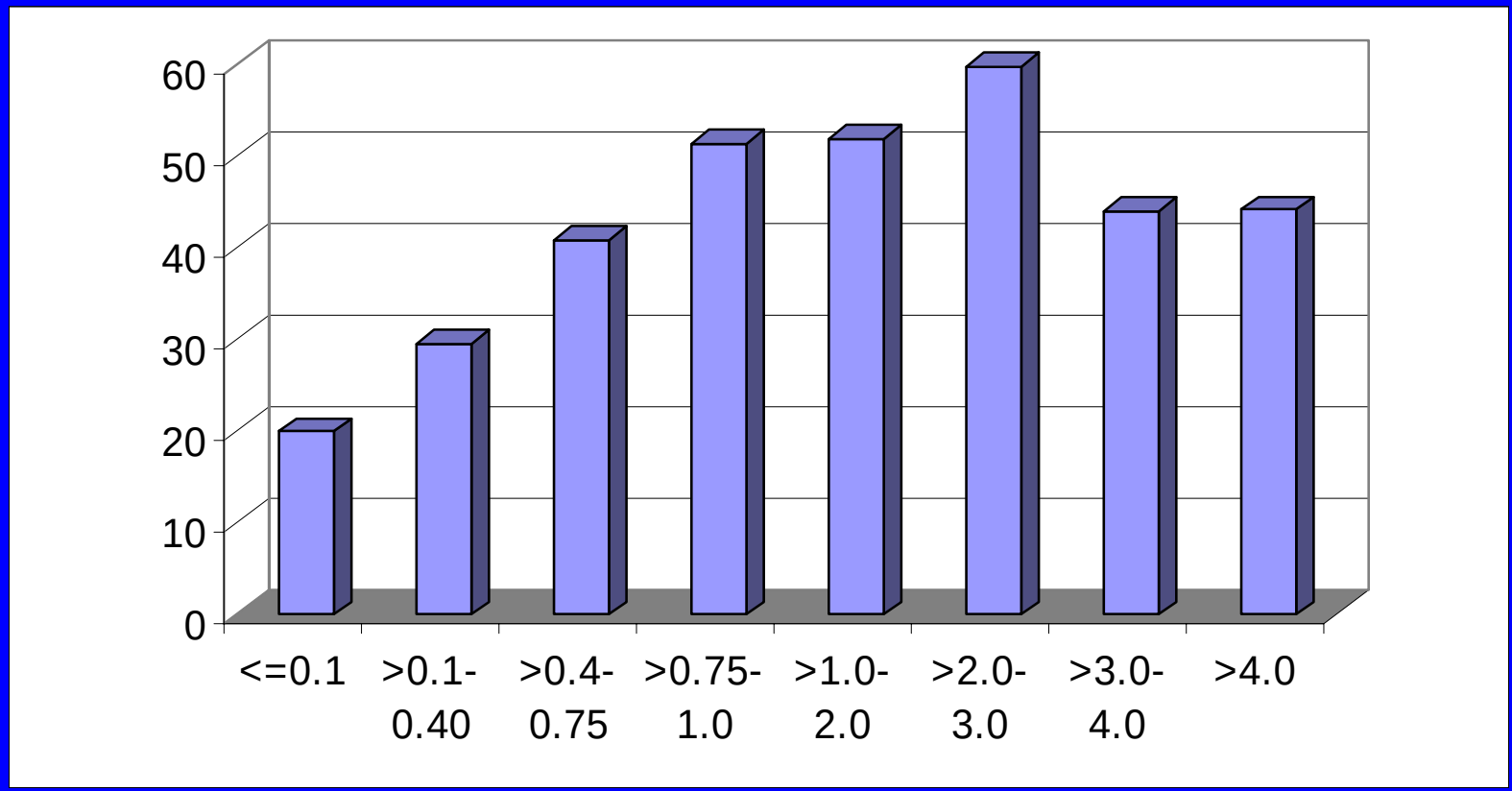
Carter HB et al. JNCI 2006; 98: 1521

PSA Velocity to Predict CaP

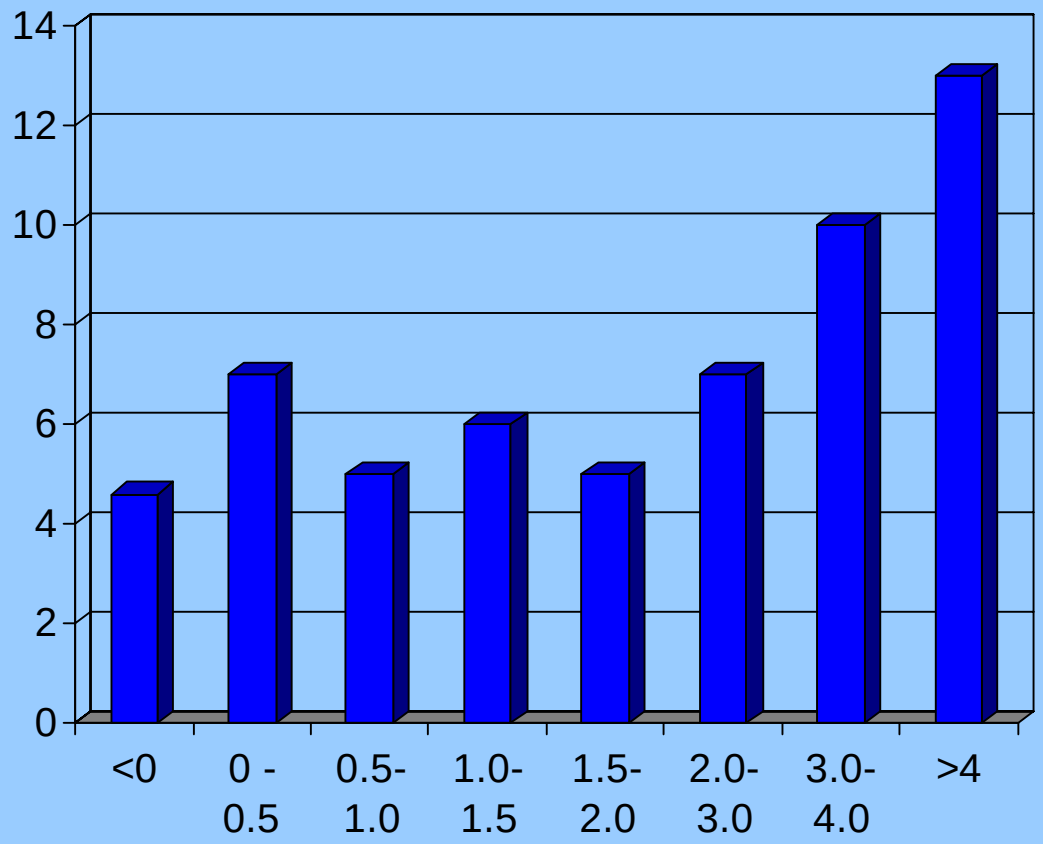
- Traditional PSAV cutoff for Bx = 0.75, established in men with PSA > 4 ng/ml
- If PSA < 4 ng/ml, a cutoff of 0.3-0.5 ng/ml/yr should be used
- 2006 National Comprehensive Cancer Center (NCCN) Guidelines recommend 0.5 ng/ml/year (0.35 in 2007)
- 2007 AUA may recommend 0.4 ng/ml/year

*Smith DS et al J Urol 1994 152 1163;Fang et al Urol 2002 59 889; Berger D, et al abstract 485, 2006.**

Cancer Detection Rate by PSAV



Rate of prostatitis on first biopsy, stratified by PSAV

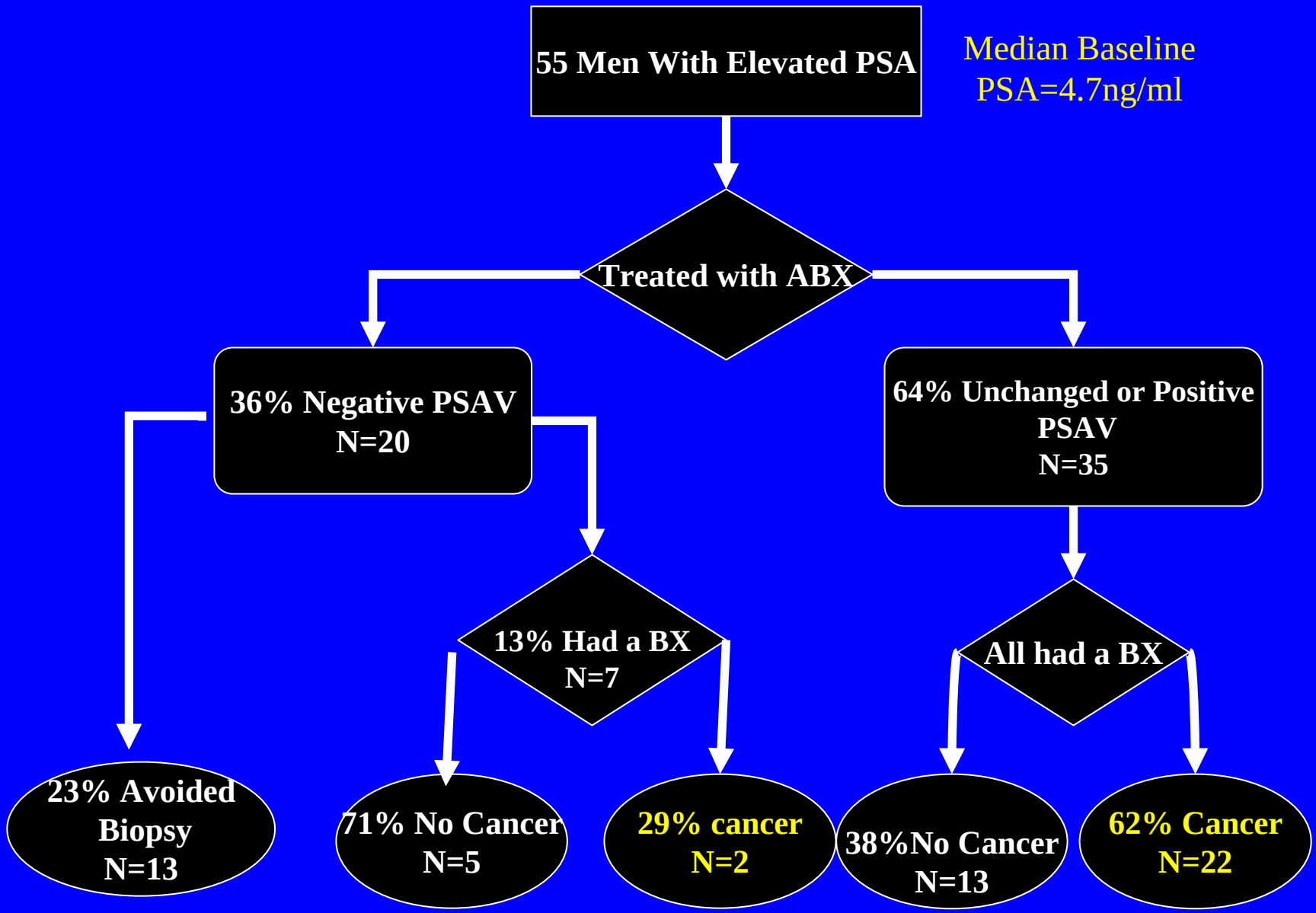


PSA Decreases with Antibiotics in Many Patients with Prostatitis

- PSA before and after 28-day course of fluoroquinolone antibiotic therapy in patients with chronic bacterial prostatitis
- Median PSA decreased from 8.3 to 5.3 ng/ml
- In 42% with PSA > 4 ng/ml, PSA decreased to < 4ng/ml after antibiotics

Schaeffer AJ et al, J Urol 174:161-4, 2005

Prospective Cohort Treated with an Empiric Antibiotics



Different PSA Standards

- Hybritech 1986 and WHO 1999
- WHO-standardized assays give PSA levels ~23% lower
- Hybritech 4.0 = WHO 3.1
- Hybritech 2.5 = WHO 2.0
- This bias affects: PSA cutoffs, PSAV, PSADT, PSA density, % free PSA

Sotelo R et al Urology 69:1143,2007

Intelligent Use of PSA

- Start annual PSA testing at age 40 and track changes
- Know the standardization of PSA assays used
- Assess PCa risk using age-group median PSA values
- Use PSA density and % free or % complexed PSA to evaluate confounding from BPH
- Rule out prostatitis with antibiotics and repeat PSA measurements
- Use PSA velocity to identify more aggressive tumors
  - Use PSAV cutoff: 0.3–0.5 ng/ml/yr